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Entzündlich-rheumatische Erkrankungen im Kontext der COVID-19-Pandemie

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Inhaltsverzeichnis

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Abbildungsverzeichnis

Abkürzungen

ANCA ..... *Anti-Neutrophile cytoplasmatische Antikörper*
BLys ..... *B-lymphocyte stimulator*
CI ..... *Konfidenzintervall*
CoV ..... *Coronaviren*
COVID-19 ..... *Coronavirus Disease 2019*
DGRh ..... *Deutsche Gesellschaft für Rheumatologie*
EMA ..... *Europäische Arzneimittel-Agentur*
ERE ..... *entzündlich-rheumatische Erkrankungen*
HCoV-229E ..... *Humanres Coronavirus 229E*
HCoV-HKU1 ..... *Humanes Coronavirus HKU1*
HCoV-NL63 ..... *Humanes Coronavirus NL63*
HCoV-OC43 ..... *Humanes Coronavirus OC43E*
HIV ..... *Human Immunodeficiency Virus*
IL-12/23i *Interleukin-12/23-Inhibitoren*
IL17i *Interleukin-17-Inhibitoren*
IL-6i *Interleukin-6-Inhibitoren*
LEOSS ..... *Lean European Open Survey on SARS-CoV-2 infected patients*
MERS ..... *Middle East Respiratory Syndrome*
mRNA ..... *messenger Ribonucleic Acid*
OR ..... *Odds Ratio*
PCV13 ..... *13-valenter Konjugat-Impfstoff*
PJP ..... *Pneumocystis jiroveci-Pneumonie*
PPSV23 ..... *23-valenter Polysaccharid-Impfstoff*
RNA ..... *ribonucleic acid*
SARS ..... *Severe Acute Respiratory Syndrome*
SARS-CoV-2 ..... *schweres, akutes respiratorisches Syndrom auslösendes Corona-Virus 2*
SECURE-IBD ..... *Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease*
suPAR ..... *soluble urokinase plasminogen receptor*
TNFi ..... *Tumornekrose-Faktor-Alpha-Inhibitoren*
WHO ..... *Welt-Gesundheitsorganisation*

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1. Einführung

1.1 Das neuartige Coronavirus SARS-CoV-2

Seit dem 11. März 2020 spricht die Welt-Gesundheitsorganisation (WHO) von einer Coronavirus-Pandemie. Erstmalig wurde das Virus im Dezember 2019 in Wuhan in der Provinz Hubei, China beschrieben [1]. Die Infektion wird verursacht durch das neuartige („2“), ein schweres, akutes respiratorisches Syndrom auslösendes Corona-Virus 2, abgekürzt SARS-CoV-2. Die Erkrankung wird COVID-19 genannt (Coronavirus Disease 2019). Bereits bis Juli 2021 wurden weltweit 192 Millionen Fälle berichtet [2]. Diese Zahl stieg bis August 2022 auf über 586 Millionen Fälle an, was die rasante Ausbreitung der Infektion widerspiegelt [3]. Trotz des wahrscheinlich zoonotischen Ursprungs war die Übertragung von Mensch zu Mensch verantwortlich für die schnelle und weltweite Verbreitung [4]. Die Übertragung erfolgt über den respiratorischen Trakt über Aerosole. Nach Eindringen in den Körper bindet das Virus an Rezeptoren und wird mithilfe von Endozytose oder Membranfusion intrazellulär aufgenommen [4]. Die Replikationsphase, die in der Regel wenige Tage beträgt, verläuft mehrheitlich asymptomatisch. In dieser Phase befällt das Virus den oberen Atemtrakt. Dies kann mit Symptomen wie Fieber, Abgeschlagenheit oder Husten einhergehen [4]. Bei ca. 20% der Infizierten kommt es zu einer Beteiligung des unteren Atemtrakts [4], die in ein akutes vaskulär-entzündliches Lungenversagen münden kann [4]. Durch die Aktivierung des Immunsystems kann es zu einer überschießenden Immunantwort kommen, die mit einem lebensgefährlichen Zytokinsturm einhergehen kann [4]. Bis Mai 2022 wurden weltweit über 6,2 Millionen Todesfälle gemeldet [3].

Coronaviren (CoV) sind RNA-Viren und gehören zur Familie der Nidovirales [5]. Zu dieser Familie gehören mehrere Hundert Virusarten, deren Auswirkungen sich bislang mehrheitlich auf Tiere konzentrierten, wie z.B. in Fledermäusen, Hühnern, Kamelen oder Katzen [2]. In den 1960er-Jahren wurde erstmalig Infektionen bei Menschen beobachtet. Diese wurde durch die Coronaviren HCoV-OC43 und HCoV-229E verursacht (s. Tabelle 1) [6]. Innerhalb der Gruppe der humanpathogenen Coronaviren (HCoV) weisen vier Virusarten einen endemischen Verlauf mit milden Symptomen auf. Zu diesen Arten gehören 229E, OC43, NL63, and HKU1 (s. Tabelle 1) [2,7,8]. Schwere Verläufe der Infektionen sind jedoch auch möglich [5]. Sie waren vor der COVID-19-Pandemie neben Influenza für ca. 5-10% der hospitalisierten Virusinfektionen der Atemwege verantwortlich [5].

Im November 2002 wurde das Schwere Akute Respiratorische Syndrom-Coronavirus (*Severe Acute Respiratory Syndrome*, SARS) entdeckt, welches schwere Atemwegsinfektionen verursacht [9,10]. Es konnte ein Zusammenhang der Übertragung mit Fledermäusen nachgewiesen werden [10,11]. Seit 2005 wurden weitere neue Arten des Coronavirus entdeckt [2]. Sowohl bei SARS als auch beim *Middle East Respiratory Syndrome* (MERS) im Jahr 2012

konnte ein Zusammenhang des Virusgenoms mit ursprünglichen Virusvarianten in Fledermäusen nachgewiesen werden [12].

Erste Fälle von MERS wurden im Jahr 2012 in Saudi Arabien gemeldet [2]. Im Verlauf kam es zu zwei weiteren Ausbrüchen in den Jahren 2015 und 2018 sowohl in Saudi Arabien als auch in Südkorea [2]. Sowohl SARS als auch MERS können schwere Symptome mit einer krankheitsassoziierten Mortalität von 10-30% verursachen [5]. Innerhalb des Zeitraums von 2002 bis 2014 wurden 774 SARS-assoziierte Todesfälle gemeldet [13].

Humanpathogene Coronaviren		
Virus	**Isolation**	**Erkrankungen**
SARS-CoV-2	2019	Coronavirus-Krankheit 2019 (COVID-19)
MERS-CoV	2012	Respiratorisches Syndrom im mittleren Osten (MERS), Mortalitätsrate über 30%
HCoV-HKU1	2005	Erkrankung der oberen & unteren Atemwege
HCoV-NL63	2004	Erkältung und leichte Atemwegserkrankung
SARS-CoV	2003	SARS, Mortalitätsrate 9%
HCoV-229E	1962	Erkältung und leichte Atemwegserkrankung
HCoV-OC43	1960	Erkältung und leichte Atemwegserkrankung

Tabelle 1: Humanpathogene Coronaviren [5]

1.1.1 Der Einfluss der COVID-19-Pandemie auf die medizinische Versorgung

Nach dem Ausbruch von SARS-CoV-2 war unklar, welches Ausmaß diese Pandemie annehmen würde. In China konnte ein rasanter Anstieg der Infektionszahlen beobachtet werden, so dass bereits im Dezember 2020 ein harter Lockdown verhängt wurde, um Neuinfektionen zu verhindern. Hierfür wurden ganze Provinzen abgeschottet. Die chinesische Politik verfolgte hierbei eine *Zero*-COVID-Politik. Es galten strenge Quarantänen, Ausgangssperren, intensive Kontaktverfolgungen und strenge Einreiseregelungen zur Eindämmung der Ausbreitung der Infektion. Trotz all dieser Maßnahmen breitete sich das Virus mit brisanter Geschwindigkeit aus, so dass in kürzester Zeit auch Fälle in Japan, Südkorea, Iran und Italien gemeldet wurden.

Der erste Fall in Deutschland wurde im Januar 2020 gemeldet [14]. Bis Februar 2020 wurden 14 Fälle berichtet, die einen gemeinsamen Infektionsbezug zu Wuhan hatten [14]. Bis zu diesem Zeitpunkt war unklar, welche Infektiosität und Inkubationszeit das Virus aufweist und wie schwer eine Infektion verlaufen kann [14]. Im März 2020 breitete sich das Virus von Ischgl (Österreich) länderübergreifend in ganz Europa aus. Bereits im März 2020 wurden über 16.000

Fälle in Deutschland und 47 Todesfälle berichtet, so dass noch im selben Monat erhebliche Maßnahmen, wie z.B. Kontaktverbote, Schließung des Einzelhandels (ausgenommen Geschäfte des Grundbedarfs und Apotheken) und pädagogischer Einrichtungen, zur Eindämmung des Infektionsgeschehens beschlossen wurden [15]. Dies wirkte sich deutlich auf die wirtschaftliche Entwicklung sowie soziale, politische und psychische Aspekte aus [16].
Im März 2020 wurde seitens der Bundesregierung beschlossen, alle planbaren Aufnahmen, Operationen und Eingriffe im Gesundheitswesen zunächst zu verschieben, um Behandlungskapazitäten für SARS-CoV-2-infizierte PatientInnen zu schaffen [17]. Dies führte auch dazu, dass PatientInnen mit chronischen Erkrankungen zunächst weniger intensiv betreut werden konnten und beispielsweise intravenöse Therapieoptionen bei PatientInnen mit entzündlich-rheumatischen Erkrankungen (ERE) nicht in den gewohnten Zeitintervallen erfolgten. Auch bei anderen medikamentösen Therapien kam es zwangsweise zu Therapiepausen, da die ärztlichen Kontakte deutlich eingeschränkt waren. Zudem wurden nicht-medikamentöse Therapien, wie z.B. physikalische Maßnahmen, oder Bewegungstherapien in der Gruppe in dieser Zeit pausiert, so dass ein weiterer wichtiger Baustein der rheumatologischen Therapie nicht erfolgen konnte. Ambulante ärztliche Vorstellungen zur Kontrolle der medikamentösen rheumatologischen Therapie sowie der Krankheitsaktivität konnten nicht wie gewohnt umgesetzt werden. Zusätzlich herrschte seitens der ÄrztInnen und PatientInnen große Unsicherheit, da bis zu diesem Zeitpunkt noch unklar war, inwiefern PatientInnen mit ERE ein höheres Risiko für einen schweren Verlauf von COVID-19 aufweisen könnten. Der fehlende Kontakt zwischen PatientInnen und ÄrztInnen begünstigte die Unsicherheit. All diese Faktoren führten dazu, dass sich eine ohnehin bereits bestehende rheumatologische Versorgungslücke für ERE-PatientInnen verschärfte und zudem ein Risiko bestand, dass durch Therapiepausen eine Exazerbation der ERE induziert werden könnte, mit potenziell lebensbedrohlichen Folgen. Verschiedene rheumatologische Kliniken und Schwerpunktpraxen versuchten, mit einem verstärkten Einsatz von Telemedizin entgegenzuwirken. Dennoch konnte der Bedarf der rheumatologischen Versorgung dadurch nicht ausreichend kompensiert werden.

1.1.2 Verlauf einer SARS-CoV-2-Infektion

Führend wurden folgende Symptome bei Infizierten gemeldet: Husten (42%), Fieber (26%), Schnupfen (31%), Einschränkung des Geruchs- oder Geschmackssinns (19%) [18]. Dabei war eine große Variation der Symptomstärke und des Krankheitsverlaufs zu beobachten. Bis November 2021 lag die COVID-19-assoziierte Letalität in Deutschland bei 1,8% [18]. Besonders ältere Menschen und Personen mit relevanten Komorbiditäten gehören zur Risikogruppe für schwere COVID-19-Verläufe [18]. Die Verteilung einer Infektion in Bezug auf die Geschlechter

ist in etwa gleich. Es konnte jedoch gezeigt werden, dass das männliche Geschlecht für schwere Verläufe prädisponiert ist [1,18].

Ein kritischer Aspekt im Krankheitsverlauf von COVID-19 stellt die Hyperinflammation dar. Zwar tritt die Hyperinflammation in seltenen Fällen auf, jedoch ist sie mit einer hohen Mortalität assoziiert [18]. Dabei kann COVID-19 drei Erkrankungsphasen aufweisen: 1) frühe Phase der Infektion mit hoher Virusreplikation, 2) pulmo-vaskuläre Erkrankung, 3) Hyperinflammation [18]. In der Phase der Hyperinflammation spielt die Virusreplikation keine führende Rolle mehr. Es kommt zu einer ungezielten Produktion und Sezernierung von proinflammatorischen Mediatoren, die schlussendlich zu einem Multiorganversagen führen kann [18].

1.1.3 Immunmodulatoren im Einsatz gegen COVID-19

Vor allem der lebensbedrohliche Zytokinsturm im Rahmen der Hyperinflammation stellt bei COVID-19 eine Herausforderung der Behandlung dar. Zu Beginn der Pandemie gab es noch keine erfolgreiche Therapieansätze zur Behandlung. Neben der damals noch nicht verfügbarenr antiviralen Therapie stand somit die Behandlung des Zytokinsturms zur möglichen Reduktion der Mortalität im Fokus. Hierbei wurden vor allem immunmodulierende Medikamente, die beispielsweise auch in der Rheumatologie eingesetzt werden, intensiv diskutiert und untersucht. Im Rahmen dieser Studien wurden jedoch PatientInnen, die beispielsweise bereits im Rahmen ihrer ERE unter einer solchen Therapie standen, ausgeschlossen.

In einer Publikationen während des Zeitraums Mai bis Juni 2020 wurden 358 PatientInnen mit einer rheumatoiden Arthritis oder Spondyloarthritis hinsichtlich ihrer SARS-CoV-2-Serologie untersucht [19]. 18% der Personen wiesen Antikörper gegen SARS-CoV-2 auf. Diese Ergebnisse waren vergleichbar mit der Kontrollgruppe [19]. Beinahe 60% der SARS-CoV-2-positiven PatientInnen wiesen hierbei einen asymptomatischen Verlauf auf. Komorbiditäten und der Einsatz von Glukokortikosteroiden waren, im Gegensatz zu konventionellen Basismedikamenten und Zytokininhibitoren, mit einem häufigeren Nachweis einer positiven SARS-CoV-Serologie assoziiert [19].

In einer weiteren Studie wurden von Februar bis April 2020 bei 213 PatientInnen mit immunvermittelten Erkrankungen in 36% der Fälle eine SARS-CoV-2-Infektion nachgewiesen [20]. Im Vergleich zur Allgemeinbevölkerung war das Vorliegen einer ERE nicht mit einer vermehrten COVID-19-bedingten Hospitalisierung oder Notwendigkeit einer Beatmung assoziiert. Der Einsatz von TNF-Hemmern war in dieser Studie mit milderen COVID-19-Verläufen assoziiert [20].

Bei PatientInnen der Gastroenterologie, Dermatologie und Rheumatologie, die unter einer Therapie mit Zytokininhibitoren standen, konnte bei signifikant weniger Personen in der ersten Welle der Pandemie Antikörper gegen SARS-CoV-2 serologisch nachgewiesen werden als bei

Personen der Kontrollgruppen [21]. Zusätzlich wurde im Zeitraum Februar bis April 2020 signifikant weniger Symptome von Atemwegserkrankungen bei diesen PatientInnen beobachtet [21]. Basierend auf diesen Daten schlussfolgerten die Autoren, dass PatientInnen mit chronisch-entzündlichen Erkrankungen aus den Bereichen Gastroenterologie, Rheumatologie und Dermatologie kein erhöhtes Risiko einer Infektion mit SARS-CoV-2 unter der Therapie mit Zytokininhibitoren im Vergleich zur Kontrollgruppe aufwiesen und dass eine Infektion durch SARS-CoV-2 möglicherweise bei diesen PatientInnen weniger schwer verlaufen könnte [21]. Die Daten wurden jedoch teilweise missinterpretiert, so dass der Hinweis verbreitet wurde, dass der Einsatz von Zytokininhibitoren PatientInnen mit chronisch-entzündlichen Erkrankungen vor einer Infektion durch SARS-CoV-2 schützen könnte. Um dieser Missinterpretation entgegenzuwirken und die Verbreitung von Fehlinformationen vorzubeugen, veröffentlichten die Autoren gemeinsam mit der Deutschen Gesellschaft für Rheumatologie eine Pressemitteilung. Diese stellte klar, dass diese Daten keinesfalls eine Schlussfolgerung dahingehend zulassen, dass PatientInnen mit entzündlichen rheumatologischen, gastroenterologischen oder dermatologischen Erkrankungen durch ihre Therapie vor einer Infektion oder vor einem potenziell auch tödlichen Verlauf einer SAR-CoV-2-Infektion geschützt sind [22].

Zu einem späteren Zeitpunkt erfolgte durch dieselben Autoren eine Querschnittsstudie, in der 2869 PatientInnen mit immunvermittelten Erkrankungen und 1639 Personen als Kontrollgruppe eingeschlossen wurden [23]. Eine positive SARS-CoV-2-Serologie konnte sowohl bei ca. 6% der PatientInnen, als auch in derselben Zahl in der Kontrollgruppe nachgewiesen werden [23]. PatientInnen unter Zytokininhibitoren wiesen niedrigere Spiegel an SARS-CoV-2-Antikörpern im Vergleich zur Kontrollgruppe auf [23]. Im Gegensatz dazu war der Antikörperspiegel unter Therapie mit den konventionellen Basismedikamenten als auch bei nicht mit Immunmodulatoren behandelten PatientInnen vergleichbar mit der Kontrollgruppe [23]. Daraus resultierte die Schlussfolgerung, dass PatientInnen mit immun-vermittelten Erkrankungen unter Therapie mit Zytokininhibitoren, eine geringere Prävalenz von SARS-CoV-2-Antikörpern aufweisen.

Nichtsdestotrotz konnte bisher nicht eindeutig geklärt werden, ob beispielsweise ERE-PatientInnen unter Immunmodulation, welche sich mit SARS-CoV-2 infizieren, genauso von einer Therapie der COVID-19-bedingten Hyperinflammation profitieren als Personen, die zuvor keine Immunmodulation erfahren haben.

Hydroxychloroquin

Das ursprüngliche Antimalariamedikament Hydroxychloroquin wird in der Rheumatologie vor allem bei Kollagenosen eingesetzt. Bereits zu Beginn der Pandemie wurden verschiedene antivirale Therapien im Einsatz gegen COVID-19 diskutiert, unter anderem auch der Einsatz

von Hydroxychloroquin [24]. Zusätzlich veröffentliche unter anderem der ehemalige amerikanische Präsident Donald Trump gemeinsam mit seinem damaligen Leibarzt Sean Conley ein Schreiben, in dem sie für den Einsatz von Hydroxychloroquin warben [25]. Dies führte unter anderem zu vorrätigen Beschaffungen von Hydroxychloroquin und dadurch zeitweise zu Lieferengpässen in der Behandlung von PatientInnen mit ERE. Aufgrund der mangelnden Verfügbarkeit waren betroffene PatientInnen von einer Zunahme der Krankheitsaktivität ihrer ERE akut bedroht. Dadurch wäre zwangsweise eine Intensivierung der Immunmodulation durch einen Steroidstoß notwendig gewesen. Dies hätte maßgeblich das Infektionsrisiko sowie das Risiko für einen schweren Verlauf negativ beeinflussen können. Die Deutsche Gesellschaft für Rheumatologie wendete sich aus diesem Grund bereits im April 2020 an das Bundesministerium für Gesundheit, um die Versorgung von rheumatologischen PatientInnen sicherzustellen. Basierend darauf veranlasste das Bundesministerium für Gesundheit, dass hydroxychloroquinhaltige Arzneimittel daher ambulant nur noch unter Angabe einer zugelassenen Indikation verordnet und abgegeben werden sollten.

Im Verlauf konnte jedoch in Studien keine Wirksamkeit von Hydroxychloroquin im Rahmen von COVID-19 nachgewiesen werden – weder als Prophylaktikum in Bezug auf die Infektion noch im Falle von schweren Verläufen von COVID-19 [24,26]. Die amerikanische Lebensmittel- und Arzneimittelbehörde (FDA) sprach sogar eine Warnung beim Einsatz im Kontext von COVID-19 aus, da lebensgefährliche Herzrhythmusstörungen und in Kombination mit einer antibiotischen Therapie sogar höhere Mortalitätsraten bei COVID-19 beobachtet werden konnten [25].

Glukokortikosteroide

Bei erhöhter Krankheitsaktivität oder einem Schub der ERE werden Glukokortikosteroide als temporäre Stoßtherapie eingesetzt und in der Regel unter Hinzunahme von steroidfreien Immunmodulatoren kontinuierlich reduziert. Eine Langzeittherapie mit Glukokortikosteroiden in einer Dosis von bis zu 5 mg pro Tag (Prednisolonäquivalent) kann als Begleittherapie zur steroidfreien Immunmodulation oder als Monotherapie durchgeführt werden, beinhaltet aber immer noch ein erhöhtes Risiko für Infektionen, v.a. bei älteren (multimorbiden) Menschen [27,28]. Eine Prednisolondosis von 5 mg pro Tag erhöhte das Risiko schwerer Infektionen in dieser Altersgruppe um 30%, 46% bzw. 100%, bei einer kontinuierlichen Einnahme über 3, 6 bzw. 36 Monate [29].

Glukokortikosteroide sind auch bei unkontrolliertem Kreislaufversagen im Rahmen der Sepsis im Einsatz [30,31]. Hierbei spielt die antiinflammatorische Rolle der Glukokortikosteroiden eine wichtige Rolle. Sie reduziert die Gefäßpermeabilität und die Migration der Leukozyten zum Inflammationsherd und begünstigt die Produktion von antiinflammatorischen Molekülen [31].

Basierend aus diesen Erkenntnissen wurde der Einsatz bereits früh bei COVID-19 diskutiert. In der RECOVERY-Studie konnte im Rahmen einer randomisierten, Placebo-kontrollierten Studie in der Gesamtkohorte eine Reduktion der 28-Tage-Mortalität unter dem Einsatz von Dexamethason um 17% gezeigt werden [32]. Auch bei PatientInnen mit Sauerstofftherapie (nicht-invasiv und invasiv) konnte eine signifikante Reduktion der Letalität erreicht werden. Im Gegensatz dazu zeigte sich ein Anstieg der Letalität im gleichen Zeitraum bei Personen ohne initiale Sauerstofftherapie [32]. Somit befürwortete die Europäische Arzneimittel-Agentur (EMA) den Einsatz von Dexamethason bei COVID-19-PatientInnen mit Sauerstofftherapie im September 2020. Die Therapie erfolgt in der Regel für maximal 10 Tage mit einer Dosierung von 6 mg Dexamethason täglich [33].

Interleukin-6-Inhibitoren

Bei der rheumatoiden Arthritis, Riesenzellarteriitis und beispielsweise juvenilen idiopathischen Arthritis wird die Interleukin-6(IL-6)-Blockade bereits seit Jahren eingesetzt.[34]. Zwei verschiedene Antikörpertherapien stehen hierfür zur Verfügung: Tocilizumab und Sarilumab. Die Therapie erfolgt bei Tocilizumab als wöchentliche subkutane Applikation oder monatliche intravenöse Gabe. Sarilumab wird alle 14 Tage subkutan injiziert.

Bei PatientInnen, die mit einer extrakorporalen Membranoxygenierung versorgt werden, können extrakorporale Zytokin-Adsorber eingesetzt werden, die bestimmte proinflammatorische Mediatoren, wie z.B. Interleukin-6, binden können. Somit kann das Ausmaß der Hyperinflammation reduziert und das Outcome der PatientInnen bei einer Sepsis verbessert werden [35].

Aus diesem Grund wurden Zytokinblocker, wie z.B. IL-6-Inhibitoren, sehr früh im Einsatz zur Reduktion der COVID-19-assoziierten Hyperzytokinämie diskutiert. Erste Daten weckten die Hoffnung eines möglichen Therapieansatzes durch IL-6-Inhibitoren im Rahmen von schweren COVID-19-Verläufen [36,37]. Leider konnten in der COVACTA-Studie weder der primäre (Verbesserung des klinischen Status des PatientInnen bei COVID-19-assoziierter Pneumonie) noch der sekundäre Endpunkt (Reduktion der COVID-19 assoziierten Mortalität) durch den Einsatz von Tocilizumab erreicht werden [36]. Auch in der EMPACTA-Studie zeigte sich keine Besserung der Überlebensrate [38]. Dagegen konnte in der REMAP-CAP-Studie durch den Einsatz von Tocilizumab in Kombination mit Glukokortikosteroide ein verbessertes Outcome sowie eine Reduktion der Mortalität bei Patienten mit Sauerstofftherapie oder nicht-invasiver Beatmung gezeigt werden [39]. Die Post-hoc-Analyse der CORIMUNO-TOC-1-Studie wies eine signifikante Reduktion der 90-Tage-Mortalität und der Notwendigkeit einer invasiven/nicht-invasiven Beatmung auf, wenn die Gabe von Tocilizumab vor dem Anstieg des C-reaktiven Protein-Spiegels über 150 mg/l erfolgte [40]. Der Einsatz wird bei COVID-19-Pneumonie mit ausgeprägter pulmonaler Hyperinflammation und radiologischen Milchglasinfiltraten in

Kombination mit Dexamethason empfohlen [33]. Die Gabe erfolgt einmalig in einer Dosierung von 8 mg pro Kilogramm Körpergewicht bis zu einer Maximaldosis von 800 mg nach Ausschluss von Kontraindikationen [33].

Aufgrund der Empfehlung des Einsatzes von IL-6-Inhibitoren bei COVID-19 kam es weltweit zu gravierenden Lieferengpässen, so dass auch hier die Versorgung von den betroffenen ERE-PatientInnen deutlich erschwert war. Somit drohte auch hier eine Zunahme der Krankheitsaktivität der ERE. Neben einer dadurch notwendigen Intensivierung der Immunmodulation in Form eine Steroidstoßes, wären PatientInnen mit einer Riesenzellarteriitis bei Zunahme der Krankheitsaktivität auch vital bedroht gewesen.

Interleukin-1-Inhibitoren

Bei bestimmten autoinflammatorischen Erkrankungen, wie z.B. beim adulten Still-Syndrom, aber auch bei der rheumatoiden Arthritis wird der Interleukin-1 Rezeptorantagonist Anakinra zur Interleukin-1-Inhibition eingesetzt. Die Gabe erfolgt täglich in einer Dosis von 100 mg subkutan.

In der randomisierten CORIMUNO-ANA-1-Studie bei hospitalisierten COVID-19-PatientInnen mit geringgradiger Sauerstofftherapie konnte zunächst keine Verbesserung der Mortalität oder des klinischen Status beobachtet werden [41]. Ende des Jahres 2021 wurde der Einsatz von Anakinra basierend auf weiteren Daten zur Behandlung von COVID-19-PatientInnen mit Sauerstofftherapie in Kombination mit Dexamethason zugelassen. Wichtig hierbei ist zu beachten, dass die Gabe sich am Spiegel des suPAR (*soluble urokinase plasminogen receptor*) orientiert. Der Spiegel sollte mindestens 6 ng/ml betragen und ein hohes Risiko für ein schweres respiratorisches Versagen vorliegen [33,42]. Die Gabe erfolgt zeitlich begrenzt über 10 Tage mit einer täglichen Dosis von 100 mg subkutan [33].

Januskinase-Inhibitoren

Seit 2017 sind Januskinase-Inhibitoren im Einsatz, unter anderem bei inflammatorischen Arthritiden. Inzwischen stehen vier verschiedene Präparate zur Verfügung, die täglich eingenommen werden: Baricitinib, Tofacitinib, Upadacitinib und Filgotinib.

Die meisten Daten zur Untersuchung einer möglichen Wirkung bei COVID-19 liegen zu Baricitinib und Tofacitinib vor. Durch den Einsatz der Januskinase-Inhibitoren konnte in Studien eine antiinflammatorische Wirkung und Inhibition der viralen Endozytose beobachtet werden [33,43]. Unter der Therapie mit dem Januskinase-Inhibitor Baricitinib konnte zwar keine Verbesserung der Sauerstoffbehandlung gezeigt werden, es kam jedoch zu einem deutlichen Rückgang der Mortalität auch bei PatientInnen, die bereits mit Glukokortikosteroiden behandelt wurden [43]. Auch unter der Kombination mit Remdesivir konnte eine Verbesserung des klinischen Status erreicht werden [44,45]. Somit wurde die Empfehlung ausgesprochen,

Baricitinib bei COVID-19-Pneumonie und Sauerstofftherapie oder nicht-invasiver Beatmung unter Beachtung der Kontraindikationen einzusetzen [46]. Die Dosierung beträgt 4 mg täglich für maximal 14 Tage und erfolgt in Kombination mit Dexamethason [33].

1.1.4 Antivirale Therapieansätze gegen COVID-19

Die antivirale Therapie hemmt direkt oder indirekt die Virusreplikation durch Einflussnahme auf den viralen Replikationszyklus oder andere Strukturen, die für die Replikation eine wichtige Rolle spielen [46]. Virusneutralisierende monoklonale Antikörper interagieren mit dem SARS-CoV-2 Spikeprotein und verhindern dadurch den Viruseintritt in die Zelle [46]. Der ideale Therapiezeitpunkt liegt hier unmittelbar nach der Virusexposition (maximal 5-7 Tage nach Symptombeginn oder nach vermuteten Infektionszeitpunkt), was die Anwendung in der Praxis häufig limitiert [47,48]. In dieser Phase ist noch keine eigene Immunantwort etabliert [47].

1.1.4.1 Monoklonale Antikörper

Initial wurde die passive Immunisierung mit SARS-CoV-2 neutralisierenden Antikörpern besonders bei vulnerablen Patientengruppen empfohlen [46]. Mit zunehmenden Virusvarianten können sich Resistenzen gegen die verfügbaren monoklonalen Antikörper entwickeln, so dass der Einsatz der Präparate kontinuierlich evaluiert werden muss.

Gemäß der Leitlinie zum Einsatz von monoklonalen Antikörpern (Stand Juli 2022) wird empfohlen, dass monoklonale Antikörper bei PatientInnen mit unvollständigem Impfschutz oder mit relevantem Risiko für unzureichendes Impfansprechen und einem Risiko für einen schweren Verlauf sowie bei PatientInnen mit Immunkompetenz und vollständiger Impfung bei komplexen Risikofaktoren eine Therapie mit Virostatika oder neutralisierenden monoklonalen Antikörper in Erwägung gezogen wird [48]. Seit 17.12.2021 ist das Präparat Sotrovimab in der Europäischen Union zugelassen, gefolgt von dem Kombinationspräparat Tixagevimab/Cilgavimab, welches seit dem 25.03.2022 von der Europäischen Union zugelassen wurde [49,50]. Beim Einsatz von Tixagevimab/Cilgavimab handelt es sich aktuell (Stand Juli 2022) noch um einen sogenannten *Off-label-Use* zur Therapie von COVID-19, so dass der Einsatz primär nur zur Präexpositionsprophylaxe empfohlen wird [48]. Aufgrund der nur mäßig reduzierten Wirksamkeit der Omikron-Variante BA.4/BA.5 in vitro, wird der Einsatz von Tixagevimab/Cilgavimab als 1. Wahl empfohlen. Sotrovimab kann als 2. Wahl eingesetzt werden [48]. In vitro konnte unter dem Einsatz von Sotrovimab bei BA.2 und BA.4/BA.5 eine deutlich reduzierte Wirksamkeit beobachtet werden, so dass hier höhere Dosen diskutiert werden [48]. Der Einsatz erfolgt in der Frühphase der Erkrankung (≤ 5 Tage nach Symptombeginn) [46]. Diese Empfehlungen basieren auf den Daten der TACKLE-Studie (Tixagevimab/Cilgavimab) und der COMET-ICE-Studie (Sotrovimab), die eine signifikante

Reduktion des Risikos für schwere COVID-19-Verläufe unter Einsatz der jeweiligen Medikamente nachweisen konnten [51,52].

Sotrovimab wird einmalig in einer Dosierung von 500 mg intravenös appliziert [46]. Bei Infektionen mit Virusvarianten mit reduzierter Empfindlichkeit kann eine Dosiserhöhung auf 1000 mg in Erwägung gezogen werden [48]. Die Applikation von Tixagevimab/Cilgavimab erfolgt mit jeweils 150 mg intramuskulär [48].

1.1.4.2 Remdesivir

In der PINETREE-Studie konnte bei nicht-hospitalisierten COVID-19-PatientInnen mit einem hohen Risiko für einen Progress der Infektion unter Einsatz von Remdesivir über 3 Tage eine Reduktion der Hospitalisierungsrate sowie der COVID-19-assoziierten Mortalität gezeigt werden [53]. Diese Studie stützt den Einsatz von Remdesivir in der Frühphase der Infektion, so dass in der Leitlinie eine Empfehlung für den Einsatz innerhalb von 7 Tagen nach Symptombeginn (Expertenmeinung) [53] bei PatientInnen ohne Impfschutz und mindestens einem Risikofaktor für einen schweren Verlauf von COVID-19 ausgesprochen wurde.

Der Einsatz bei späteren Krankheitsstadien ist bisher nicht eindeutig geklärt. Die Studienergebnisse diesbezüglich variieren stark [54–58]. In einer Meta-Analyse der zur Verfügung stehenden Studien bei insgesamt 7865 PatientInnen konnte kein Vorteil bei hospitalisierten PatientInnen in Hinsicht der 28-Tage-Sterblichkeit nachgewiesen werden [46]. Die Behandlung von invasiv-beatmeten COVID-19-PatientInnen wird nicht empfohlen [46]. Remdesivir wird über drei Tage in einer Dosierung von 200 mg an Tag 1 und 100 mg an den Tagen 2 und 3 intravenös appliziert [46].

1.1.4.3 Nirmatrelvir/Ritonavir

Der Einsatz von Nirmatrelvir/Ritonavir zu Beginn der Infektion wurde bei 2246 in einer randomisierten Studie bei ungeimpften COVID-19-PatientInnen mit einem hohen Risikoprofil für eine Exazerbation der Infektion untersucht [59]. In dieser Studie konnte ein positiver Effekt auf den kombinierten Endpunkt (COVID-19 assoziierte Hospitalisierung und 28-Tage-Sterblichkeit) nachgewiesen werden [59]. Der Einsatz in einer späteren Phase der Infektion ist bisher nicht eindeutig geklärt.

Ritonavir dient durch die Inhibition von CYP-3A4 als pharmakologischer Booster. Dadurch bestehen Wechselwirkungen mit anderen Medikamenten wie z.B. Statinen und oralen Antikoagulantien [46]. Aufgrund dessen müssen, trotz der guten Verträglichkeit und dem positiven Sicherheitsprofil, vor Beginn der Therapie Interaktionen mit bestehenden Medikamenten überprüft werden [46].

Die Dosierung von Nirmatrelvir/Ritonavir beträgt (300 mg+100 mg) 2x/d oral über 5 Tage [46].

1.1.4.4 Molnupiravir

In 4 verschiedenen randomisierten Studien bei insgesamt 1930 PatientInnen konnte eine positive Wirkung auf den kombinierten Endpunkt (COVID-19 assoziierte Hospitalisierung und 28-Tage-Sterblichkeit) bei PatientInnen in der Frühphase (innerhalb von 5 Tagen nach Symptombeginn) der Infektion nachgewiesen werden [60–62].

Der Einsatz in einer späteren Krankheitsphase wies bei insgesamt 293 hospitalisierten PatientInnen keinen Benefit auf und war in manchen Fällen sogar mit einer erhöhten Sterblichkeit assoziiert [63].

Basierend auf diesen Daten wurde in der Leitlinie aufgrund des günstigen, jedoch schwachen Effekts auf das Risiko der Hospitalisierung oder Tod vor dem Auftreten der Omikron-Variante eine Empfehlung für den Einsatz in der Frühphase der Infektion bei nicht-immunsupprimierten PatientInnen innerhalb von 5 Tagen nach Symptombeginn ausgesprochen [46]. Diese Empfehlung gilt, falls keine anderen Therapieoptionen verfügbar und klinisch angemessen sind [46].

Unter der Therapie mit Molnupiravir konnten im Tiermodell teratogene Effekte nachgewiesen werden, so dass unter dieser Therapie bei Frauen im gebärfähigen Alter eine Kontrazeption notwendig ist und Männer während der Behandlung bis 3 Monate danach kein Kind zeugen sollten [46,64].

Die Dosierung von Molnupiravir beträgt 2 x 800 mg als Tablette für 5 Tage [46,64].

1.2 Entzündlich-rheumatische Erkrankungen und Virusinfektionen der Atemwege

Arthralgien treten häufig bei viralen Infektionen auf, unabhängig von dem Vorliegen einer entzündlich-rheumatischen Erkrankung [65]. Die Symptome sind dabei zeitlich begrenzt und es konnte beispielsweise bei Infektionen mit Röteln oder Parvovirus-B19 gezeigt werden, dass die Arthropathien auch selbstlimitierend sind, da das Immunsystem die Infektion selbst kontrolliert und nach Abschluss der Infektion keine weiteren Symptome verbleiben. Viele Virusinfektionen gehen mit der Produktion von Autoantikörpern einher, und virale Proteine haben tiefgreifende Auswirkungen sowohl auf die Antigenpräsentation als auch auf die ausführende Wirkung des Immunsystems. Als mögliche Ursache hierfür wird ein sogenanntes *molekulares Mimikry* diskutiert, da Erreger und Menschen ähnliche Aminosäuremotive präsentieren können und dadurch eine Autoimmunität durch eine Infektion induziert werden kann [66]. Die Chronifizierung der Arthropathie könnte mit einer Viruspersistenz oder latenten Virusinfektion, virusinduzierter Autoimmunität, Aktivierung von polyklonalen B-Zellen oder einer Virus-induzierten Immundefizienz assoziiert sein [65].

ERE beruhen auf einer Fehlregulation des Immunsystems, welche unabhängig von der Therapie mit einer verstärkten Infektanfälligkeit einhergehen können [67]. Literaturquellen

weisen auf eine erhöhte Infektneigung von PatientInnen mit rheumatologischen Erkrankungen hin, auch in Anbetracht der Immunmodulation [68,69]. Um das Infektionsrisiko für diese PatientInnen abschätzen zu können, sind individuelle Betrachtungen von Grunderkrankung und immunmodulierender bzw. immunsuppressiver Therapie notwendig. Ein weiterer wichtiger Aspekt für das Infektionsrisiko ist die Krankheitsaktivität. Das Infektionsrisiko sinkt bei Remission [70]. Weitere unabhängige Faktoren, die das Infektrisiko beeinflussen, sind das Alter (Immunoseneszenz) und die Komorbiditäten der PatientInnen [68,71]. Die erhöhte Infektneigung kann zudem durch die Organmanifestation der ERE begünstigt werden, wie z.B. bei pulmonaler Beteiligung in Form einer interstitiellen Lungenerkrankung [72]. Eine idiopathischen Lungenfibrose ohne zugrundeliegende Erkrankung kann zu einer ausgeprägten Verschlechterung der Lungenfunktion durch eine akute Infektion führen [73]. Auch bei ERE mit Lungenfibrose wurden vermehrt Infektionen beobachtet.

In einer Studie zur Untersuchung des Infektionsrisikos bei Personen mit rheumatoider Arthritis waren in einer multivariaten Analyse die Faktoren rheumatoide Arthritis in Kombination mit einer interstitiellen Lungenerkrankung im Rahmen der Grunderkrankung als Prädiktor für Infektionen gewertet worden [68]. Neben der direkten pulmonalen Manifestation können weitere Umstände das Risiko für Infektionen der oberen Atemwege begünstigen, wie z.B. die Ösophagusbeteiligung bei der systemischen Sklerose. Aufgrund der Motilitätsstörung, der damit verbundenen Dysphagie und des Refluxes können Infektionen der Atemwege begünstigt werden [74].

1.2.1 Virale Atemwegsinfektionen in der Rheumatologie am Beispiel von Influenza

Trotz vieler klinischer Parallelen zu einer viralen Infektion der oberen und unteren Atemwege mit Influenzaviren, mit einer vergleichbaren initialen Klinik (Husten, Fieber, Cephalgien und Myalgien), dem Übertragungsweg (Tröpfcheninfektion) und der sehr variablen Symptomatik von symptomlos bis zu kurzen letalen Verläufen, gab es bis zu dieser COVID-19-Pandemie keine Handlungsempfehlungen zum Umgang mit Virusinfektionen basierend auf evidenzbasierten Daten für PatientInnen mit ERE. Dasselbe galt für die Bedeutung oder den Einfluss einer dauerhaften immunsuppressiven oder immunmodulierenden Therapie bei Virusinfektionen [75]. Es konnte somit kein Wissen aus bisherigen Virusinfektionen auf die COVID-19-Pandemie transferiert werden.

In der Influenza-Saison vor der COVID-19-Pandemie (40. Meldewoche (MW) 2018 bis 20. MW 2019) wurden laut des Robert-Koch-Instituts (RKI) 182.000 labordiagnostisch bestätige Fälle dokumentiert. Davon waren 98,5 % durch Influenza A verursacht. Lediglich bei 0,7 % der

PatientInnen konnte Influenza Typ B nachgewiesen werden. Dies legt laut RKI die Vermutung nahe, dass eine höhere Immunität gegen Influenza Typ B herrscht und könnte dadurch begründet sein, dass die vorausgegangene Influenza-Saison vordergründig durch Influenza Typ B verursacht wurde. 33 % der Fälle wurden in der Altersgruppe 35–59 dokumentiert. 25 % der Betroffenen waren über 59 Jahre. Die Altersgruppe 5–14 Jahre war dagegen am wenigsten betroffen. Unter den diagnostisch bestätigten Fällen befanden sich 40.000 hospitalisierte Fälle. Diese teilten sich auf in 54 % Betroffenen über 60 Jahre, 19 % in der Altersgruppe 35–59 Jahre und 6 % in der Altersgruppe 5–14 Jahre auf. 64 % der hospitalisierten Fälle wiesen ein Alter über 79 Jahre auf. Schwere Komplikationen, wie z. B. eine schwere Pneumonie oder Lungenversagen (ARDS), waren in allen Altersgruppen nachweisbar. Bei der älteren Patientengruppe (>79 Jahre) war ein höherer Anteil an letalen Verläufen als Fälle mit notwendiger Beatmung zu verzeichnen. Der Altersmedian der gemeldeten Fälle lag bei 40 Jahren, bei den hospitalisierten Fälle bei 63 Jahren und bei den letal verlaufenden Fällen bei 78 Jahren. Insgesamt wurden 954 Influenza-bedingte Todesfälle gemeldet. 52 % der Verstorbenen waren männlich, 86 % über 59 Jahre und 12 % in der Altersgruppe 35–59 Jahre. Da die Meldung von Influenza an den labordiagnostischen Nachweis gekoppelt ist, die meisten Erkrankungen im Verlauf einer Grippewelle aber rein klinisch diagnostiziert werden, liegt wahrscheinlich eine erhebliche Untererfassung von Influenza-Erkrankungen vor [76]. Nichtsdestotrotz zeigt sich, dass auch hier Personen über 60 Jahren einen schwereren Verlauf aufwiesen. In Anbetracht der Tatsache, dass beispielsweise die rheumatoide Arthritis als häufigste Vertreterin der ERE mehrheitlich im Alter von 50 bis 70 Jahre auftritt, kann das höhere Lebensalter bei PatientInnen mit ERE mit einem höheren Infektionsrisiko bzw. Risiko für einen schweren Verlauf der Infektion einhergehen.

In einer Studie zur Untersuchung des Verlaufs einer Influenza bei PatientInnen mit einer inflammatorischen Arthritis konnte innerhalb des Zeitraums 2015-2019 zwar ein erhöhtes Risiko für einen schweren Verlauf einer Influenza sowie einer diesbezüglichen Mortalität im Vergleich zur Allgemeinbevölkerung in Schweden nachgewiesen werden, das Risiko war jedoch durch den Einsatz von Biologika oder JAK-i nicht zusätzlich erhöht [77]. Zusätzlich zeigte sich, dass der Unterschied zur Allgemeinbevölkerung mit Hinzunahme von weiteren Faktoren, wie z.B. anderen relevanten Komorbiditäten, sank [77].

1.3 Differentialdiagnosen der COVID-19-assoziierten Pneumonie im Kontext von ERE

Die Symptome von COVID-19 variieren stark und können, neben Husten und Fieber, auch Myalgien, Kopfschmerzen und Luftnot aufweisen. Aber auch Diarrhöen, Übelkeit und Einschränkungen des Geschmack- und Geruchssinns treten auf. Die Symptome sind nicht

spezifisch für COVID-19 und können somit auch bei anderen Infektionen oder nicht-infektiösen Erkrankungen auftreten [78]. Pneumokokken-induzierte Pneumonien sowie Pneumocystis jirovecii-induzierte Pneumonien spielen bei ERE-PatientInnen eine wichtige Rolle und stellen eine Differentialdiagnose zur COVID-19-Pneumonie dar.

Pneumokokken-induzierte Pneumonie

Die Streptokokken-induzierte Pneumonie gehört weltweit zu den führenden Infektionen und ist für etwa 30-50% der ambulant erworbenen Pneumonien in den Vereinigten Staaten von Amerika und in Europa verantwortlich [79]. PatientInnen mit ERE weisen ein erhöhtes Risiko für eine Pneumokokken-Infektion auf [68,80–83]. Die respiratorische Klinik ähnelt sehr einer COVID-19-Pneumonie. Dennoch gibt es Unterschiede. Im Vergleich zur COVID-19-Pneumonie konnten bei Pneumokokken-induzierten Pneumonien höhere Spiegel des C-reaktiven Proteins und niedrigere Lymphozytenzahlen nachgewiesen werden. Radiologisch betrifft die Pneumokokken-induzierte Pneumonie selten beide Lungen [84]. Obwohl PatientInnen mit Pneumokokken-Pneumonie in den Scores klinisch schlechter abschnitten, wiesen PatientInnen mit COVID-19-Pneumonien eine höhere Hospitalisierungs- und Mortalitätsrate auf [84].

Pneumocystis jirovecii-induzierte Pneumonien

Pneumocystis jirovecii gehört zu den opportunistischen Erregern, der bei immunsupprimierten oder immundefizienten PatientInnen und bei malignen Erkrankungen mit einer erhöhten Mortalität assoziiert ist [85–87]. Die Rolle der Pneumocystis jirovecii-induzierten Pneumonie ist in den letzten Jahren aufgrund von zunehmenden Organtransplantationen, Chemotherapien und Einsatz von Immunmodulatoren bedeutsamer geworden [88]. Der Einsatz von Glukokortikosteroiden, verschiedenen Biologika und Cyclophosphamid kann das Risiko einer Pneumocystis jirovecii-induzierten Pneumonie (PJP) bei ERE-PatientInnen erhöhen [87,89,90]. Die PJP-assoziierte Mortalität bei Personen ohne HIV (*Human Immunodeficiency Virus*)-Infektion liegt schätzungsweise bei 39-59% [91], was die Notwendigkeit einer Prophylaxe zur Reduktion der Mortalität untermauert. Neben der ERE und Immunmodulation selbst, können Begleiterkrankungen, wie z.B. interstitielle Lungenerkrankungen, das Risiko für PJP erhöhen [87].

Die Diagnose einer PJP basiert neben klinischen Parametern auf typischen radiologischen Infiltraten und wenn möglich auf dem Erregernachweis aus der bronchoalveolären Lavage [92]. Trotz der hohen Letalität und der damit verbundenen Empfehlung einer Prophylaxe mit Cotrimoxazol, stehen nur wenigen Daten zur Verfügung. Diese konzentrieren sich auf den Einsatz von Cotrimoxazol bei PatientInnen mit ANCA (antineutrophile zytoplasmatische

Antikörper)-assoziierten Kleingefäßvaskulitiden unter Therapie mit Cyclophosphamid [92]. Aufgrund dieser Daten wird die Ausdehnung auf andere ERE bei entsprechendem Risikoprofil diskutiert [90,92,93].

Folgende Faktoren scheinen hierbei das Risiko einer PJP besonders zu erhöhen [93]:

- Lymphopenie, Mangel an CD4-positiven T-Zellen
- Einsatz von Cyclophosphamid, Rituximab oder TNF-Hemmern
- Glukokortikosteroide > 60 mg (Prednisolonäquivalent)/Tag

Basierend auf diesen bisherigen Daten wurde seitens der DGRh im Kontext der COVID-19-Pandemie empfohlen, bei ERE-PatientInnen unter Therapie mit Cyclophosphamid oder Glukokortikosteroiden > 10 mg (Prednisolon)/Tag eine PJP-Prophylaxe mit Cotrimoxazol durchzuführen, um das Risiko einer Begleitinfektion zu reduzieren [94].

1.4 Der Einfluss von Immunmodulatoren auf das Infektionsrisiko

Neben der entzündlich-rheumatischen Erkrankung selbst, kann die immunmodulierende Therapie ebenfalls mit einer gewissen Infektneigung assoziiert sein [67]. In Tabelle 2 sind alle Immunmodulatoren/Immunsuppressiva, die in der Rheumatologie in Deutschland bis zum Mai 2022 im Einsatz sind, in Bezug auf das Risiko von Atemwegserkrankungen aufgelistet. Die Tabelle verdeutlich die limitierende Datenlage bezüglich viraler Atemwegserkrankungen bei ERE.

Wirkstoff	**Daten bezüglich Atemwegserkrankungen**
Glukokortikosteroide	• Nachweis eines erhöhten Infektionsrisikos für Virusinfektionen unter dem Einsatz von Glukokortikosteroiden bei ERE, wie z.B. rheumatoide Arthritis oder systemischer Lupus erythematodes, [95–97] • Dosis der Glukokortikosteroide und Therapiedauer ausschlaggebend [27,98–100] • Infektionsrisiko unter 5 mg Prednisolon/Tag für schwere Infektionen steigt bei älteren Patienten um 30%, 46% bzw. 100% über eine Therapiedauer von 3, 6 bzw. 36 Monaten [29]
Konventionelle Basismedikamente	
Hydroxychloroquin	• ursprünglich als Antimalariamedikament eingesetzt • vor allem im Einsatz bei Kollagenosen • bislang keine eindeutigen Hinweise für ein erhöhtes Infektionsrisiko oder Infekt-assoziierter Mortalität [97,101] • mögliche protektive Wirkung bei PatientInnen mit systemischen Lupus erythematodes bezüglich Infekt-assoziierter Mortalität in Diskussion [97,101].

Sulfasalazin	• kaum Daten verfügbar • Einsatz von Sulfasalazin ist möglicherweise mit einem geringeren Risiko für Pneumonien bei PatientInnen mit rheumatoider Arthritis assoziiert [82,102].
Leflunomid	• kaum Daten verfügbar • signifikante Assoziation von Leflunomid mit Infektionen der unterem Atemwege sowie eine dadurch notwendige stationäre Behandlung in einer prospektiven Studie [102] • keine Kongruenz der Ergebnisse zu Leflunomid in anderen Studien, da hier nur geringe Infektassoziation nachweisbar [83,103,104].
Methotrexat	• kein Nachweis eines erhöhten Risikos für Infektionen der unteren Atemwege bei 1522 PatientInnen mit rheumatoider Arthritis; PatientInnen ohne Immunmodulation wiesen im Vergleich dazu ein höheres Risiko für Infektionen der untere Atemwege auf [105] • kein erhöhtes Risiko für Pneumonien bei 16.788 PatientInnen mit rheumatoider Arthritis [82] • Meta-Analyse von Daten aus den Jahren 1980-2017 zeigte ebenfalls kein erhöhtes Infektionsrisiko auf [106]
Immunsuppressiva	
Azathioprin	• kaum Daten verfügbar • 1%-ige Inzidenz einer Pneumonie bei 111 SLE-PatientInnen [107]
Mycophenolat	• Einsatz vor allem bei mittelschwerer Organmanifestation im Rahmen des systemischen Lupus erythematodes, meist in Kombination mit Glukokortikosteroiden [108] • keine spezifischen Untersuchungen zum Auftreten von Virusinfektionen der Atemwege • in Studien mit geringer Patientenzahl lag die Inzidenz von Infektionen der Atemwege zwischen 13-32% [109] • Einflussfaktoren, wie z.B. Krankheitsaktivität und Einsatz von Glukokortikosteroiden als Begleittherapie, nicht ausreichend zu unterscheiden
Ciclosporin	• Keine ausreichenden Daten verfügbar
Cyclophosphamid	• Keine ausreichenden Daten verfügbar • Einsatz der Präparate bei höherer Krankheitsaktivität der ERE, vor allem bei Cyclophosphamid, und in Kombination mit Glukokortikosteroiden
Biologika	
Tumornekrose-Faktor-Alpha-Inhibitoren (TNFi)	• Einsatz bei inflammatorischen Arthritiden und Spondylitis ankylosans • Wirkstoffe: Golimumab, Etanercept, Infliximab, Adalimumab, Certolizumab • kein signifikant häufigeres Auftreten von Atemwegserkrankungen im Vergleich zur Placebo-Gruppe [97,110–123].

	• bisher keine eindeutigen Daten, die auf ein höheres Infektionsrisiko bezüglich Virusinfektionen der Atemwege hindeuten • dies scheint für alle Wirkstoffe der TNFi zu gelten [97]
Interleukin-17-Inhibitoren (IL17i) Interleukin-12/23-Inhibitoren (IL12/23i)	• IL17i werden vor allem bei Psoriasisarthritis und Spondylitis ankylosans eingesetzt • IL17i-Wirkstoffe: Secukinumab, Ixekizumab • kein höheres Risiko für das Auftreten von Infektionen der Atemwege unter IL17i [97,124–128] • IL-12/23i werden vor allem bei der Psoriasisarthritis eingesetzt • IL12/23i-Wirkstoffe: Ustekinumab (IL-12/23i) und Guselkumab (IL-23i) [129–131] • kein höheres Risiko für Virusinfektionen der Atemwege unter IL12/23i oder IL-23i bislang erkennbar [132]
Interleukin-1-Inhibitoren (IL-1i)	• Einsatz bei refraktärer rheumatoider Arthritis, autoinflammatorischen Erkrankungen oder unkontrollierbarer Formen einer Gichtarthropathie • Wirkstoffe: Anakinra und Canakinumab • kein erhöhtes Auftreten von respiratorischen Infektionen Placebo-kontrollierten Studien [133,134] oder im Vergleich zu anderen Immunmodulatoren [135,136] zu beobachten
Interleukin-6-Inhibitoren (IL-6i)	• Therapie der rheumatoiden Arthritis und Großgefäßvaskulitis • In Placebo-kontrollierten Studien kein höheres Auftreten von respiratorischen Infektionen zu beobachten [97,137–140]
Abatacept	• T-Zell-gerichtete Therapie • in Placebo-kontrollierten Studien [141,142] und gepoolten Analysen [143] Auftreten von viralen Infektionen der Atemwege vergleichbar mit Placebogruppe [97]
Rituximab	• bei refraktärer rheumatoider Arthritis und bei ANCA (Anti-Neutrophile cytoplasmatische Antikörper) - assoziierten Vaskulitiden eingesetzt • B-Zell-gerichtete Therapie • Therapie erfolgt in der Regel in Kombination mit Glukokortikosteroiden • bei rheumatoider Arthritis zusätzlich in Kombination mit Methotrexat • geringe allgemeine Infektionsrate in Phase-III-Studie zur Zulassung bei PatientInnen mit rheumatoider Arthritis [144] • insgesamt kaum Daten bezüglich konkreter Erfassung von Virusinfektionen der Atemwege verfügbar • Inzidenz für Infektionen der oberen Atemwege in verschiedenen Studien bei 30-35% [109,145–148], jedoch Vergleichbar mit Placebo-Gruppe [149,150]

	• Limitation der Studien: Beobachtungszeitraum von meist ca. 3 Jahren, somit keine Aussage über Langzeittherapie möglich
Belimumab	• Seit 2011 in Europa zugelassen • zur Behandlung des systemischen Lupus erythematodes • bindet an den löslichen B-Zell aktivierenden Faktor BLys (*B-lymphocyte stimulator*) und reduziert dadurch die Lebensdauer von B-Lymphozyten[151] • Meta-Analyse bei insgesamt 7974 PatientInnen zeigt kein erhöhtes Infektionsrisiko unter Therapie mit Belimumab [151]
Anifrolumab	• Seit Februar 2022 in Europa zugelassen • Zur Behandlung des moderaten bis schweren systemischen Lupus erythematodes[152] • Monoklonaler Antikörper gegen Typ-1-Interferon-Rezeptor[152] • Vermehrtes Auftreten von Herpes-Zoster-Infektionen sowie Infektionen der Atemwege[152] • Einsatz bei höherer Krankheitsaktivität der ERE und in Kombination mit Glukokortikosteroiden[152]
Mepolizumab	• Seit 2015 in Europa zugelassen • Zur Behandlung von schwerem eosinophilem Asthma, der eosinophilen Granulomatosen mit Polyangiitis, chronischer Rhinosinusitis mit Nasenpolypen und des hypereosinophilen Syndroms • Monoklonaler Antikörper gegen Interleukin-5 • Keine eindeutigen Daten hinsichtlich des Infektionsrisikos der Atemwege
Januskinase-Inhibitoren (JAKi)	
	• Seit 2017 in Deutschland zugelassen • zur Behandlung der inflammatorischen Arthritiden und mittlerweile auch zur Behandlung der Spondylitis ankylosans [153] • Wirkstoffe: Tofacitinib, Baricinitinib, Upadacitinib und Filgotinib [153] • führen intrazelluär über den Januskinase-Signalweg zu einer Immunmodulation • Signalweg spielt bei Virusinfektionen eine wichtige Rolle, deswegen vermehrtes Auftreten von Zoster-Infektionen und Zoster-Reaktivierungen unter dieser Therapie [153] • geringgradige Häufung von viralen Atemwegserkrankungen [154–162] • Limitation der Studien: kurzer Beobachtungszeitraum & geringe Fallzahl
Weitere Immunmodulatoren und Antirheumatische Medikamente	
Apremilast	• Einsatz bei Psoriasis, Psoriasisarthritis und M. Behcet • in Placebo-kontrollierter Studie und gepoolter Analyse im Vergleich zur Placebogruppe keine relevanten Unterschiede

	hinsichtlich des Auftretens von Infektionen der oberen Atemwege [52, 117, 118].
Colchicum	• Therapie der Gicht und autoinflammatorische Erkrankungen, wie z.B. Familiäres Mittelmeerfieber • keine eindeutige Datenlage • nach aktuellem Stand nicht mit einem erhöhten Infektionsrisiko assoziiert [163]
Nichtsteroidale Antirheumatika (NSAR)	• bei sehr milden Varianten einer rheumatoiden Arthritis. Erstlinientherapie bei einer Spondylitis ankylosans oder bei Arthrose • in Placebo-kontrollierter Studie bei Personen mit Arthrose sowie in einer Studie zum direkten Vergleich von Celecoxib und Diclofenac keine Hinweise für ein vermehrtes Auftreten von Infektionen der oberen Atemwege [97,164,165]

Tabelle 2: Übersicht der Immunmodulatoren/Immunsuppressiva und deren Rolle bei viralen Atemwegsinfektionen

1.5 Impfungen bei PatientInnen mit rheumatologischen Erkrankungen

Um das Risiko einer Infektion bzw. eines schweren Verlaufs einer Infektion zu reduzieren, spielen Impfungen eine besondere Rolle. Durch die Grunderkrankung und durch den Einsatz verschiedener Immunmodulatoren kann ein höheres Infektionsrisiko vorliegen [166]. Impfungen bieten eine gute Möglichkeit das Risiko von Infektionen und schweren Verläufen zu reduzieren. Die Ständige Impfkommission empfahl im Jahr 2005 bei PatientInnen mit Immunsuppression altersunabhängig die Impfung gegen Pneumokokken, Influenza, Meningokokken und Haemophilus influenzae B [167]. Bislang zeigte sich im europaweiten Vergleich eine unzureichende Umsetzung dieser Empfehlungen [168–170]. Neben der mangelnden Empfehlung seitens der behandelnden ÄrztInnen stellten sich in den Untersuchungen auch die Unsicherheit bezüglich der Effektivität und Verträglichkeit der Impfungen seitens der ÄrztInnen und PatientInnen als Hürden für eine Impfung dar [167–170]. Da bei den Zulassungsstudien der Impfpräparate in der Regel PatientInnen mit ERE ausgeschlossen werden, werden die Aspekte der Effektivität, des Sicherheitsprofils und eine mögliche Zunahme der Krankheitsaktivität der ERE bzw. Auslösen einer ERE bei jeder Impfung diskutiert.

Generell gilt, dass unter Immunmodulation bei ERE keine Lebendimpfungen empfohlen werden [171]. Lebendimpfstoffe enthalten vermehrungsfähige Viren oder Bakterien in abgeschwächter Form. Aufgrund der möglichen Replikation sollte deswegen keine Lebendimpfung unter Immunmodulation erfolgen. In der letzten Dekade nahm die Zahl der Studien, die den Einfluss von Immunmodulatoren auf die Impfantwort untersuchen, stetig zu [172–182]. Mehrheitlich wurde der Einfluss von Immunmodulatoren auf die Pneumokokken- und Influenza-Impfung untersucht. Zudem ist nicht ausreichend untersucht, inwiefern PatientInnen mit ERE von einem Pausieren der Immunmodulation vor oder/und nach der Impfung bezüglich

der Impfantwort profitieren und ob dies mit einer Zunahme der Krankheitsaktivität einhergehen kann. Es ist auch bisher unklar wie lange eine Therapiepause andauern sollte, um das Risiko eine vermehrten Krankheitsaktivität so gering wie möglich zu halten und dennoch eine adäquate Immunantwort zu erzielen. Sicherlich hängt das auch damit zusammen, dass der Krankheitsverlauf bei ERE sehr individuell ist. Die bisherigen Daten deuten darauf hin, dass der Einsatz von Zytokinblockern keinen wesentlichen Einfluss auf die Impfantwort bei Impfungen gegen Pneumokokken und Influenza nimmt, wohingegen die Therapie mit Rituximab eine Impfantwort einschränken kann [174,176,182–185]. Auch unter dem Einsatz von Methotrexat wird eine Reduktion der Impfantwort bei verschiedenen Impfungen beobachtet [178,181,186].

1.5.1 Influenza-Impfung

Die meisten Daten zu Impfungen liegen zu den Influenza-Impfungen vor. Da der Impfstoff saisonal erneuert wird, ähnelt die Auffrischung am ehesten den COVID-19-Impfungen. Zudem handelt es sich bei beiden Erkrankungen um eine Virusinfektion, die primär die Atemwege befällt. Die WHO schätzt, dass die Inzidenz der Influenza 5-10% in der Erwachsenenbevölkerung beträgt [187]. Da das Risiko für eine Infektion bei Personen mit rheumatoider Arthritis höher ist, sollte das Risiko einer schweren Infektion durch den Einsatz der Impfung reduziert werden. Der Einsatz von trivalentem Impfstoff gegen Influenza reduzierte den Anteil an Hospitalisierungen sowie letale Verläufe signifikant bei PatientInnen mit rheumatoider Arthritis und systemischen Lupus erythematodes [188].

Trotz der Erkenntnis, dass PatientInnen mit ERE ein höheres Risiko für eine Influenza-Infektion sowie für schwerere Krankheitsverläufe aufweisen, wurde die Impfempfehlung gegen Influenza bislang nur in einem geringem Maße wahrgenommen. In einer Untersuchung bei 975 PatientInnen mit ERE lag der Anteil der gegen Influenza Geimpften bei der rheumatoiden Arthritis bei ca. 20%, bei der ankylosierenden Spondylitis bei 12% und bei der Psoriasisarthritis bei 15% in Deutschland [189]. Diese Resultate untermauern die bestehende Vermutung einer inadäquaten Impfquote unter PatientInnen mit ERE und die Notwendigkeit einer Intensivierung der Impfempfehlung und Impfaufklärung im Rahmen der ärztlichen Vorstellungen der PatientInnen.

1.5.2 Pneumokokken-Impfung

PatientInnen mit ERE weisen ein erhöhtes Risiko für eine Pneumokokken-Infektion auf [68,80–83]. Zur Reduktion des Risikos für eine schwere Infektion ist der Einsatz des Pneumokokken-Impfstoffes bei Personen mit einem erhöhten Infektionsrisiko empfohlen. Trotz der Impfempfehlung weist nur ein geringer Anteil an ERE-PatientInnen eine Pneumokokken-

Impfung auf [189]. Lediglich 20-30% ERE-PatientInnen wiesen bei einer Untersuchung eine Pneumokokken-Impfung auf [186]. Zudem ist nicht eindeutig geklärt, inwiefern eine immunmodulatorische Therapie der ERE die Impfantwort beeinflussen kann. In einer Meta-Analyse von insgesamt 2077 Personen (1623 Personen unter Immunmodulation, 454 Personen als Kontrollgruppe) konnte unter Immunmodulation eine Reduktion der Impfantwort beobachtet werden [190]. Dieser Effekt war weniger stark ausgeprägt unter Therapie mit TNF-Hemmern [190].

Aus diesem Grund wird empfohlen, wenn möglich, mindestens 2 Wochen vor Therapiebeginn mit einer Immunmodulation die Pneumokokken-Impfung durchzuführen [172].

Für eine bessere Immunantwort wird entsprechend den Empfehlungen der Ständigen Impfkommission eine sequentielle Impfung mit dem 13-valenten Konjugat-Impfstoff (PCV13) gefolgt von dem 23-valenten Polysaccharid-Impfstoff (PPSV23) nach 6–12 Monaten empfohlen [172]. PPSV23 kann frühestens 2 Monate nach PCV13 geimpft werden. Ein Abstand von 6-12 Monaten ist jedoch aufgrund des Booster-Effekts mit einer besseren Impfantwort assoziiert [172].

1.5.3 COVID-19-Impfungen

Ende des Jahres 2020 bot die Aussicht einer Impfung gegen COVID-19 während des sehr dynamischen Pandemiegeschehens große Hoffnung. Neben der Bewältigung eines neuartigen Virus wurden auch neuartige Impfstoffe in Aussicht gestellt, deren Wirkweise über die mRNA (*messenger ribonucleic acid*) sowohl für Anerkennung als auch für Kritik sorgten. Auch die mögliche Notwendigkeit einer Auffrischimpfung/Boosterung wurde vor allem bei ERE-PatientInnen ohne adäquate Impfantwort diskutiert und konnte zunächst nicht beantwortet werden. Insgesamt galt, dass der Impfstatus im Allgemeinen zur Reduktion einer Co-Infektion so aktuell wie möglich gehalten werden sollte, was im klinischen Alltag zu einem Anstieg der Impfnachfrage gegen Pneumokokken und Influenza führte.

Seit Beginn der Impfkampagne gegen COVID-19 hat die Anzahl der Impfstoffe zugenommen, so dass bis zum April 2022 fünf verschiedene Impfstoffe in Deutschland zur Verfügung standen (s. Tabelle 3). Keiner der zugelassenen Impfstoffe gegen COVID-19 ist ein Lebendimpfstoff und somit auch bei PatientInnen mit ERE und unter Immunmodulation einsetzbar. Dennoch blieben die Fragen bezüglich der Effektivität, des Sicherheitsprofils und einer möglichen Zunahme der Krankheitsaktivität nach COVID-19-Impfung zunächst offen.

In der EU zugelassene Impfstoffe gegen COVID-19 (Stand 18.04.2022)			
Firma	**Name**	**Impfstofftyp**	**EU-Zulassung**
BioNTech/Pfizer	Comirnaty® (BNT162b2)	mRNA	21. Dezember 2020
Moderna	Spikevax® (mRNA-1273)	mRNA	06. Januar 2021
AstraZeneca/Oxford University	Vaxzevria® (AZD1222)	Vektorimpfstoff	29. Januar 2021
Janssen-Cilag International NV	COVID-19 Vaccine Janssen (Ad26.COV2.S)	Vektorimpfstoff	11. März 2021
Novavax CZ a.s.	Nuvaxovid® (NVX-CoV2372)	Protein-basierter Impfstoff	20. Dezember 2021

Tabelle 3: Übersicht COVID-19-Impfstoffe [191]

2. Fragestellung und Zielsetzung der Arbeit

Trotz der saisonalen Influenza und zurückliegenden Herausforderungen mit Coronaviren, wie z.B. MERS oder SARS, gab es weltweit nur begrenzte evidenzbasierte Daten zum Umgang von Virusinfektionen bei ERE-PatientInnen und einem möglichen Einfluss der Immunmodulation. Die wenigen wissenschaftlichen Daten, die zur Verfügung standen, basierten oftmals auf einer geringen Patientenzahl und einer kurzen Beobachtungsdauer der ERE-PatientInnen im Rahmen der Zulassungsstudien der Immunmodulatoren. Zudem gelten bei klinischen Studien entsprechende Ein- und Ausschlusskriterien, so dass in der Regel PatientInnen im höheren Alter, mit relevanten Komorbiditäten oder komplikativen Verläufen der ERE nicht ausreichend erfasst werden. Diese PatientInnen weisen jedoch per se ein höheres Risiko für Infektionen und damit verbunden schwerere Verläufe von Infektionen auf.

Aus diesem Grund beschäftigen sich die wissenschaftlichen Studien, die dieser vorliegende Habilitationsschrift zugrundeliegend, mit folgenden Themen:

1) Einfluss der COVID-19-Pandemie auf ERE-PatientInnen
2) Darstellung des Verlaufs einer Infektion durch SARS-CoV-2 bei ERE-PatientInnen
3) Einfluss der Immunmodulation zur Behandlung der ERE im Kontext einer Infektion durch SARS-CoV-2
4) Handlungsempfehlungen zur bestmöglichen Betreuung von ERE-PatientInnen im Kontext der Pandemie
5) Veränderungen des Infektionsgeschehens im Laufe der Pandemie unter Einsatz der Impfungen bei ERE

Hierbei handelte es sich, analog des Verlaufs der Pandemie um einen dynamischen Prozess, welchen es wissenschaftlich zu analysieren galt, um zukünftig eine bestmögliche Betreuung von PatientInnen sicherzustellen.

Ziel der vorliegenden Arbeit war es daher, anhand des Aufbaus des COVID19-Rheuma.de-Registers und den damit verbundenen Erkenntnissen zum Verlauf dieser neuen Entität die Bedeutung eines Infektionsregisters bei ERE als Instrument der internationalen Pandemiebewältigung darzulegen, dessen Limitationen aufzuzeigen aber auch neue Strategien zu entwickeln. Das Register und auch die hieraus resultierenden weiteren Projekte entsprechen den Anforderungen des Datenschutzes gemäß DSGVO. Die Daten der PatientInnen werden von Rechenzentren in Deutschland aus verwaltet.

Für die hier vorgestellten Arbeiten wurden verschiedene Projekte, die auf dem COVID19-Rheuma.de-Registers basieren, umgesetzt und ausgewertet. Ihnen gemeinsam ist die Wissensgenerierung zur Bewältigung der COVID-19-Pandemie in Bezug auf PatientInnen mit ERE, national wie international. Dieses Register bildet zum Einreichungsdatum dieser Arbeit auch die bisher größte europäische Kohorte von ERE-PatientInnen mit COVID-19 ab.

3. Ergebnisse

3.1 Der Einfluss der SARS-CoV-2-Pandemie auf die Behandlung von ERE

Originalarbeit 1:

Schmeiser T, Broll M, Dormann A, Fräbel C, Hermann W, Hudowenz O, Keil F, Müller-Ladner U, Özden F, Pfeiffer U, Saech J, Schwarting A, Stapfer G, Steinchen N, Storck-Müller K, Strunk J, Thiele A, Triantafyllias K, Wassenberg S, Wilden E, **Hasseli R**.

Einstellung von Patienten mit entzündlich-rheumatischen Erkrankungen zur immunsuppressiven Therapie im Rahmen der COVID-19 Pandemie – eine Situationsanalyse.

Z Rheumatol. 2020 May;79(4):379-384. doi: 10.1007/s00393-020-00800-8

Originalarbeit 2:

Hasseli R, Müller-Ladner U, Keil F, Broll M, Dormann A, Fräbel C, Hermann W, Heinmüller CJ, Hoyer BF, Löffler F, Özden F, Pfeiffer U, Saech J, Schneidereit T, Schlesinger A, Schwarting A, Specker C, Stapfer G, Steinmüller M, Storck-Müller K, Strunk J, Thiele A, Triantafyllias K, Vagedes D, Wassenberg S, Wilden E, Zeglam S, Schmeiser T.

The influence of the SARS-CoV-2 lockdown on patients with inflammatory rheumatic diseases on their adherence to immunomodulatory medication - a cross sectional study over 3 months in Germany.

Rheumatology (Oxford). 2021 Oct 9;60(SI):SI51-SI58. doi: 10.1093/rheumatology/keab230

Zusammenfassung

Die adäquate Therapie der ERE stellt den bestmöglichen Schutz vor Infektionen und damit verbundenen schweren Verläufen dar [70]. Mithilfe einer steroidfreien, immunmodulierenden Therapie sollte eine klinische Remission der Grunderkrankung erzielt werden, um unnötig hohe Steroiddosen zu verhindern und insgesamt das Infektrisiko zu minimieren. Dies setzt, neben einer adäquaten rheumatologischen Betreuung, auch eine entsprechende Compliance der PatientInnen voraus. Die Covid-19-Pandemie stellte daher eine Herausforderung für beide Aspekte dar. Vor allem zu Beginn der Pandemie fehlte die Erfahrung zur Handhabung der immunmodulatorischen Therapie bei einer Infektion durch SARS-CoV-2. Aus diesem Grund

war es wichtig zu analysieren, wie ERE-PatientInnen die aktuelle Situation in Bezug auf ihre antirheumatische (immunsuppressive oder -modulierende) Therapie wahrnehmen.

In einer initialen Befragung mithilfe eines standardisierten Fragebogens wurden ERE-PatientInnen an bundesweit fünf rheumatologischen Kliniken und sechs rheumatologischen Schwerpunktpraxen befragt (Originalarbeit *1*). Die Befragung erfolgte unmittelbar nach Beginn der hochaktiven Phase der COVID-19-Pandemie. In dem Zeitraum vom 16.03.2020–03.04.2020 konnten 656 PatientInnen in die Befragung eingeschlossen werden. Die Befragung erfolgte anonym ohne Angabe des Geschlechts. Im Fragebogen wurde die entzündlich-rheumatische Erkrankung, das Alter in Altersintervallen, die aktuelle antirheumatische Medikation und die Meinung bezüglich der immunmodulierenden Therapie erfragt. Mehr als die Hälfte der Befragten war über 50 Jahre alt (51%) und litt an einer rheumatoiden Arthritis (56%). Eine Therapie mit Methotrexat zum Zeitpunkt der Befragung wurde von 36% der Befragten angegeben. Über 90% der Befragten gaben an, der ärztlichen Empfehlung zur Fortführung der immunmodulatorischen Therapie zu folgen. Lediglich ein geringer Prozentsatz wollte die Therapie selbstständig beenden. Diese Einstellung der PatientInnen war unabhängig von der jeweiligen immunmodulatorischen Therapie und ERE. Dieses Ergebnis ist aus rheumatologischer Sicht erfreulich, da ein eigenständiges Absetzen der Immunmodulation mit Zunahme der Krankheitsaktivität einhergehen kann. Das Infektionsrisiko wird zum einen durch allgemeine Faktoren, wie das Alter des/der PatientIn, vorhandene Komorbiditäten, zum anderen krankheitsbezogen durch die Aktivität der Grunderkrankung selbst und durch die laufende – insbesondere immunsuppressive – Therapie bestimmt. Dementsprechend zählt zu wichtigsten risikoverringernden Maßnahmen eine optimale Kontrolle der ERE [92].

Da es sich jedoch bei der initialen Befragung um eine kurze Befragungsperiode handelte und nicht ausreichend die Therapieadhärenz während des weiteren Verlaufs der COVID-19-Pandemie widerspiegelt, wurde die Studie über insgesamt 3 Monate fortgesetzt und um weitere bundesweite Standorte erweitert (Originalarbeit *2*). Insgesamt nahmen acht rheumatologische Schwerpunktpraxen und neun Kliniken an der Befragung teil. Im Zeitraum von 16. März bis 15. Juni 2020 wurde 4252 ERE-PatientInnen befragt. Erneut litten mehr als die Hälfte der Befragten an einer rheumatoiden Arthritis (54%). Die Mehrheit der PatientInnen gab an ihre Therapie fortzuführen (84%). Lediglich 3% der Befragten gab an, selbstständig die Immunmodulation aufgrund der COVID-19-Pandemie beendet zu haben. Die Entscheidung für die Fortführung/Absetzen der Therapie war unabhängig von der ERE und Art der Immunmodulation. Jüngere PatientInnen gaben häufiger an, ihre Therapie zu beenden, verglichen mit Personen über 60 Jahre. In einer Google Trends-Analyse wurde zudem

untersucht, welche Suchbegriffe in Bezug auf COVID-19 und rheumatische Erkrankungen vermehrt verwendet wurden. Dabei standen ausreichende Daten zu den Begriffen „Corona Kortison“, „Corona Humira“ und „Corona Rheuma“ zur Verfügung. Die Häufigkeit der genannten Suchbegriffe wurde mit den Antworten der PatientInnen im Rahmen der Befragung korreliert. Hierbei zeigt sich, dass mit zunehmender Suchhäufigkeit auch der Anteil der Therapieabbrüche in der Befragung zunahm. Dies könnte die Verunsicherung der PatientInnen, darstellen, welche sich im Rahmen der Internetrecherche ausdrückt, da zu diesem Zeitpunkt keine qualitativ ausreichenden Informationsquellen vorlagen.

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Hot Topics

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Einstellung von Patienten mit entzündlich-rheumatischen Erkrankungen zur immunsuppressiven Therapie im Rahmen der COVID-19 Pandemie – eine Situationsanalyse

Seit 11.03.2020 spricht die WHO von einer Coronavirus Pandemie. Verursacht wird die Coronavirus Krankheit (COVID-19) durch das SARS-CoV-2 Virus. Die Erkrankung manifestiert sich als Infektion der Atemwege mit den Leitsymptomen Fieber und Husten. Bei 81 % Patienten ist der Verlauf mild, 14 % erkranken schwer und 5 % der Patienten kritisch [1]. Das erste Auftreten wurde im Dezember 2019 in der Millionenstadt Wuhan in der Provinz Hubei (China) dokumentiert. Am 07.04.2020 meldete die Johns-Hopkins-Universität bereits 1.348.628 registrierte, die Welt umspannende Infektionsfälle. Die Letalität lag zu diesem Zeitpunkt der Pandemie bei 5,6 % (n = 74.834 an Covid-19 Verstorbene). Zu diesem Zeitpunkt war bereits klar, dass das Vorhandensein und die Zahl von Komorbiditäten (wie Diabetes mellitus, arterielle Hypertonie und koronare

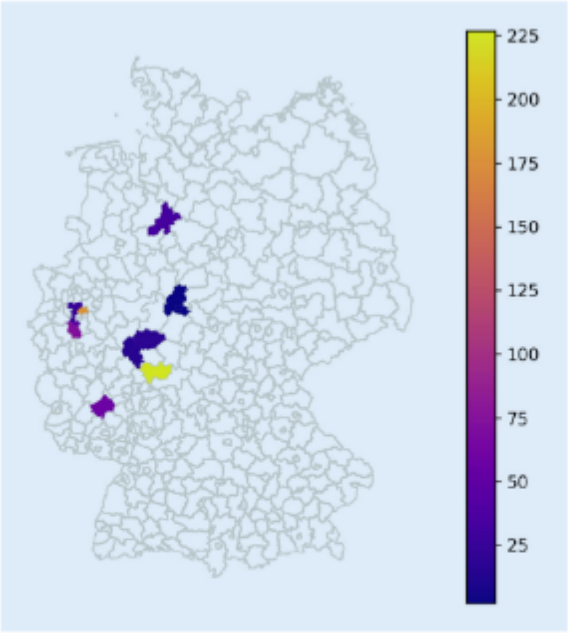

Abb. 1 ◀ Verteilung der Studienzentren und deren Aktivität (regionenbezogen)

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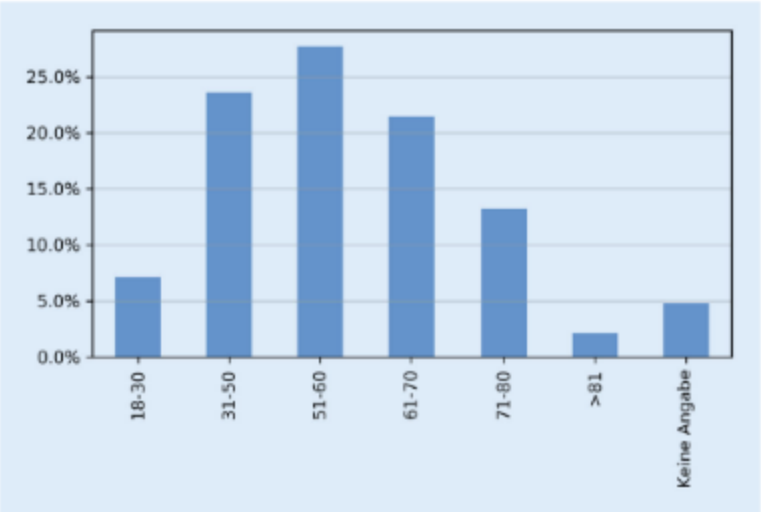

Abb. 2 ▲ Prozentuale Altersverteilung der bis zum 07.04.2020 befragten Patienten

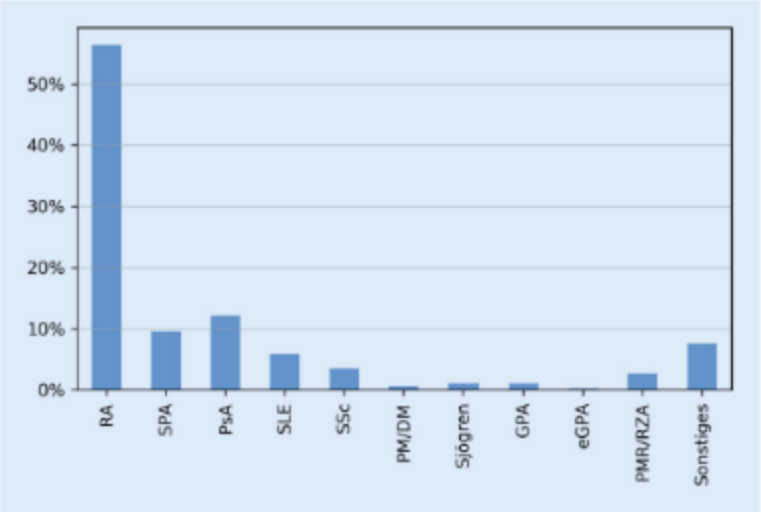

Abb. 3 ▲ Prozentuale Verteilung der entzündlich-rheumatischen Erkrankungen der bis zum 07.04.2020 befragten Patienten

Herzerkrankungen) mitentscheidend ist für das Outcome der Patienten [2].

Trotz vieler klinischer Parallelen zu einer viralen Infektion der oberen und unteren Atemwege mit Influenzaviren, SARS oder MERS, alle mit einer vergleichbaren initialen Klinik (Husten, Fieber, Cephalgien und Myalgien), dem Übertragungsweg (Tröpfcheninfektion) und der sehr variablen Symptomatik von symptomlos bis zu kurzen letalen Verläufen, gab es bis zu dieser Pandemie keine Handlungsempfehlungen basierend auf evidenzbasierten Daten für Patienten mit entzündlich-rheumatischen Erkrankungen. Dasselbe galt für die Bedeutung oder den Einfluss einer dauerhaften immunsuppressiven oder immunmodulierenden Therapie. Wöchentlich zunehmende Daten aus China und Italien zeigen aber, dass schwere Verlaufsformen und Komplikationen in jedem Alter auftreten können, und bei Patienten ab dem 60. Lebensjahr und solchen mit chronischen Grunderkrankungen deutlich häufiger.

In der letzten Influenza-Saison (40. Meldewoche (MW) 2018 bis 20. MW 2019) wurden laut dem Robert-Koch-Institut (RKI) 182.000 labordiagnostisch bestätige Fälle dokumentiert. Davon waren 98,5 % durch Influenza A verursacht. Lediglich bei 0,7 % der Patienten konnte Influenza Typ B nachgewiesen werden. Dies legt laut RKI die Vermutung nahe, dass eine höhere Immunität gegen Influenza Typ B herrscht und könnte dadurch begründet sein, dass die letzte Grippe-Saison vordergründig durch Influenza Typ B verursacht wurde. 33 % der Fälle wurden in der Altersgruppe 35–59 dokumentiert. 25 % der Betroffenen waren über 59 Jahre. Die Altersgruppe 5–14 Jahre war dagegen am wenigsten betroffen. Unter den diagnostisch bestätigten Fällen befanden sich 40.000 hospitalisierte Fälle. Diese teilten sich auf in 54 % Betroffene über 60 Jahre, 19 % in der Altersgruppe 35–59 Jahre und 6 % in der Altersgruppe 5–14 Jahre auf. 64 % der hospitalisierten Fälle wiesen ein Alter über 79 Jahre auf. Schwere Komplikationen, wie z. B. eine schwere Pneumonie oder Lungenversagen (ARDS), waren in allen Altersgruppen nachweisbar. Bei der älteren Patientengruppe (>79 Jahre) war ein höherer Anteil an letalen Verläufen als Fälle mit notwendiger Beatmung zu verzeichnen. Der Altersmedian der gemeldeten Fälle lag bei 40 Jahren, bei den hospitalisierten Fälle bei 63 Jahren und bei den letal verlaufenden Fällen bei 78 Jahren. Insgesamt wurden 954 Influenza-bedingte Todesfälle gemeldet. 52 % der Verstorbenen waren männlich, 86 % über 59 Jahre und 12 % in der Altersgruppe 35–59 Jahre. Da die Meldung von Influenza an den labordiagnostischen Nachweis gekoppelt ist, die meisten Erkrankungen im Verlauf einer Grippewelle aber rein klinisch diagnostiziert werden, liegt wahrscheinlich eine erhebliche Untererfassung von Influenza-Erkrankungen vor [3].

Diverse Literaturquellen weisen auf eine erhöhte Infektneigung von Patienten mit rheumatologischen Erkrankungen oder immunsuppressiven Therapien hin [4, 5]. Um das Infektionsrisiko für diese Patienten abschätzen zu können, sind individuelle Betrachtungen von Grunderkrankung und immunsuppres-

siver Therapie notwendig. Eine relevante Rolle hierbei spielt (vor allem in Langzeitdosierung) der Einsatz von Corticosteroiden. So konnte in einer Analyse des RABBIT Registers gezeigt werden, dass das Risiko für Infektionen mit der Dosis deutlich ansteigt und z. B. eine Steroiddosis zwischen 7,5 und 14 mg ein höheres Infektionsrisiko birgt als unter TNF-α-Hemmern [6]. Ein weiterer wichtiger Aspekt für das Infektionsrisiko ist die Krankheitsaktivität. Das Infektionsrisiko sinkt bei Remission [7]. Weitere Faktoren, die die Infektwahrscheinlichkeit beeinflussen, sind das Alter (Immunoseneszenz) und die Komorbiditäten der Patienten [4, 8].

Zusammenfassend ergibt sich hieraus, dass in erster Linie mithilfe der antirheumatischen Therapie eine klinische Remission der Grunderkrankung erzielt werden sollte, um unnötig hohe Steroiddosen zu verhindern und insgesamt das Infektrisiko zu minimieren. Dies setzt, neben einer adäquaten rheumatologischen Betreuung, auch eine entsprechende Compliance der Patienten voraus. Diese noch nie dagewesene Pandemie stellt daher eine Herausforderung für beide Aspekte dar. Bislang fehlt die Erfahrung zur Handhabung der antirheumatischen Therapie bei einer COVID-19-Infektion. Aus diesem Grund war es für die Initiatoren dieser Studie in erster Linie wichtig zu erfahren, wie unsere Patienten die aktuelle Situation in Bezug auf ihre antirheumatische (immunsuppressive oder -modulierende) Therapie wahrnehmen.

Nach unmittelbarer Erteilung des Ethikvotums durch die Justus-Liebig Universität Giessen als federführende Institution wurde mithilfe eines Fragebogens Patienten mit einer entzündlich-rheumatischen Erkrankung bezüglich ihrer Einschätzung zu ihrer immunmodulierenden Therapie befragt. Bis zum Zeitpunkt der Einreichung dieser Publikation nahmen an dieser Untersuchung 5 rheumatologische Kliniken aus 3 Bundesländern und 6 rheumatologische Schwerpunktpraxen, ebenfalls aus 3 Bundesländern teil (**Abb. 1**).

In dem Zeitraum 16.03.2020–03.04.2020 konnten 656 Patienten in die Befragung eingeschlossen werden. Die Befragung erfolgte komplett anonym

Zusammenfassung · Abstract

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T. Schmeiser · M. Broll · A. Dormann · C. Fräbel · W. Hermann · O. Hudowenz · F. Keil · U. Müller-Ladner · F. Özden · U. Pfeiffer · J. Saech · A. Schwarting · G. Stapfer · N. Steinchen · K. Storck-Müller · J. Strunk · A. Thiele · K. Triantafyllias · S. Wassenberg · E. Wilden · R. Hasseli

Einstellung von Patienten mit entzündlich-rheumatischen Erkrankungen zur immunsuppressiven Therapie im Rahmen der COVID-19 Pandemie – eine Situationsanalyse

Zusammenfassung

Die aktuelle Pandemie mit COVID-19 stellt die behandelnden Rheumatologen vor eine bisher nicht dagewesene Herausforderung. Auf der einen Seite können antirheumatische Medikamente das Infektrisiko erhöhen und den Verlauf einer Infektion beeinflussen. Auf der anderen Seite erhöht eine unzureichend kompensierte entzündlich-rheumatische Erkrankung ebenfalls das Infektionsrisiko. Gemäß der Empfehlung der Deutschen Gesellschaft für Rheumatologie (www.dgrh.de) empfehlen wir unseren Patienten trotz Pandemie eine Fortführung der antirheumatischen Therapie zum Erhalt der Remission. Im Rahmen dieser Studie wurden Patienten mit einer entzündlich-rheumatischen Erkrankung bezüglich ihrer Meinung zu ihrer immunmodulierenden Therapie unmittelbar nach Beginn der hochaktiven Phase der Pandemie befragt. An der Datenerhebung waren 5 Kliniken und 6 niedergelassene rheumatologische Versorger beteiligt. Hierbei zeigte sich, dass über 90 % der Befragten der ärztlichen Empfehlung zur Fortführung der antirheumatischen Therapie folgten. Lediglich ein geringer Prozentsatz wollte die Therapie eigenmächtig beenden. Diese Einstellung der Patienten war unabhängig von der jeweiligen antirheumatischen Therapie. Dieses Ergebnis ist aus rheumatologischer Sicht erfreulich, spiegelt die vertrauensvolle und kompetente Betreuung der rheumatologischen Patienten wider, und zeigt, dass trotz solcher Herausforderungen unsere Patienten unseren Empfehlungen folgen.

Schlüsselwörter

COVID-19 · Antirheumatische Therapie · Rheumatische Grunderkrankungen · Patientenbefragung

A cross sectional study on patients with inflammatory rheumatic diseases in terms of their compliance to their immunsuppressive medication during COVID-19 pandemic

Abstract

The current COVID-19 pandemic inherits an unprecedented challenge for the treating rheumatologists. On the one hand, antirheumatic drugs can increase the risk of infection and potentially deteriorate the course of an infection. On the other hand, an active inflammatory rheumatic disease can also increase the risk for an infection. In the recommendations of the German Society for Rheumatology (www.dgrh.de), it is recommended that our patients continue the antirheumatic therapy to maintain remission or low state of activity despite the pandemic. In this study, patients with inflammatory rheumatic disease were asked in the first weeks of the pandemic on their opinion of their immunomodulating therapy. The result shows that over 90% of the patients followed the recommendation of the rheumatologist to continue the antirheumatic therapy, and only a small percentage of the patients terminated the therapy on their own. This result was independent of the individual antirheumatic therapy. Taken together, the results of this study illustrate not only the trustful patient-physician partnership in a threatening situation but also the high impact of state-of-the art recommendations by the respective scientific society.

Keywords

COVID-19 · Antirheumatic therapy · Rheumatic diesease · Patient questionnaire

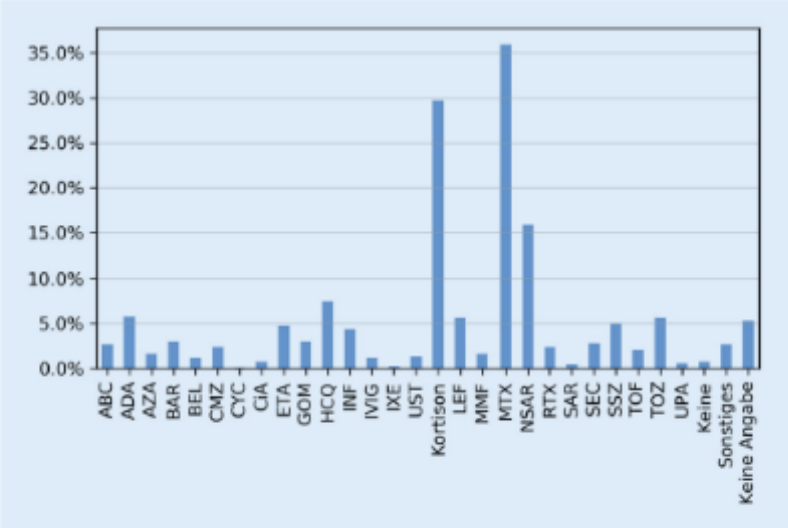

Abb. 4 ▲ Prozentuale Verteilung von DMARDs der in der Studie untersuchten Patienten

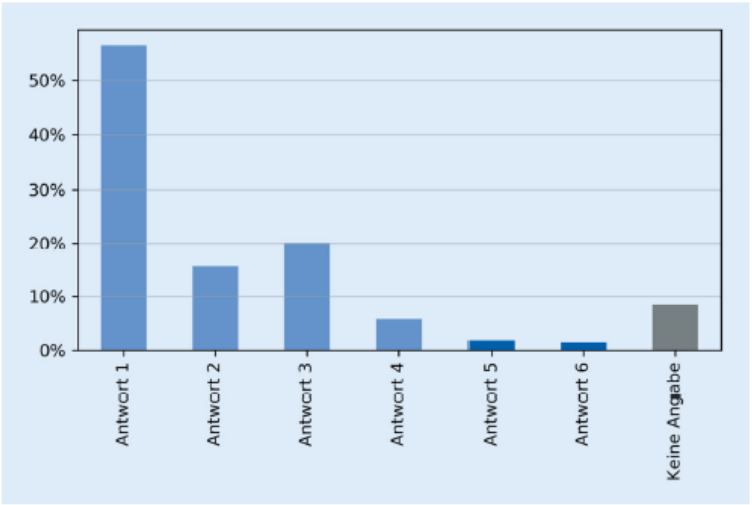

Abb. 5 ▲ Prozentuale Verteilung der Antworten der in der Studie untersuchten Patienten

ohne Angabe des Geschlechts. Im Fragebogen wurde die entzündlich-rheumatische Erkrankung, das Alter in Altersintervallen, die aktuelle antirheumatische Medikation und die Meinung bezüglich der immunmodulierenden Therapie erfragt. Die Altersverteilung gestaltete sich bislang wie folgt: 28% im Alter von 51–60 Jahren; 24% im Alter von 31–50 Jahren; 21% im Alter von 61–70 Jahren; 7% im Alter von 18–30 Jahren; 2% im Alter von über 81 Jahre (◘ **Abb. 2**).

56% der Patienten wiesen eine rheumatoide Arthritis auf, gefolgt von einer Psoriasisarthritis (12%) und Spondylitis ankylosans (10%). Die restlichen 22% der Erkrankungen verteilten sich auf die in (◘ **Abb. 3**) dargestellten Entitäten. Unter sonstige Erkrankungen (8%) wurden u. a. (noch) nicht klassifizierbare rheumatologische Erkrankungen, Sarkoidose, Kristallarthropathien zusammengefasst.

36% der Befragten befanden sich unter einer Therapie mit Methotrexat (MTX). Bei 30% der Patienten lag eine Mono- oder Kombinationstherapie mit Corticosteroiden vor. NSAR (nicht-steroidale Antirheumatika) wurden als Mono- oder Kombinationstherapie bei 16% verwendet. 8% der Patienten standen unter Therapie mit Hydroxychloroquin (HCQ). Tocilizumab und Adalimumab (ADA) wurden in 6% und Etanercept in 5% der Fälle angewendet. Die übrigen Therapieoptionen wurden bei unter 5% der Patienten eingesetzt (◘ **Abb. 4**). Bezüglich der persönlichen Meinung zur antirheumatischen Therapie standen 7 Antwortmöglichkeiten zur Auswahl:

1. Therapiefortführung ohne Bedenken
2. Fortführung der antirheumatischen Therapie, da das Risiko einer Zunahme der Entzündungsaktivität höher ist als die einer COVID-Infektion
3. Fortführung der Medikation, da keine Alternative besteht
4. Fortführung gemäß der ärztlichen Empfehlung, persönlich würde die Medikation lieber abgesetzt werden
5. Eigenmächtiges Absetzen
6. Absetzen gemäß ärztlicher Empfehlung
7. Bislang keine Meinung bezüglich der antirheumatischen Therapie und einer Corona-Infektion

Die Verteilung der Antworten gestaltete sich wie folgt: 57% Antwort 1, 16% Antwort 2, 20% Antwort 3, 6% Antwort 4. Die Antworten 5–7 lagen bei unter 2% (◘ **Abb. 5**). Insgesamt würden somit 98% der Patienten die Therapie ohne oder sogar trotz Bedenken fortführen. Lediglich 2% der Befragten würden die Medikation eigenmächtig absetzen. Interessanterweise zeigt sich eine örtliche Häufung der Patienten, die eine Therapie absetzen würden (◘ **Abb. 6**). Die Standorte Porz am Rhein, Köln-Ehrenfeld, Bad Kreuznach, Bad Nauheim und Wuppertal waren davon häufiger betroffen. Möglicherweise hängt dies mit der Prävalenz der COVID-19-Infektionen in den Regionen zusammen, oder aber auch, dass Schwerpunktpraxen noch mehr Hausarztfunktionen mit engerem Kontakt zu den Patienten übernehmen als überregionale rheumatologische Referenzkliniken. Die Auswahl der Antworten unterschied sich interessanterweise nicht in den jeweiligen Krankheitsentitäten (◘ **Abb. 7**).

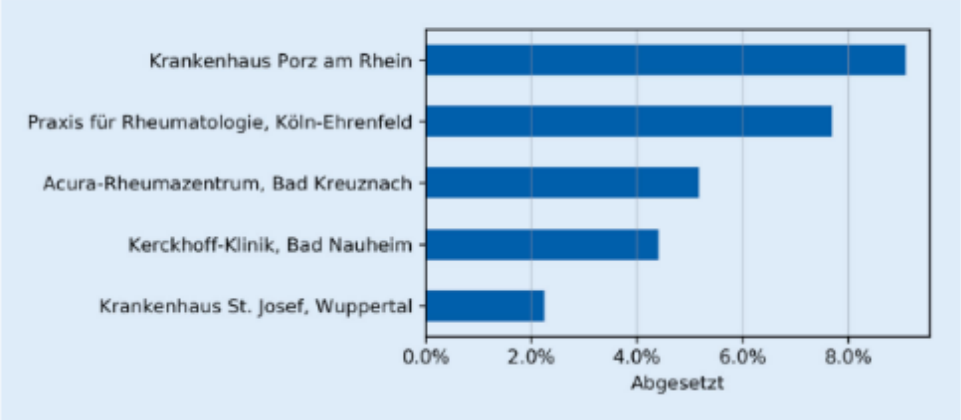

Abb. 6 ◂ Prozentuale Verteilung der Antwort „eigenmächtiges Absetzen" nach Standorten

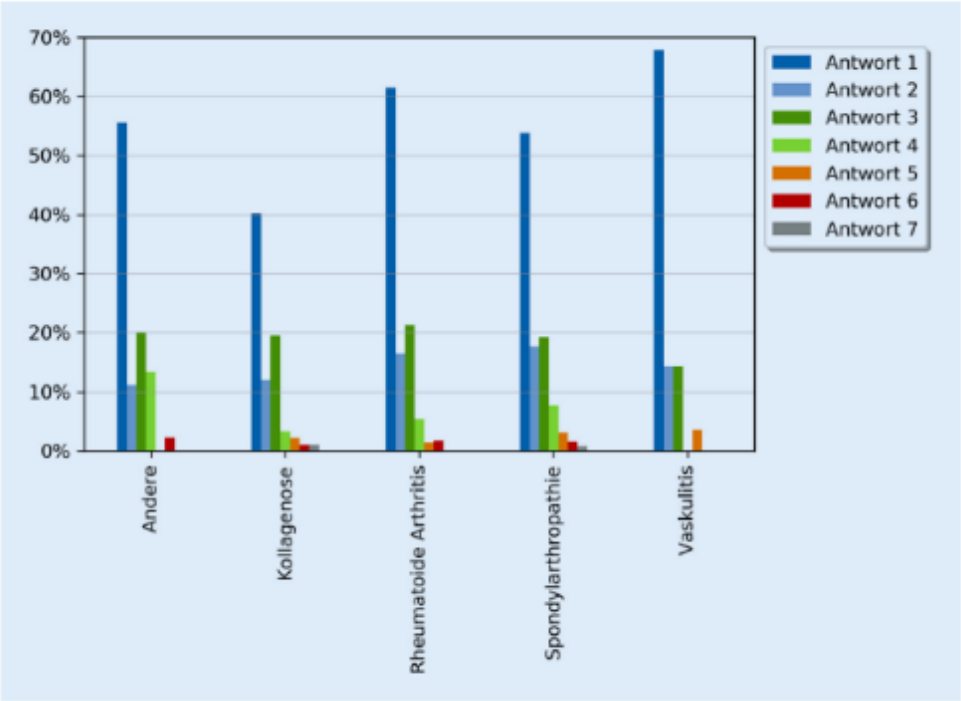

Abb. 7 ◂ Prozentuale Verteilung der Antworten nach Krankheitsgruppen

Zusammenfassend ist festzuhalten, dass der überwiegende Anteil der Befragten unabhängig von der Erkrankung oder Medikation keine Bedenken bezüglich der Fortführung der Therapie auch in Zeiten der COVID-19 Pandemie aufwiesen. Die individuelle Patientenentscheidung zur Fortführung der DMARD Therapie deckt sich zum aktuellen Zeitpunkt mit den Expertenempfehlungen der DGRh, die durch Rezidive bzw. einen Schub der Grunderkrankung ein höheres Infektrisiko postulieren und die u. a. in einer solchen Situation bei dann möglicher Intensivierung der antirheumatischen Therapie (z. B. durch Steroidstoß) eine größere Gefährdung der Patienten implizieren. Die Auswertung der Umfrage zeigt jedoch auch, dass die Mehrheit der Patienten den ärztlichen Empfehlungen folgt. Dieses spiegelt in diesen außergewöhnlichen Zeiten die vertrauensvolle Beziehung zwischen Patienten und Rheumatologen wider. Prospektiv sollen auch in der nun kommenden Phase der Pandemie weitere Daten gesammelt werden, um die Entwicklung der Einstellung der Patienten erfassen und für zukünftige Szenarien beurteilen zu können.

Fazit für die Praxis

- **Über 90 % der befragten Patienten folgen der rheumatologischen Empfehlung, ihre antirheumatische Medikation trotz der COVID-19-Pandemie fortzuführen.**
- **Lediglich 4 % der Patienten würden ihre Therapie lieber absetzen, folgen aber der ärztlichen Empfehlung.**

Abkürzungen

ABC	Abatacept
ADA	Adalimumab
AZA	Azathioprin
BAR	Baricitinib
BEL	Belimumab
CiA	Ciclosporin A
CMZ	Certolizumab
CYC	Cyclophosphamid
eGPA	Eosinophile GPA
ETA	Etanercept
GOM	Golimumab
GPA	Granulomatose mit Polyangiitis
HCQ	Hydroxychloroquin
INF	Infliximab
IVIG	Immunglobuline
IXE	Ixekizumab
LEF	Leflunomid
MMF	Mycophenolat-Mofetil
MTX	Methotrexat
NSAR	Nicht-steroidale Antirheumatika
PM/DM	Polymyositis/Dermatomyositis
PMR/RZA	Polymyalgia rheumatica/Riesenzellarteriitis
PSA	Psoriasisarthritis
RA	Rheumatoide Arthritis
RTX	Rituximab
SAR	Sarilumab
SEC	Secukinumab
SLE	Systemischer Lupus erythematodes
SPA	Spondylitis ankylosans
SSc	Systemische Sklerose
SSZ	Sulfasalazin
TOF	Tofacitinib
TOZ	Tocilizumab
UPA	Upadacitinib
UST	Ustekinumab

- **1 % der Befragten setzt die Medikation eigenmächtig ab**
- **Die Resultate spiegeln eine vertrauensvolle Arzt-Patienten Beziehung auch in Zeiten einer bedrohlichen Pandemie wider**

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Einhaltung ethischer Richtlinien

Interessenkonflikt. T. Schmelser, M. Broll, A. Dormann, C. Fräbel, W. Hermann, O. Hudowenz, F. Keil, U. Müller-Ladner, F. Özden, U. Pfeiffer, J. Saech, A. Schwarting, G. Stapfer, N. Steinchen, K. Storck-Müller, J. Strunk, A. Thiele, K. Triantafyllias, S. Wassenberg, E. Wilden und R. Hasseli geben an, dass kein Interessenkonflikt besteht.

Für diesen Beitrag wurden von den Autoren keine Studien an Menschen oder Tieren durchgeführt. Für die aufgeführte Umfrage gelten die jeweils dort angegeben ethischen Richtlinien.

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Original article

The influence of the SARS-CoV-2 lockdown on patients with inflammatory rheumatic diseases on their adherence to immunomodulatory medication: a cross sectional study over 3 months in Germany

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Abstract

Objectives. To evaluate the influence of the SARS-CoV-2 pandemic on the adherence of patients with inflammatory rheumatic diseases (IRD) to their immunomodulatory medication during the three-month lockdown in Germany.
Methods. From 16th March until 15th June 2020, IRD patients from private practices and rheumatology departments were asked to answer a questionnaire addressing their behaviour with respect to their immunomodulating therapy. Eight private practices and nine rheumatology departments that included rheumatology primary care centres and university hospitals participated. A total of 4252 questionnaires were collected and evaluated.
Results. The majority of patients (54%) were diagnosed with RA, followed by psoriatic arthritis (14%), ankylosing spondylitis (10%), connective tissue diseases (12%) and vasculitides (6%). Most of the patients (84%) reported to continue their immunomodulatory therapy. Termination of therapy was reported by only 3% of the patients. The results were independent from the type of IRD, the respective immunomodulatory therapy and by whom the patients were treated (private practices *vs* rheumatology departments). Younger patients (<60 years) reported just as often as older patients to discontinue their therapy.
Conclusion. The data show that most of the patients continued their therapy in spite of the pandemic. A significant change in behaviour with regard to their immunomodulatory therapy was not observed during the three months of observation. The results support the idea that the immediate release of recommendations of the German Society of Rheumatology were well received, supporting the well-established physician–patient relationship in times of a crisis.

Key words: SARS-CoV-2 pandemic, adherence, immunomodulatory drugs, influence, patient's behaviour, doctor–patient relationship

Introduction

Over 48 million cases of infection with severe acute respiratory syndrome coronavirus (SARS-CoV-2) were reported globally and >1.2 million fatal courses from

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Rheumatology key messages

- The majority of IRD patients continued their immunomodulatory therapy during the SARS-CoV-2 pandemic lockdown.
- The results were independent of age, type of therapy and IRD.
- This could reflect a trustful physician–patient relationship in times of crisis and that patients followed the recommendations during the pandemic.

resulting coronavirus disease 2019 (COVID-19) have been registered as of 5 November 2020 [1]. Regardless of these high numbers it has not been fully elucidated whether patients with inflammatory rheumatic diseases (IRD) or specific immunomodulatory treatments have a higher risk to develop a severe course of COVID-19, although data suggest that patients with IRD are at higher risk for bacterial, viral and opportunistic infections compared with the general population [2, 3]. At the beginning of the pandemic, no clear recommendations for patients with IRD were available in Germany. On 16 March 2020, hospitals were ordered by the respective authorities to reduce and postpone elective procedures substantially and to prioritize the remaining operative and personnel resources to facilitate treating patients with severe COVID-19. It was recommended that patients should reduce their visits to hospitals and private practices, if not essential for disease management. This caused a dramatic reduction of in- and outpatient visits. In some cases, patients did not even receive their immunomodulatory treatment, intravenous application of immunomodulatory drugs were prolonged, necessary adaptions of treatment strategies in case of disease relapse were postponed and personal appointments were nearly completely cancelled to reduce the overall risk of a SARS-CoV-2 infection in Germany [4]. In addition, on 22 March 2020, the German government restricted personal contacts outside of family circles to not more than two people, resulting in social isolation. One can quite easily imagine how these measures left some patients completely on their own. In April 2020, the German Society for Rheumatology (DGRh), similar to other societies, such as EULAR, BSR and ACR published preliminary recommendations for the management of patients with IRD in the context of the current pandemic [5–7]. All of them suggested the maintenance of immunomodulating therapies during the SARS-CoV-2 pandemic to avoid disease relapses.

In order to be able to estimate the patients' behaviour with respect to their immunomodulatory therapy, a Germany-wide survey was established during the SARS-CoV-2 pandemic, with a distinct focus on the patients' view on their immunomodulatory therapy. This was based upon the hypothesis that, influenced by public media, personal restrictions in the lockdown situation and possibly also by recommendations released from the national rheumatological societies, patients may have changed their behaviour regarding immunomodulatory therapy [8, 9].

Indeed, this hypothesis was challenged by the data of pulmonologists, who showed that pneumological appointments at the beginning of 2020 resulted in an increased adherence to therapy in chronic obstructive pulmonary disease (COPD) patients by 15%. However, it could not conclusively be clarified whether improved compliance was due to the context of the impending pandemic [10].

Methods

From 16 March until 15 June 2020, IRD patients from private practices and rheumatology departments were anonymously asked for adherence to their immunomodulating therapy. Nine private practices and eight rheumatology departments from six federal states across Germany participated. A one-page questionnaire was developed that included the range of age, type of IRD and immunomodulatory treatment (see supplementary material 1, available at *Rheumatology* online). Patients had to choose one out of seven options to answer this question (see supplementary material 1, available at *Rheumatology* online). The inclusion criteria were: (i) age $\geq$18 years and (ii) presence of an IRD. There were no inclusion/exclusion criteria for the participating general and private practices and departments. Participation was voluntary and without reimbursement. The time period from 16 March until 20 March 2020 was defined as 'before lockdown' and the time period from 21 March until 15 June 2020 was defined as 'during and after lockdown'.

Google trends analysis

To investigate further potential reasons why patients could have discontinued their immunomodulatory therapy, we performed an analysis on 'Google Trends' which is a free accessible online portal of Google Inc. [11]. Google Trends allows users to interact with internet search data, which can provide deep insights into behaviours of the population and health-related phenomena [11]. Google Trends answers queries and keeps a record of such searches. The data is compiled to display trends automatically. The weekly trends can be accessed from Google Trends, a special open-access domain of Google (https://trends.google.com/trends/) [12]. We, therefore, systematically searched for the following queries:

- corona cortisone (German: Corona Kortison)

- corona rheuma
- corona mtx
- corona adalimumab
- corona Humira
- covid-19 cortisone
- covid-19 rheuma
- covid-19 mtx
- covid-19 adalimumab
- covid-19 Humira

After approval of the study by the ethics committee of the Justus-Liebig-University Giessen (#32–20) and registration (EuDRACT 2020–004064-25), the survey started on 16 March 2020. The survey was announced to German rheumatologists on a nationwide basis, which resulted in an increasing number of participating private practices and rheumatology departments.

Statistical analysis

First, the proportion of patients' characteristics (age, type of IRD, IRD therapy) and opinion were calculated to evaluate relevant changes. Second, exact binomial tests were used to assess significant differences between patients' characteristics and the opinion. Python version 3.8.2 in conjunction with several libraries was used for statistical analyses and for the graphs. *P*-values were two-sided, and statistical significance was set at $P \leq 0.05$.

Results

Most of the participating centres were located in North Rhine-Westphalia (eight), followed by centres in Hesse (five), Lower Saxony (one), Schleswig-Holstein (one), Bavaria (one), Rhineland-Palatinate (one; see supplementary material 2, available at *Rheumatology* online). A total of 4252 questionnaires were collected and evaluated, 279 questionnaires before lockdown and 3973 questionnaires during and after lockdown. Most patients (29%) were aged between 51–60 years, followed by 22% of patients between 61–70 or 31–50 years old, and 15% were 71–80 years (Fig.1A). Patients reported to suffer from RA (54%), psoriatic arthritis (14%), ankylosing spondylitis (10%), systemic lupus erythematosus (6%), polymyalgia/giant cell arteritis (5%), systemic sclerosis (3%) and Sjögren's syndrome (2%). Approximately 1% of patients had a granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis or polymyositis/dermatomyositis. Gout, fever syndromes and other rare diseases were grouped together under 'other diseases'.

Around 22% of patients were on monotherapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARD). A combination of csDMARDs and biological (b)DMARDs was reported in 11% of the patients. Only <1% received glucocorticoids (GC) as monotherapy, in 31% of the cases a combination with GC was reported. One-fifth of the patients (20%) received a therapy with NSAIDs, of which 16% reported combination therapy with other immunomodulating drugs. Biologics were used in 34% of the patients (TNF-inhibitors 20%, IL-6-inhibitors 5%, IL-17-inhibitors 3%, abatacept 2%, rituximab 2%, IL-12/23-inhibitor 1%, IL-1-inhibitor 1%, belimumab 1%) and Janus kinase inhibitors (JAK-i) in 6% of the patients (Fig. 1B). From March till June 2020, 84% of the patients reported to continue their immunomodulatory therapy. In Fig. 2, the influence of the pandemic before, during and after the lockdown on the patient's behaviour regarding their therapies is displayed. Before the national lockdown, only 4% of the patients reported to discontinue their medication on their own or in consultation with their rheumatologists (Fig. 2A). During and after the national lockdown, the number of reported discontinuations even decreased (Fig. 2B). There was no relevant difference in the behaviour before, during and after the lockdown. Younger patients (18–30 years old, 2.8%) and patients between 71–80 of age (2.2%) reported to discontinue their medication less often compared with patients between 31–50 years old (4.4%) being the largest group (Fig. 3). The difference was not found to be significant as more younger patients (<60 years) participated in the survey (Fig. 1A). There was no relevant difference in patients' opinion with regard to the type of IRD (data not shown).

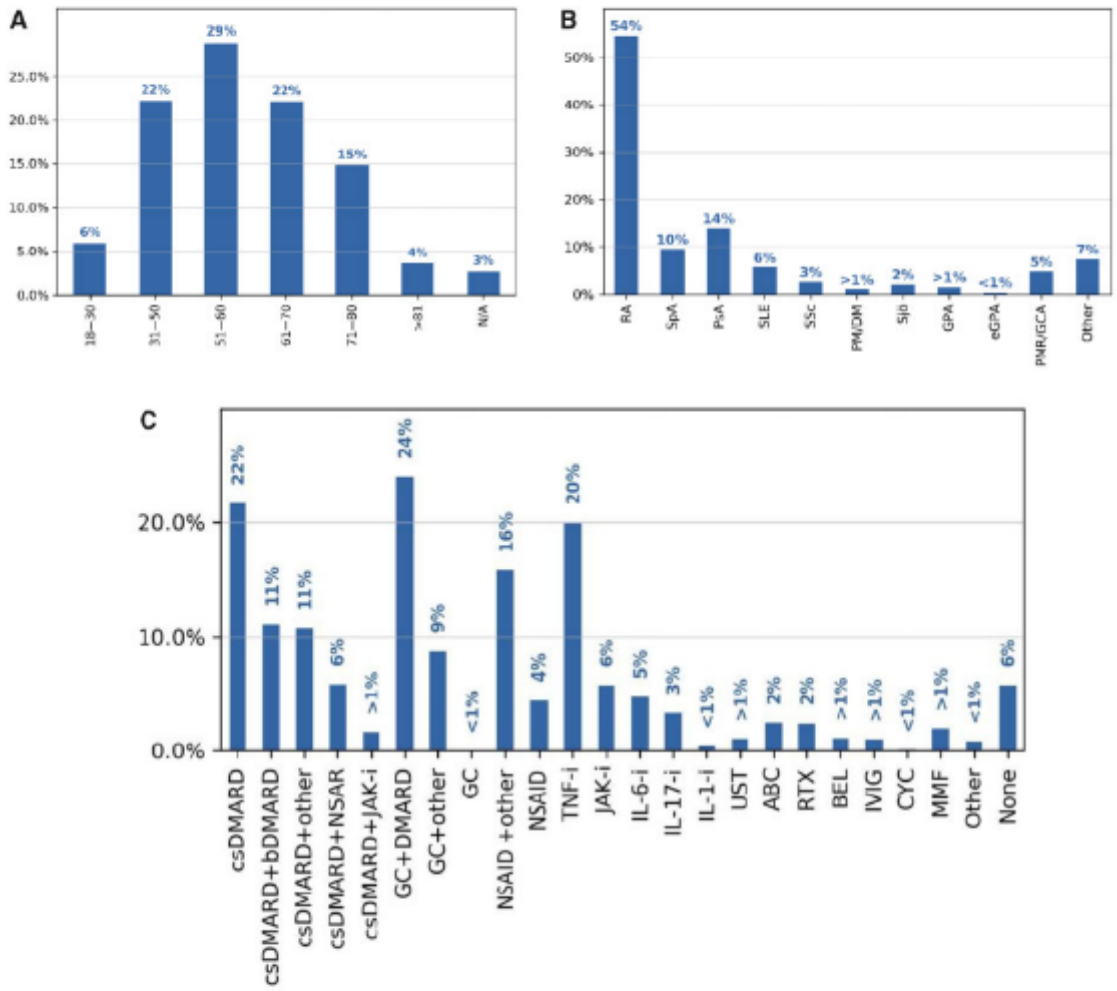
There were no obvious differences in patients' adherence regarding specific immunomodulatory therapies (data not shown). In Fig. 4A the development of patients' opinion over time is displayed. No significant difference could be detected over time. At the beginning of the pandemic, more patients reported to discontinue their medication than the number of patients who reported to discontinue their immunomodulatory therapy by their own decreased slightly (Fig. 4B). With a decreasing number of infected patients in the general population, fewer patients with IRD reported to discontinue their therapy. When SARS-CoV-2 infections spread again, the number of patients reporting to discontinue their medication increased as well (Fig. 4B).

In the Google Trends analysis, sufficient results could be detected only for the items 'corona steroids', 'corona humira' and 'corona rheuma'. Humira® (adalimumab, manufacturer AbbVie) has been the best-selling bDMARD in Germany for years. We correlated the weekly results of Google Trends for the selected queries with the number of patients who reported to discontinue their immunomodulatory therapy. The weekly course of the number of queries was similar to the course of the number of patients who reported to discontinue their medication (Fig. 5).

Discussion

To our knowledge, this study is the largest investigation to light up patients' opinions on immunomodulating therapy in IRD during the SARS-CoV-2 pandemic. The study reflects the behaviour of IRD patients over a period of 3 months in a lockdown setting with very limited or even no access to rheumatologists nationwide in Germany. In view of these circumstances, rheumatologic societies

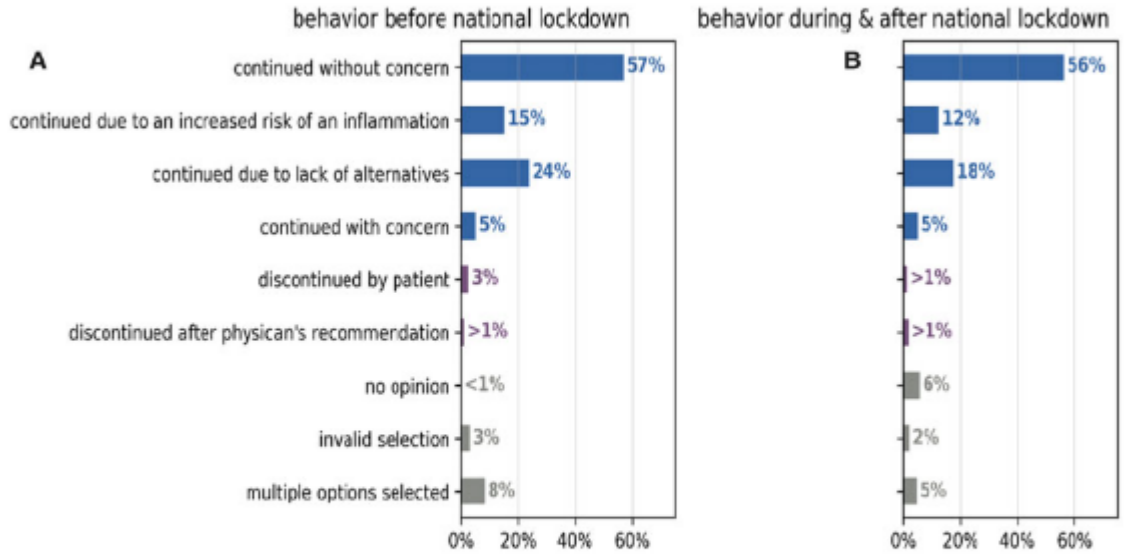
FIG. 1 Basic characteristics of IRD patients



(A) Age of the patients (in %): Most of the patients (29%) were between 51–60 years old followed by 22% of the patients which were between 61–70 years or 31–50 years old and 15% of the patients which were 71–80 years old. The minority of the patients were 18–30 years (6%) old or >81 years (4%) old. In 3% of the cases, no age was reported. **(B)** Distribution of the reported inflammatory rheumatic diseases (in %): 54% of the reported patients suffered from RA; 14% from PsA; 10% from AS; 6% from SLE, 3% from SSc, >1% from PM/DM and granulomatosis with polyangiitis (GPA), <1% from eosinophilic granulomatosis with polyangiitis (eGPA), 2% from Sjö, 5% from PMR/GCA and 7% from other IRD. **(C)** Distribution of immunomodulatory drugs reported in the survey (in %): 22% were on monotherapy with csDMARD, 11% on combination therapy with csDMARD and bDMARD, 11% with csDMARD and other immunomodulatory drugs (e.g. GC), 6% on csDMARDs & NSAID, >1% were on csDMARD and JAK-i, 24% on GC & DMARD, 9% on GC and other immunomodulatory drugs, <1% were only on GC, 16% on NSAID and other immunomodulatory drugs, 4% on monotherapy with NSAR, 20% on TNF-i, 6% on JAK-i, 5% on IL-6-i, 3% on IL-17-i, around 1% each received IL-1-i, ustekinumab (UST), belimumab (BEL), immunoglobulins (IVIG), CYC and MMF, 6% reported no therapy and <1% received other immunomodulatory drugs.

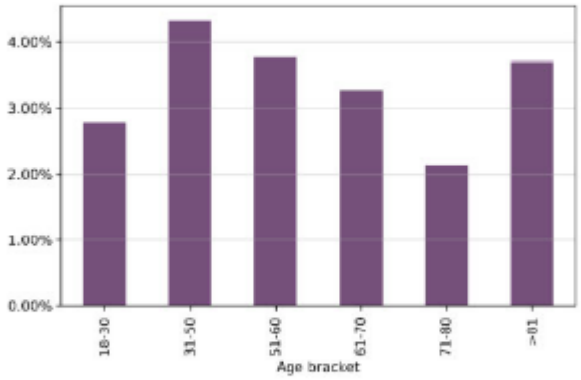
did not recommend discontinuing the immunomodulatory therapy to avoid disease relapse necessitating new or higher dosage of glucocorticoids and putting patients at substantial risk for infections. Our study shows that patients followed these recommendations of rheumatologists. In view of the fact that the management of patients with IRD was highly impacted by the pandemic, this can be interpreted as a hint for a trustful physician–patient relationship. Other studies could also observe a high number of patients who reported to continue their immunomodulatory therapy [13, 14]. In comparison to these results, medication adherence in patients with

Fig. 2 Patients' behaviour before, during and after the national lockdown in Germany



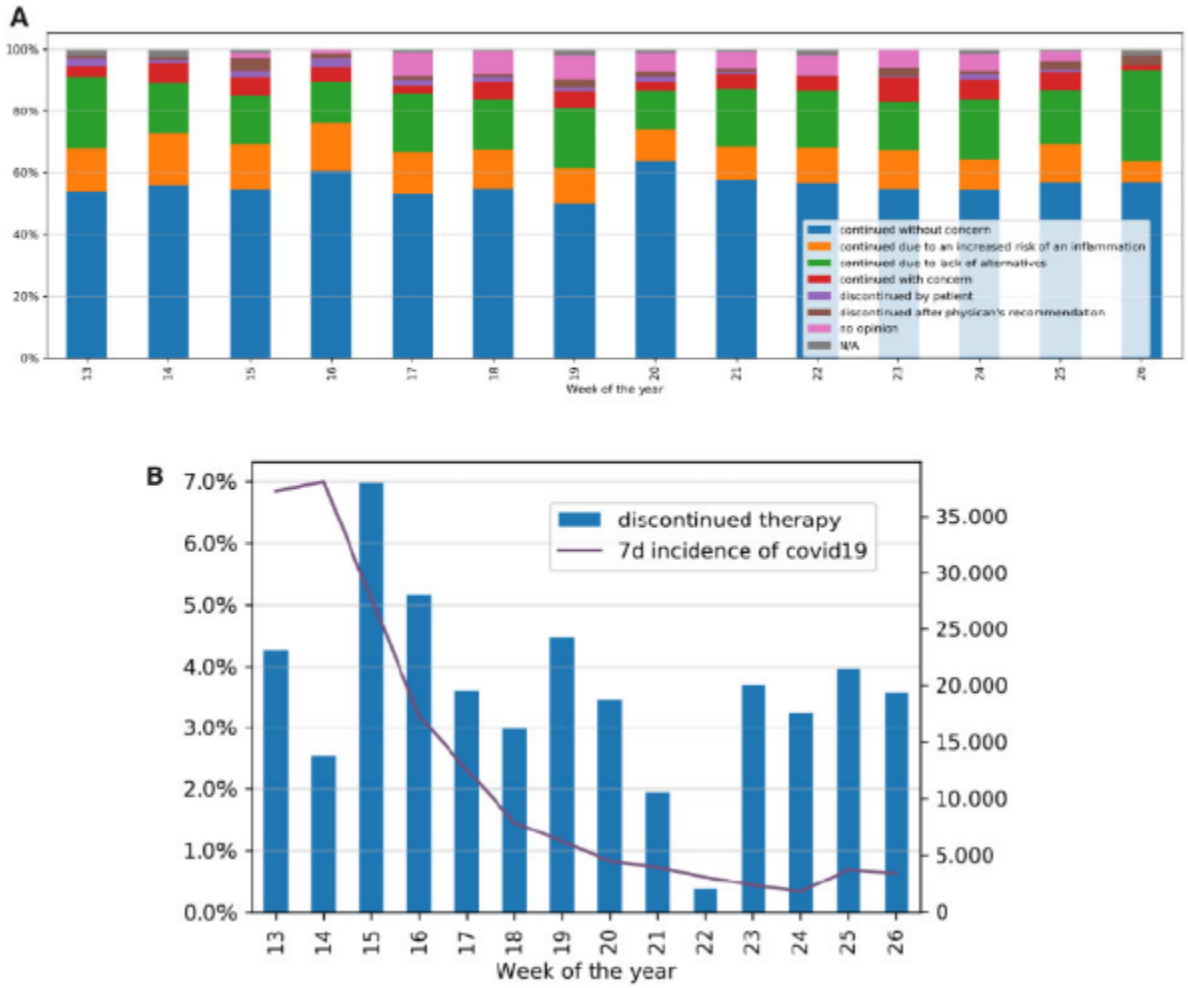
Patients had the opportunity to choose between seven answers to describe their adherence to their immunomodulatory medication. Some of the patients chose more than one answer (before: 8%, during and after lockdown 5%). **(A)** Patients' behaviour before the national lockdown in Germany: Patients had the opportunity to choose between seven answers to describe their adherence to their immunomodulatory medication. Some of the patients chose more than one answer. Before the national lockdown 57% of the patients reported to continue their immunomodulatory treatment without concern, 15% to continue due to an increased risk of a disease flare, 24% due to lack of alternatives and 5% continued their immunomodulatory drug with concern. Only 3% of the patients reported to discontinue their medication on their own and around 1% in consultation with their rheumatologists. <1% of the patients reported to have no opinion of their treatment and 2% did not choose any option. **(B)** Patients' behaviour during and after the national lockdown in Germany: During and after the national lockdown, 56% of the patients reported to continue their immunomodulatory treatment without concern, 12% to continue due to an increased risk of a disease flare, 18% due to lack of alternatives and 5% continued their immunomodulatory drug with concern. Around 1% of the patients reported to discontinue their medication on their own and around 1% in consultation with their rheumatologists. 6% of the patients reported to have no opinion of their treatment and <1% did not choose any option.

Fig. 3 Distribution of discontinuation of medication by age



Younger patients (18–30 years old, 2.8%) and patients between 71–80 years old (2.2%) reported less often discontinuing their medication compared with patients between 31–50 years old (4.4%), which were the biggest group followed by 3.7% of the patients between 51–60 years and around 3.6% >81 years old and 3.3% of the patients between 61–70 years old.

Fig. 4 Changes in patients' opinion over the course of the pandemic



(A) Proportion of patients' opinion over the course of the pandemic: The proportion of patients' opinion did not change relevantly over the course of the pandemic. The different answers are displayed in blue (continued without concern), orange (continued due to an increased risk of a disease flare), green (continued due to lack of alternatives), red (continued with concern), purple (discontinued by patient), brown (discontinued after physician's recommendation), pink (no opinion) and grey (no answer given). **(B)** Number of patients who reported to discontinue their medication over the course of the study: Blue columns display the number of patients who reported to discontinue their medication in % (left scale), purple line displays the 7 days incidence of SARS-CoV-2 infection in the general population (number of patients, right scale).

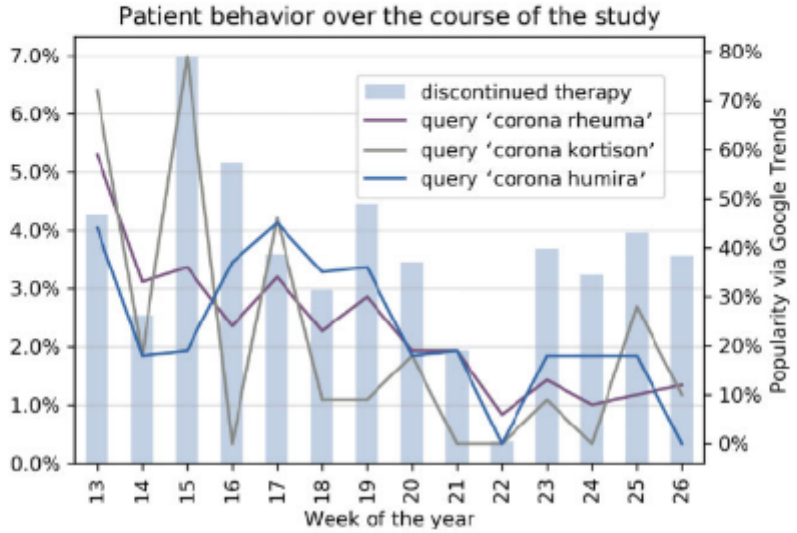
arterial hypertension in Germany is estimated to be around 66% in a non-pandemic setting [15].

Of note, no relevant difference in discontinuation rate could be observed with respect to age, type of IRD, type of immunomodulatory drug and the time elapsed since start of the pandemic. As the distribution of age in the study population is comparable to IRD patients in general, the results can be probably transferred to the entirety of IRD patients in Germany.

The results in the Google Trends analysis, which show a time-dependent interest for the topics 'corona & rheuma', 'corona & cortisone' and 'corona & Humira', could reflect an influence on patients' decision to discontinue their immunomodulatory therapy. A possible reason could be the fear of developing a severe course of SARS-CoV-2 infection due to the immunomodulatory drug.

However, this study has some limitations. Firstly, in order to rule out that patients were repeatedly asked for their opinion, the examination interval was limited to three months. Due to the anonymous survey, it is not possible to exclude that patients have participated in the survey more than once. However, as the majority of the patients did not have more than one outpatient visit within three months, a repetition of the survey is most

FIG. 5 Rate of patients who discontinued their therapy over the pandemic in comparison to the amount of Google Trends queries for selected items



Blue columns display the number of patients who reported to discontinue their medication in % (left scale), purple line displays the query 'corona rheuma', grey line 'corona cortisone' (German: corona Kortison) and blue line 'corona Humira' in % (right scale) over the pandemic (scale below, week of the year).

likely only the case for a neglegible number of patients. Secondly, as the questionnaire was completely anonymous, gender was not recorded, and thirdly, because it would not be clear at the beginning of the survey that disease activity and the dose of GC could have an influence on the course of COVID-19, these aspects were not included in the questionnaire. Fourthly, the pandemic is peaking in different regions at different times, which might have an influence on opinion. Although general practitioner and private practices and departments from six federal states were involved in the recruitment of the patients, data from other federal states are missing, which could have an impact on the results. In most of the represented federal states, the prevalence of SARS-CoV-2-infections was higher compared with the missing federal states [16]. Fifthly, the study population consists of patients with diseases that are associated with a higher risk of severe organ involvement, e.g. vasculitides and connective tissue disease. The prevalence of these diseases in the study population is higher compared with the prevalence among IRD patients in general (see supplementary material 3, available at *Rheumatology* online). It is possible that these patients attended their medical visits despite lockdown, so the distribution of patients could have been different without a lockdown scenario. These might have an impact on the decisions of the patients. Unfortunately, there are no data available about the distribution of the diseases treated in general practioner and private practices and rheumatology departments in general.

Taken together, the results of the study not only illustrate and reflect the patient's relation to their immunomodulatory therapy on a large-scale basis but specifically the essential value of the patient–physician partnership in the crisis.

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Data availability statement

All datasets generated for this study are included in the article/supplementary material.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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3.2 Aufbau eines nationalen Registers zur Erfassung SARS-CoV-2-Infektionen bei PatientInnen mit entzündlich-rheumatischen Erkrankungen

Originalarbeit 3:

Hasseli R, Müller-Ladner U, Schmeiser T, Hoyer BF, Krause A, Lorenz HM, Regierer AC, Richter JG, Strangfeld A, Voll RE, Pfeil A, Schulze-Koops H, Specker C.

National registry for patients with inflammatory rheumatic diseases (IRD) infected with SARS-CoV-2 in Germany (ReCoVery): a valuable mean to gain rapid and reliable knowledge of the clinical course of SARS-CoV-2 infections in patients with IRD.

RMD Open. 2020 Sep;6(2):e001332. doi: 10.1136/rmdopen-2020-001332

Originalarbeit 4 (Übersichtsarbeit):

Hasseli R, Pfeil A, Hoyer BF, Lorenz HM, Regierer AC, Richter JG, Schmeiser T, Strangfeld A, Voll RE, Krause A, Schulze-Koops H, Müller-Ladner U, Specker C.

German registry www.Covid19-Rheuma.de: Status report after 1 year of the pandemic.

Z Rheumatol. 2021 Sep;80(7):641-646. doi: 10.1007/s00393-021-01034-y

Zusammenfassung:

Um Erkenntnisse zum adäquaten Umgang mit der immunmodulatorischen Therapie bei PatientInnen mit ERE im Kontext der COVID-19-Pandemie zu gewinnen, sind Registerdaten mit einer hohen Fallzahl nötig, da keine prospektiven Daten zu dieser Erkrankung vorlagen. Diese erlauben, das Risiko für einen schweren Verlauf einer Infektion durch SARS-CoV-2 bei PatientInnen mit verschiedenen ERE oder unter einer bestimmten Therapie besser abzuschätzen. Aus diesem Grund wurde bereits im März 2020 ein Online-Register (www.covid19-rheuma.de) initiiert, mit dessen Hilfe nachgewiesene Infektion durch SARS-CoV-2 (positiver PCR- oder Antikörpertest) bei PatientInnen mit ERE innerhalb weniger Minuten erfasst werden können.

Im Register werden u. a. folgende Aspekte erfasst: Bundesland, Alter, Geschlecht, Gewicht, Größe, Impfstatus (Grippe-, Pneumokokken- und COVID-19-Impfung), Komorbiditäten, Krankheitsaktivität und Therapie der rheumatischen Grunderkrankung zum Zeitpunkt der Infektion durch SARS-CoV-2 und deren Verlauf. Dieses Register sollte auch dazu dienen, den Verlauf oder den Ausgang von COVID-19 bei PatientInnen mit ERE in Deutschland mit anderen Ländern vergleichen zu können, die sich z. B. im Hinblick auf die medizinische Versorgung und das jeweilige Gesundheitssystem unterscheiden (Originalarbeit *4*).

Bereits bei der Konzeption des COVID19-Rheuma.de Registers wurde deshalb darauf geachtet, Inhalte und Datenbankstruktur so zu gestalten, dass die Daten auch mit anderen

nationalen und internationalen Registern vergleichend ausgewertet werden können. Die Daten des deutschen Registers konnten so auch in das europäische Register (EULAR-COVID-19-Registry) sowie in das internationale Register (COVID-19-Global Rheumatology Alliance) übertragen werden, sodass keine Doppeleingabe der deutschen PatientInnen in die internationalen Register nötig war.

Neben der Verbindung zu den anderen rheumatologischen COVID-19-Registern wurde eine Kooperation zwischen dem DGRh-Register und dem Lean European Open Survey on SARS-CoV-2 infected patients (LEOSS)-Register aufgebaut, welches Infektion durch SARS-CoV-2 insgesamt europaweit erfasst [192].

Zusätzlich zeigte sich in der ersten Auswertung der Daten nach einem Dokumentationszeitraum von 4 Wochen, dass der Einsatz von Glukokortikosteroiden als ein Risikofaktor für eine Hospitalisierung im Rahmen von COVID-19 darstellen könnte. Innerhalb dieses Zeitraums wurden 104 PatientInnen erfolgreich dokumentiert, was auch die Akzeptanz des Registers bei den behandelnden RheumatologInnen widerspiegelte (Originalarbeit *3*).

RMD Open
Rheumatic & Musculoskeletal Diseases

Original research

National registry for patients with inflammatory rheumatic diseases (IRD) infected with SARS-CoV-2 in Germany (ReCoVery): a valuable mean to gain rapid and reliable knowledge of the clinical course of SARS-CoV-2 infections in patients with IRD

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ABSTRACT

Objectives Patients with inflammatory rheumatic diseases (IRD) infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be at risk to develop a severe course of COVID-19. The influence of immunomodulating drugs on the course of COVID-19 is unknown. To gather knowledge about SARS-CoV-2 infections in patients with IRD, we established a registry shortly after the beginning of the pandemic in Germany.

Methods Using an online questionnaire (www.COVID19-rheuma.de), a nationwide database was launched on 30 March 2020, with appropriate ethical and data protection approval to collect data of patients with IRD infected with SARS-CoV-2. In this registry, key clinical and epidemiological parameters—for example, diagnosis of IRD, antirheumatic therapies, comorbidities and course of the infection—are documented.

Results Until 25 April 2020, data from 104 patients with IRD infected with SARS-CoV-2 were reported (40 males; 63 females; 1 diverse). Most of them (45%) were diagnosed with rheumatoid arthritis, 59% had one or more comorbidities and 42% were treated with biological disease-modifying antirheumatic drugs. Hospitalisation was reported in 32% of the patients. Two-thirds of the patients already recovered. Unfortunately, 6 patients had a fatal course.

Conclusions In a short time, a national registry for SARS-CoV2-infected patients with IRD was established. Within 4 weeks, 104 cases were documented. The registry enables to generate data rapidly in this emerging situation and to gain a better understanding of the course of SARS-CoV2-infection in patients with IRD, with a distinct focus on their immunomodulatory therapies. This knowledge is valuable for timely information of physicians and patients with IRD, and shall also serve for the development of guidance for the management of patients with IRD during this pandemic.

Key messages

What is already known about this subject?

- Management of patients with inflammatory rheumatic diseases (IRD) in the current pandemic is a major challenge for rheumatologists and they may be at an increased risk due to the IRD itself as well as due to immunomodulating drugs.

What does this study add?

- In this group of 104 patients with IRD, hospitalised patients were more often treated with glucocorticoids while bDMARDs were used less often.
- As in the general population, patients with IRD having comorbidities are at higher risk to develop a more severe course of COVID-19.

How might this impact on clinical practice?

- Also, in view of the actual COVID-19 pandemic, GC should be kept as low as possible in the therapy of patients with IRD as they seem to enhance the risk of hospitalisation. This was not the case for bDMARD.
- Whether, and if so which single biological DMARD enhances or alleviates the risk of hospitalisation in COVID-19 may become clear with recruitment of more patients in the future.

INTRODUCTION

Since 12 March 2020, the WHO has declared the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease

Originalarbeit 3: Aufbau des Registers

2019 (COVID-19) a pandemic. The main symptoms of respiratory infection include fever and cough.[1 2] Eighty-one per cent of the patients show a mild course, 14% are seriously affected and 5% of the patients are critically ill.[2] On 25 April 2020, the Johns Hopkins University reported 2 954 106 confirmed cases worldwide.[3] The mortality rate at that time point was 6.95% (n=205 398).[3] The presence and the number of comorbidities (eg, arterial hypertension (AHT), coronary heart disease), age (immunosenescence) and lifestyle factors (eg, smoking) appear to have deteriorating effects on the course of the infection.[2] In this situation, patients with inflammatory rheumatic diseases (IRD) may face a particular risk as their disease, especially when clinically active, and their immunomodulatory treatment may impact the course of COVID-19 infection. However, firm knowledge of the course of SARS-CoV-2 infection in patients with IRD is missing, and therefore, evidence-based recommendations for the management of COVID-19 in patients with rheumatic disorders and antirheumatic treatments are lacking.

The German Society for Rheumatology (DGRh) developed at an early-stage first concise recommendations for the management of patients with IRD during the COVID-19 pandemic.[4] Interruption or reduction of immunomodulators is not recommended as this might result in relapses, which would increase the risk of infections, and in addition maylead to the necessity of an even riskier treatment (ie, additional glucocorticoids (GC)).[5] In a cross-sectional multicentric study, patients with IRD were asked anonymously in the first weeks of the pandemic on their opinion of their immunomodulating therapy. Over 90% of the patients followed the recommendation of the rheumatologists to continue the antirheumatic therapy, and only a small percentage of patients terminated the therapy on their own.[6] Whether first recommendations based on responsible care and expert's opinion is indeed the best option for the management of patients with IRD urgently needs to be validated.

Incidence and course of COVID-19, including lethal outcomes, vary considerably in different cohorts according to pre-existing conditions and healthcare systems. Investigation of special disease groups may contribute to a better understanding of the role of the immune system regarding the risk to get infected or to develop a more severe course of COVID-19. Therefore, patients with IRD, who are treated with different types, combinations and dosages of immunomodulatory therapies represent an interesting population to collect data regarding SARS-CoV-2 infection.

Registries with a large number of case reports are required to answer the questions, whether antirheumatic drugs increase or decrease the risk for a severe course of SARS-CoV-2 infection. As necessary data cannot be extracted from clinical charts or health insurance records, the DGRh and the Justus-Liebig University Giessen decided to establish a web-based registry, which allows a rapid and timely collection of IRD cases with confirmed SARS-CoV-2 infections in Germany to analyse the clinical course of SARS-CoV-2 infections in patients with IRD and to develop guidance for the management of patients with IRD during the COVID-19 pandemic.

PATIENTS AND METHODS

On 18 March 2020 the COVID-19 Registry Task Force was founded by the DGRh consisting of rheumatologists, epidemiologists and information technology specialists. In cooperation with biostatisticians and data-protection specialists to ensure mutual understanding of research objectives and scientifically and legally appropriate data collection, a database-driven online questionnaire was developed and has been launched on 30 March 2020.

Following are the key questions of the registry:

- What is the course of COVID-19 in patients with IRD?
- Does geographical location/different access to healthcare within Germany affect the course?
- Does a specific immunomodulatory treatment ameliorate or deteriorate the course of COVID-19?
- Which other factors are associated with a poor outcome of COVID-19 in patients with IRD?

Patients with a known IRD and positive testing for SARS-CoV-2 were included by their treating rheumatologists after registration. Patients had to have positive PCR-swabs for SARS-CoV-2 for inclusion in our registry. In contrast to other registries, presumptive diagnosis of COVID-19 based on suggestive symptoms, X-ray or CT findings or on other 'unknown' findings was not included.

The database includes, for example, federal state, age, weight, height, detailed rheumatological diagnosis, comorbidities, global disease activity antirheumatic medication at time of study and changes due to the infection. In addition, the course and outcome of the SARS-CoV-2 infection are also key parameters. Missing data on diagnosis, outcome and therapies can be queried by directly contacting the participating physicians. Periodic critical evaluation of the registry is carried out by the task force to ensure that the objectives are being met.

The disease activity from the last rheumatological visit was reported and divided into four groups: remission, low disease activity, moderate disease activity and high disease activity. This classification and approach are concordant to the EULAR/Global Rheumatology Alliance (GRA) database. Specific disease activity scores, for example, DAS-28, are not included in the survey.

Data entered in an electronic case report form with the URL https://www.COVID19-rheuma.de/ are directly stored into an SQL-database on a dedicated server located in Germany and certified according to DIN ISO/IEC 27001 using encryption and secure communication protocols (SSL/TLS and HTTPS). Data entered in these forms are checked for plausibility immediately. Web-forms use dynamic menus and subquestions. Data allowing for identification of individual patients are

omitted, and reidentification is only possible via local files in the respective rheumatological unit.

In addition, patients with IRD affected by SARS-CoV-2 can contact a rheumatologist at the coordination site of the project, who collects the respective data sets via a telephone-interview (after informed consent of the patient) entering the pseudonymised data also directly into the same web-form/database. The lockdown appointments of in- and outpatients were reduced remarkably to spare capacity for the treatment of patients with severe COVID-19 infections and to minimise patients and physician's infection risks during outpatients' appointment. Especially, visits of patients which showed controlled disease activity were skipped or postponed. However, to give these patients the opportunity to report their case if they were tested positive for SARS-CoV-2, the physician telephone interview was set up. However, these data entries will be flagged and can be analysed separately from those directly entered by their treating physician.

After the study was approved by the ethics committee of the Justus-Liebig-University Giessen (#52-50) and registered (EuDRACT 2020-001958-21), the web-based questionnaire was announced to German rheumatologists on 30 March 2020. Later, the German database was, in part, adjusted to the EULAR COVID-19 database when the latter was launched (https://www.eular.org/eular_COVID-19_database.cfm) to facilitate the transfer of German anonymised data into the European database in the future.

Participating centres consist of academic and non-academic rheumatology clinics, and private practices in Germany. Most of them have been informed directly using established dissemination channels of the DGRh. Announcements of the project have been posted and are being regularly updated on the website of the DGRh, the homepage of the 'www.COVID19-rheuma.de' registry, via social media channels, and print media. The registry is also fully supported by the Professional Association of German Rheumatologists 'Berufsverband Deutscher Rheumatologen', and by the national patient organisation 'Deutsche Rheuma-Liga', its state representatives, the Association of Rheumatology Clinics 'Verband der Rheumatologischen Akutkliniken e.V' and several other disease-specific patient associations.

The completed data were reviewed and queried in case of uncertainties. Analysis was performed descriptively using SPSS Statistics. Median was calculated for age and body mass index (BMI) of the fatal courses. Data in figures are shown in percentages using GraphPad Prism 6 (GraphPad Software).

RESULTS

Between 30 March (first patient in) and 25 April, 104 patients with IRD and a SARS-CoV-2 infection were documented in the database by rheumatologists. The development of recruitment during the first 4 weeks is depicted in figure 1. To date, 138 rheumatologists have registered to take part in the project and 71 have already documented at least one patient. Entering a patient case took on average 5 min. Each data entry is logged by a time stamp allowing calculations of the time used for the documentation procedure up to the time required for single items in the survey.

The 104 patients reported so far included 40 males, 63 females and 1 diverse, the age range was between 23 and 87 years (median age 56 years; figure 2A). Most patients

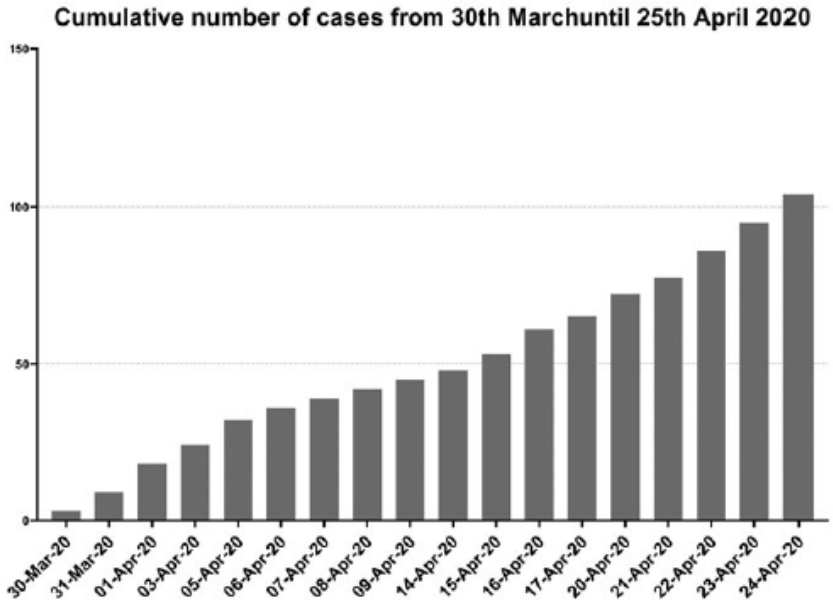

Figure 1 Cumulative number of cases which have been reported until 25 April 2020.

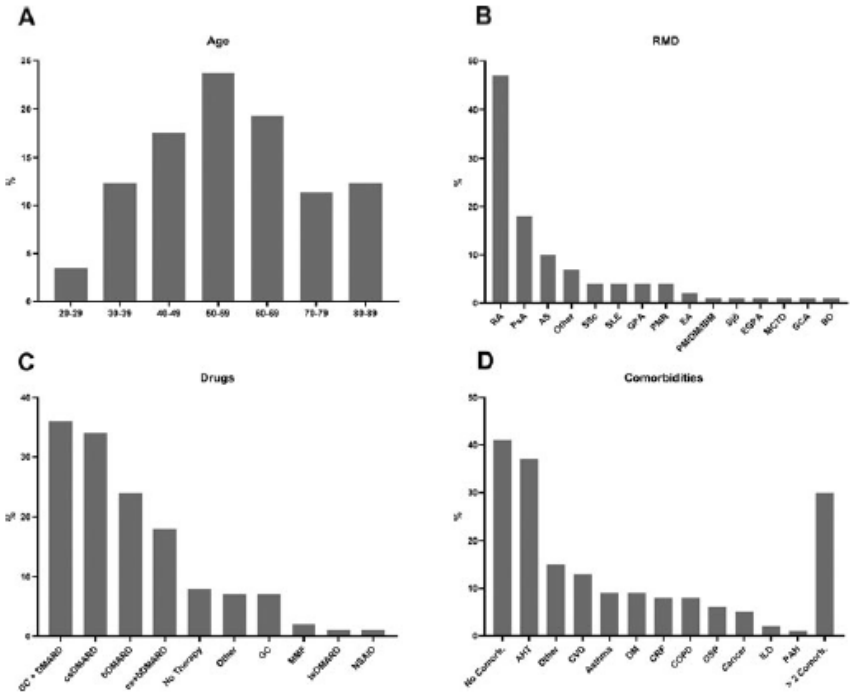

Figure 2 Overview of the reported data. (A) Age of the reported patients (in %): 4% of the patients were aged between 20 and 29 years, 12% between 30 and 39 years, 18% between 40 and 49 years, 24% between 50 and 59 years, 20% between 60 and 69 years, 11% between 70 and 79 and 12% between 80 and 89 years. (B) Distribution of inflammatory rheumatic diseases in the database (in %): 45% of the reported patients suffered from RA; 18% from PsA; 10% from AS; 7% from other inflammatory diseases (eg, gout, fever syndromes); 4% each from SSc, SLE, GPA and PMR; 2% from EA; 1% each from PM/DM/IBM, Sjö, MCTD, GCA and BD. (C) Distribution of antirheumatic drugs reported in the database (in %): 36% were with GC 6 DMARDs, 34% with csDMARDs, 24% with bDMARDs, 18% with csDMARDs and bDMARDs, 8% had no therapy, 7% received other medication, 7% were treated with glucocorticosteroids, 2% with MMF and 1% each with NSAIDs and tsDMARDs. (D) Distribution of comorbidities (in %): 41% had no comorbidities, 37% suffered from AHT, 15% from other relevant comorbidities, 13% from CVD, 9% each from bronchial asthma and DM, 8% each from COPD and CRF, 6% from OSP, 5% from cancer/history of cancer, 2% from ILD, 1% from PAH and 15% from other relevant comorbidities, 30% had more than two comorbidities. AHT, arterial hypertension; AS, ankylosing spondylitis; bDMARD, biological disease-modifying antirheumatic drugs; Comorb, comorbidities; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVD, cardiovascular diseases; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; DM, diabetes mellitus; DMARDs, disease-modifying antirheumatic drugs; EA, enteropathic arthritis; EGPA, eosinophilic granulomatosis with polyangiitis; GCA, giant cell arteritis; GPA, granulomatosis with polyangiitis; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; MMF, mycophenolate-mofetil; NSAIDs, nonsteroidal anti-inflammatory drugs; OSP, osteoporosis; PAH, pulmonary arterial hypertension; PM/DM/IBM, polymyositis, dermatomyositis, inclusion body myositis; PMR, polymyalgia rheumatica; PsA, psoriatic arthritis; RA, rheumatoid arthritis; Sjö, Sjögren-syndrome; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs.

with COVID-19 (24%) were between 50 and 59 years old. About two-thirds of the patients were reported from private practices, 32% from hospitals and 6% of the patients had a telephone interview by a rheumatologist at the coordination site. In relation to population numbers, most cases have been notified from Hamburg, Baden-Württemberg, Berlin, North Rhine-Westphalia and Rhineland Palatinate (table 1). The presence of antibodies was not included in our registry, which is comparable to the EULAR and GRA COVID-19 database.

Regarding diagnosis, 45% of the patients with IRD had rheumatoid arthritis, 18% were diagnosed with psoriatic arthritis, 10% with ankylosing spondylitis and 5% systemic sclerosis. The proportion of other IRD was below 5% (figure 2B).

Prior to the SARS-CoV-infection, 34% of the patients were receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), 42% were on bDMARDs, 24% in monotherapy and 18% in combination with csDMARDs. Forty-three per cent were treated with GC, 7% without any other immunomodulation and 8% of the patients did not receive DMARDs or GC (figure 2C).

In 59% of the cases, relevant comorbidities were reported. This included AHT in 37% of the patients, other relevant comorbidities in 15%, cardiovascular

Table 1 Epidemiological situation in Germany with distribution to the federal states on 25 April 2020

Federal state	COVID-19-affected patients with IRD in national registry	COVID-19-affected patients in general population of the federal state[7]
Baden-Wuerttemberg	16 (15%)	30.169 (20%)
Bavaria	21 (20%)	40.547 (27%)
Berlin	6 (6%)	5.525 (4%)
Brandenburg	3 (3%)	2.627 (2%)
Bremen	0 (0%)	719 (0,4%)
Hamburg	11 (11%)	4.400 (3%)
Hesse	12 (12%)	7.837 (5%)
Mecklenburg-West Pomerania	0 (0%)	667 (0,4%)
Lower Saxony	5 (5%)	9.691 (6%)
North Rhine-Westphalia	14 (13%)	31.465 (21%)
Rhineland-Palatinate	8 (8%)	5.767 (4%)
Saarland	1 (1%)	2.468 (2%)
Saxony	3 (3%)	4.406 (3%)
Saxony-Anhalt	1 (1%)	1.480 (1%)
Schleswig-Holstein	2 (2%)	2.612 (2%)
Thuringia	1 (1%)	2.058 (1%)
Deaths	6 (6%)	5.500 (4%)
Total number	104	152.438

IRD, inflammatory rheumatic diseases.

diseases (CVD) in 13%, 9% each suffered from bronchial asthma and diabetes, 8% each from chronic obstructive pulmonary disease and chronic renal failure, 6% from osteoporosis, 5% from cancer/history of cancer, 2% from interstitial lung disease, 1% from pulmonary arterial hypertension and 30% had more than two comorbidities (figure 2D). In 41% of the cases, no relevant comorbidities were reported.

Thirty-nine per cent of the patients had been vaccinated against seasonal influenza, 26% against pneumococci and 22% against both. Ten per cent of the documented patients were smokers, 1% were using e-cigarettes and 8% of the patients were drinking alcohol on a regular basis.

The most common reported symptoms of COVID-19 included cough (69%), fever (59%), fatigue (42%), headache (36%), myalgia (33%), dyspnea (32%), loss of odour (26%) or taste (25%), rhinitis (23%), loss of appetite (16%), vertigo (15%), diarrhoea (15%), expectoration (13%), other relevant symptoms (13%), abdominal pain (3%) and vomiting (2%) (figure 3A). Most of the patients (86%) had more than two symptoms, and 7% of the patients were reported as asymptomatic.

One-third (32%) of the patients was hospitalised, in 70% (23/33) of these cases, oxygen supply was necessary, 15% (5/33) received non-invasive and 24% (8/33) invasive ventilation. Unfortunately, six patients (6%) died in the context of COVID-19 (figure 3B), three male and three female patients (table 2). The median age in this group was 71 years (range 59–80 years), the median BMI 27.8 kg/m^2 (range 23.9–40.6 kg/m^2). All patients had at least AHT and/or other CVD (table 2). All deceased patients needed to be ventilated invasively. Five of the six patients were treated with low-dose GC (≤7.5 mg/day), which was not interrupted due to the infection in four cases. Only two of eight patients recovered after invasive ventilation.

Hospitalised patients were older than non-hospitalised patients (median age 69 vs 52 years). Even though women represented 62% of all registered patients, the hospitalisation rate was equal in both genders (48% male vs 52% female). More hospitalised patients were on GC (64% vs 34%), but less were treated with bDMARD (33% vs 48%). In addition, more comorbidities (>2) were documented in hospitalised patients (48% vs 21%, figure 4).

At the last rheumatological visit, 37% (38/104) of the patients were in remission, 17% (18/104) patients were reported to have low disease activity, 13% (13/104) moderate and 2% (2/104) high disease activity. In 29% (30/104), disease activity was not reported. Interestingly, the two cases with reported high disease activity developed a severe course of COVID-19 leading to hospitalisation. Comparing remission (33% vs 38%) and moderate (9% vs 14%) disease activity, the proportion was similar in the hospitalised versus non-hospitalised groups, and different in patients with low disease activity (27% vs 13%).

DISCUSSION

Patients affected by IRD are at an increased overall risk of infection compared to the general population.[8–10] However, the infection risk varies and is highly dependent on the type and activity of the autoimmune disease, on comorbidities and on the intensity of the immunosuppressive/immunomodulatory treatment.[8 11] Most patients with IRD are treated with GC, csDMARDs, bDMARDs and tsDMARDs on a regular basis. Especially, GC increase the risk of serious infection in a dose-dependent manner. Moreover, treatment with DMARDs can be associated with infectious complications. Most frequently, these are of bacterial origin,[12] but also certain viral infections like Herpes zoster may complicate the course of many antirheumatic therapies.[13] Treatment with tumour necrosis factor (TNF) inhibitors is associated with an increased risk of serious infections at the beginning of treatment, but when effective, the risk decreases due to better functional capacity and decreased use of GC.[14]

Currently, there is no evidence, whether and to what extent patients with IRD are at an increased risk for COVID-19 and if antirheumatic treatment, especially GC and DMARDs, are harmful to patients in the context

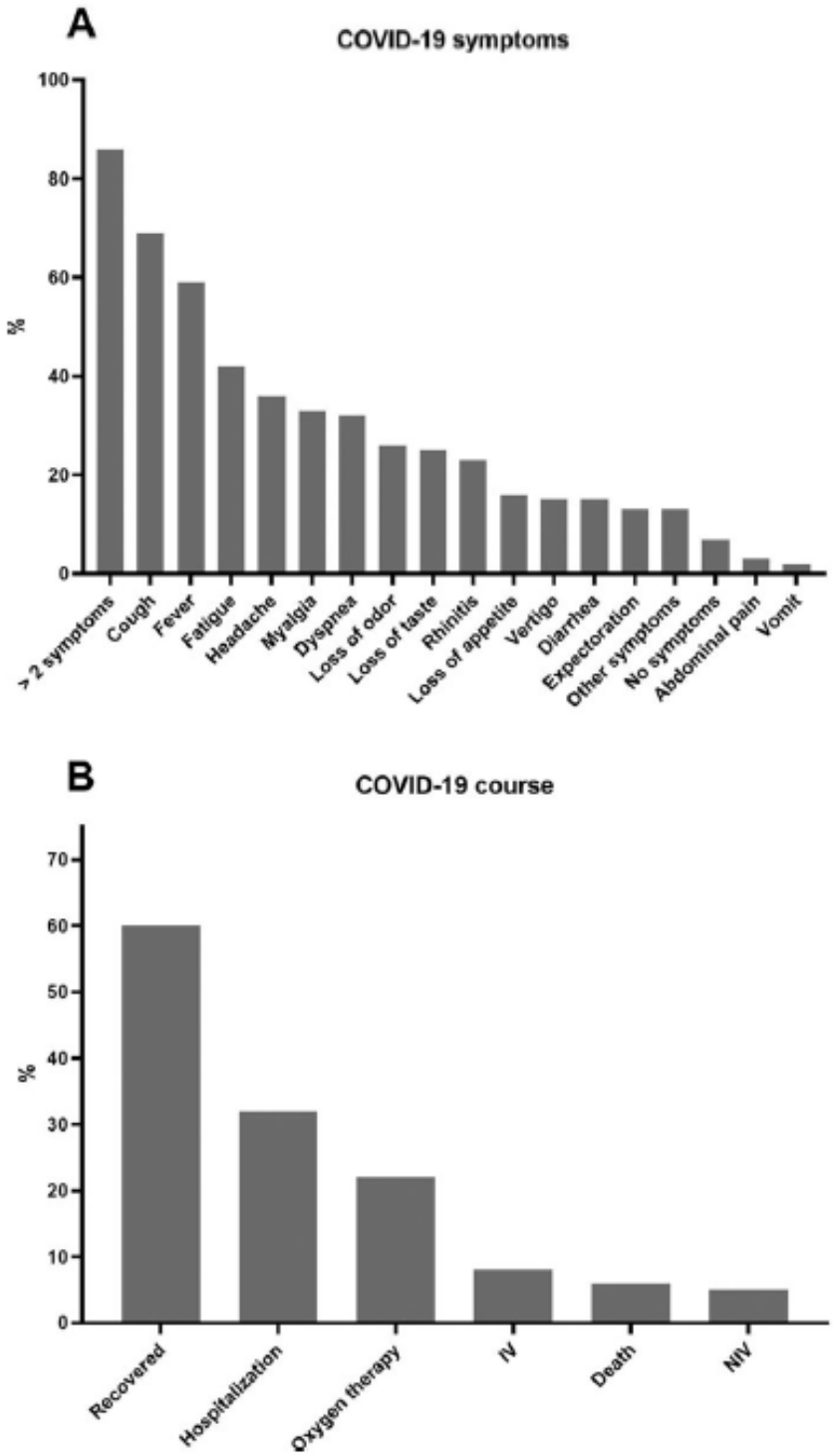

Figure 3 Symptoms and courses of COVID-19 infection (in %). (A) Distribution of the symptoms of COVID-19 infection (in%): 86% of the affected patients had more than two symptoms, 69% reported cough, 59% fever, 42% fatigue, 36% headache, 33% myalgia, 32% dyspnea, 26% loss of odour, 25% loss of taste, 23% rhinitis, 16% loss of appetite, 15% vertigo, 15% diarrhoea, 13% expectoration, 13% other symptoms, 7% had no symptoms, 3% abdominal pain and 2% vomit. (B) Distribution of the course of COVID-19 infection (in%): 60% of the patients already recovered, 32% of the patients needed to be hospitalised, 22% of the patients were treated with oxygen (5% non-invasive ventilation (NIV), 8% invasive ventilation (IV)). Six deadly courses were already reported.

Table 2 Characteristics of fatalities

IRD	PsA	RA	RA	RA	PsA	RA
Age (years)	64	70	80	80	59	72
Gender	M	M	F	F	M	F
BMI (kg/m^2)	40.6	27.8	28.7	23.9	27.8	26.6
Antirheumatic therapy	GC	SSZ	GC, MTX	GC, MTX, RTX	GC, SSZ	GC, MTX, ABC
Comorbidities	CVD COPD	AHT	CVD AHT COPD	AHT Osteoporosis	CVD AHT Cancer Other	AHT COPD
Disease duration (COVID-19)	6 days	8 days	14 days	21 days	18 days	20 days
Symptoms (COVID-19)	Fever Dyspnea	Fever Cough	Fever Dyspnea Chest pain	Fever Cough Dyspnea Vertigo Fatigue	Fever Dyspnea Cough	Dyspnea
Invasive ventilation	Yes	Yes	Yes	Yes	Yes	Yes
Interruption DMARD	Yes	Yes	Yes, MTX	Yes, MTX and RTX	No	Yes, ABC and MTX

ABC, abatacept; AHT, arterial hypertension; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular diseases; DMARD, disease-modifying antirheumatic drugs; F, female; GC, glucocorticosteroids; IRD, inflammatory rheumatic diseases; M, male; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RTX, rituximab; SSZ, sulphasalazine.

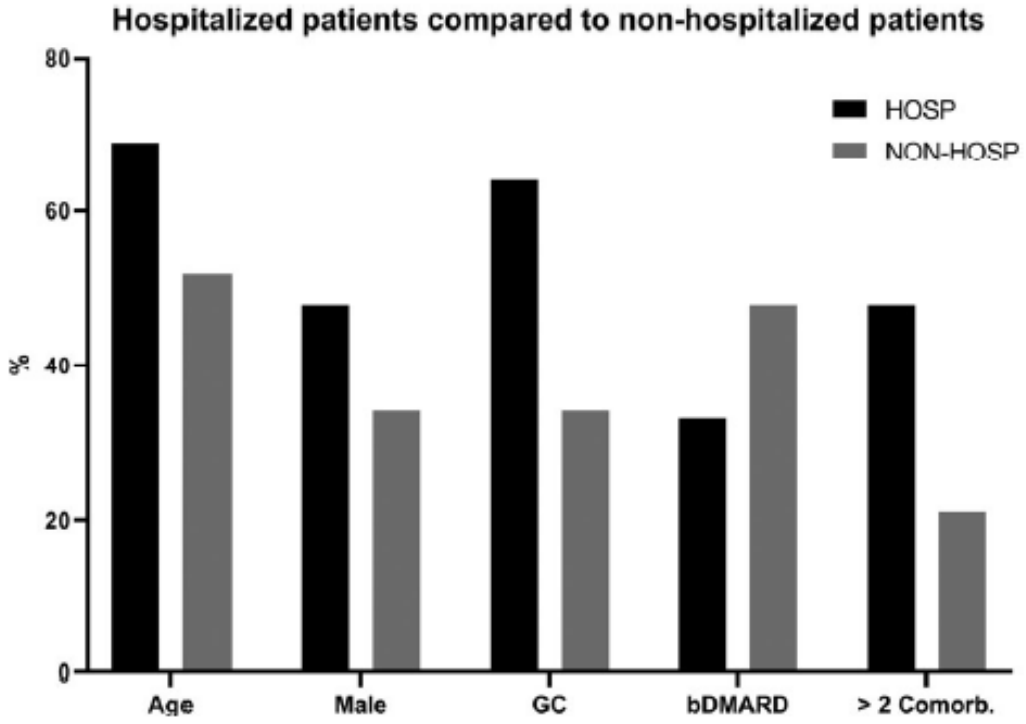

Figure 4 Distribution between hospitalised and non-hospitalised patients. Median age in group of hospitalised patients (HOSP) was 69 years and in non-hospitalised (NON-HOSP) was 52 years. More male patients were hospitalised (48%) compared to NON-HOSP (34%). HOSP were treated in 64% of the cases with GC, NON-HOSP in 34%. Thirty-three per cent of HOSP received bDMARDs compared to 48% of NON-HOSP. In HOSP, more comorbidities were observed (48%) compared to NON-HOSP (21%). bDMARD, biological disease-modifying antirheumatic drugs; Comorb., comorbidities; GC, glucocorticosteroids.

of COVID-19. Interestingly, some of the antirheumatic drugs such as hydroxychloroquine,[15 16] anakinra and interleukin 6 inhibitors[17 18] have been discussed to have a beneficial role in the course of SARS-CoV-2 infection, whereas others may exert deleterious effects similar to that recently observed in rituximab-treated patients.[19 20] Data from the global rheumatology alliance physician-reported registry indicate that GC exposure of ≥10 mg/day is associated with higher ORs of hospitalisation.[21]

This is the first report of a cross-sectional study of patients with IRD and COVID-19 in Germany. The distribution of cases within the 16 federal states of Germany is consistent with the validated infection rates in the general German population that have been electronically reported to the Robert Koch Institute (table 1). Of all patients in our database, more women were affected by COVID-19 (62% female/38% male, what had to be expected, since most IRD show a considerable preponderance of females (~78%).[22] In our cohort, there was a slight relative preponderance of male patients with IRD suffering from severe COVID-19, which is consistent with data from the Chinese general population.[2] The proportion of male patients with IRD was even considerably higher in our register among those who needed to be hospitalised, in which both genders were represented nearly equally (52% female/48% male, figure 4). This was not as clear in the global register, in which the distribution for hospitalised patients was 67% females vs 33% males and 74% vs 36% for non-hospitalised patients, respectively.[21] These findings argue that—as in the general population—also in IRD, male patients tend to develop COVID-19 more than female patients[23] and might be at risk for a more severe course of COVID-19.[22]

With respect to infections of the airways, TNF-α is discussed to mediate pulmonary inflammation in viral pneumonia.[24] Of note, TNF-α inhibition might inherit positive effects on symptoms and severity of virus-specific lung immunopathology, especially the inflammatory burst that finally damages the lungs.[25] In the RABBIT registry (German register for the long-term observation of therapy with biologics in adult patients with rheumatoid arthritis), TNF-inhibitors seemed to be beneficial for the course of severe infections by lowering the risk of sepsis and fatal outcome.[14] In the global registry, anti-TNF treatment was associated with a decreased hospitalisation rate.[21]

In our case series, 24 patients (23%) were treated with TNF-α-inhibitors, and none of these needed oxygen treatments. Conversely, hospitalised patients tended to be treated predominantly with GC and/or csDMARDs, and 33% of them have been treated with bDMARDs compared to 48% in the non-hospitalised group. However, at present, the use of bDMARDs other than TNF-inhibition is too scarce to draw conclusions regarding risks or benefits of individual biologics, but with growing numbers of patients entered, we are confident in being able to do so in the near future.

Taken together, as a first result of our project, it could be shown that establishing an online-registry of patients with IRD and COVID-19 is feasible in short time and allows for rapid collection of possibly relevant data in the context of the SARS-CoV-2 pandemic. As in the general population, also in our study, male gender might be a potential risk factor for COVID-19 in patients with IRD, and as in the global register, treatment with GC seemed to be a disease-related risk factor in patients with IRD. With recruitment of more patients in the near future the trend of lower hospitalisation rates in patients with IRD treated with bDMARDs compared to those treated with csDMARDs will be further investigated. It is also worthwhile to compare data from Germany with those from other countries in and outside the European Union.

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Contributors RH, UM-L, TS, HS-K and CS performed the study design. RH performed the research, analysed, and interpreted the data. RH, UM-L, TS, HS-K and CS wrote the manuscript. RH, UM-L, TS, BFH, AK, H-ML, ACR, JGR, AS, REV, HS-K and CS performed physician recruitment. All authors contributed to preparation of the project, and read and approved the final manuscript.

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Deutsches Register www.Covid19-Rheuma.de

Statusbericht nach 1 Jahr der Pandemie

Mit dem Ausbruch des Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 bzw. COVID-19) in Wuhan im Dezember 2019 entwickelte sich aus einem lokalen Infektionsgeschehen binnen 3 Monaten eine Pandemie [1]. Die Deutsche Gesellschaft für Rheumatologie (DGRh) veröffentlichte am 30.03.2020 erste, konsentierte Handlungsempfehlungen für die Betreuung[1] mit entzündlich rheumatischen Erkrankungen (ERE) im Rahmen der COVID-19-Pandemie, die sich naturgemäß noch nicht auf Studien zu Infektionen mit SARS-CoV-2 stützen konnten [2]. Basis hierfür waren Daten von bekannten viralen Infektionen der oberen und unteren Atemwege, z. B. mit Influenzaviren oder bekannten Coronaviren, wie SARS (schweres akutes respiratorisches Syndrom) oder MERS (Middle East Respiratory Syndrome), welche mit einer COVID-19 vergleichbaren initialen Klinik (Husten, Fieber, Zephalgien und Myalgien), demselben Übertragungsweg (Tröpfcheninfektion) und variabler Symptomatik, von symptomlos bis zu kurzen letalen Verläufen, einhergehen. Im Hinblick auf die immunmodulierende Therapie wurde von einem Pausieren oder einer Reduktion aus Sorge vor einer Infektion ausdrücklich abgeraten, da man – wiederum in Analogie zu bekannten Infektionen bei ERE – davon ausging, dass dadurch Krankheitsschübe begünstigt werden, die auch das Risiko für eine SARS-CoV-2-Infektion erhöhen dürften, spätestens wenn man zur Behandlung eines Schubes wieder höhere Glukokortikoiddosen (GC) einsetzen müsste [2]. Die Fortsetzung der immunmodulierenden Therapie setzt neben einer adäquaten und engmaschigen rheumatologischen Betreuung mit enger Arzt-Patienten-Kommunikation, auch eine entsprechende Compliance der Patienten voraus. In einer longitudinalen Befragung von Patienten aus rheumatologischen Ambulanzen und Praxen in Deutschland über einen Zeitraum von 3 Monaten konnte gezeigt werden, dass die Mehrheit der Patienten angab, ihre Therapie gemäß der DGRh-Empfehlung fortzuführen [3].

Um Erkenntnisse zum adäquaten Umgang mit der immunmodulatorischen Therapie bei Patienten mit ERE im Kontext der COVID-19-Pandemie zu gewinnen, sind Registerdaten mit einer hohen Fallzahl sehr hilfreich. Diese erlauben, das Risiko für einen schweren

Abkürzungen

COVID-19	Corona Virus Disease 2019
DGRh	Deutsche Gesellschaft für Rheumatologie
GC	Glukokortikoide
LEOSS	Lean European Open Survey on SARS-CoV-2 Infected patients
RA	Rheumatoide Arthritis
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SpA	Spondyloarthritis

[1] In dieser Arbeit wird aus Gründen der besseren Lesbarkeit das generische Maskulinum verwendet. Weibliche und anderweitige Geschlechteridentitäten werden dabei ausdrücklich mitgemeint, soweit es für die Aussage erforderlich ist.

Originalarbeit 4: Aufbau des Registers

Infobox 1 Zugang zum Register und zur Impferfassung für Patienten

Zugang zum Register:
www.covid19-rheuma.de

Zugang zur Impferfassung für Patienten:
https://www.covid19-rheuma.de/patienten-information-impfung

Zugang zur Papierversion der Impferfassung:
https://www.covid19-rheuma.de/pdf/fragebogen-impfung-20210413.pdf

Tab. 1 Patientenverteilung nach den Bundesländern (Stand: 21.03.2021)

	DGRh COVID-19-Register	COVID-19-Fälle in der Allgemeinbevölkerung (laut Robert Koch-Institut)
Bayern	412 (21 %)	472.427 (18 %)
Nordrhein-Westfalen	262 (13 %)	577.480 (22 %)
Hessen	241 (12 %)	205.734 (8 %)
Baden-Württemberg	239 (12 %)	343.165 (13 %)
Berlin	215 (11 %)	138.205 (5 %)
Sachsen	148 (7 %)	209.156 (8 %)
Brandenburg	116 (6 %)	82.945 (3 %)
Rheinland-Pfalz	82 (4 %)	109.639 (4 %)
Hamburg	71 (4 %)	56.992 (2 %)
Niedersachsen	69 (3 %)	183.678 (7 %)
Saarland	66 (3 %)	30.668 (1 %)
Schleswig-Holstein	39 (2 %)	46.969 (2 %)
Sachsen-Anhalt	18 (< 1 %)	67.601 (3 %)
Thüringen	18 (< 1 %)	87.286 (3 %)
Mecklenburg-Vorpommern	7 (< 1 %)	27.936 (1 %)
Bremen	2 (< 1 %)	19.635 (1 %)
Gesamt	*2005*	*2.659.516*

Verlauf einer SARS-CoV-2-Infektion bei Patienten mit verschiedenen ERE oder unter einer bestimmten Therapie besser abzuschätzen. Aus diesem Grund initiierte die DGRh bereits im März 2020 gemeinsam mit der Justus-Liebig-Universität Gießen ein Online-Register (www.covid19-rheuma.de), mit dessen Hilfe nachgewiesene SARS-CoV-2-Infektionen (positiver PCR- oder Antikörpertest) bei Patienten mit ERE innerhalb weniger Minuten erfasst werden können. Im Register werden u. a. folgende Aspekte erfasst: Bundesland, Alter, Geschlecht, Gewicht, Größe, Impfstatus (Grippe-, Pneumokokken- und SARS-CoV-2-Impfung), Komorbiditäten, Krankheitsaktivität und Therapie der rheumatischen Grunderkrankung zum Zeitpunkt der SARS-CoV-2-Infektion und deren Verlauf. Dieses bundesdeutsche Register soll auch dazu dienen, den Verlauf oder den Ausgang von COVID-19 bei Patienten mit ERE in Deutschland mit anderen Ländern vergleichen zu können, die sich z. B. im Hinblick auf die medizinische Versorgung und das jeweilige Gesundheitssystem unterscheiden [4].

Vernetzung des COVID-19-Rheuma Registers

Bereits bei der Konzeption des COVID19-Rheuma.de Registers wurde darauf geachtet, Inhalte und Datenbankstruktur so zu gestalten, dass die Daten auch mit anderen nationalen und internationalen Registern vergleichend ausgewertet werden können. Die Daten des deutschen Registers können so auch in das europäische Register (EULAR-COVID-19-Registry) sowie in das internationale Register (COVID-19-Global Rheumatology Alliance) übertragen werden, sodass keine Doppeleingabe der deutschen Patienten in die internationalen Register nötig ist. Aus dieser Zusammenarbeit resultierte bereits eine weitere, wichtige Publikation zu Faktoren, die mit einer verstärkten Hospitalisierung bei COVID-19 und ERE assoziiert sind [5]. Neben der Verbindung zu den anderen rheumatologischen COVID-19-Registern wurde eine Kooperation zwischen dem DGRh-Register und dem Lean European Open Survey on SARS-CoV-2 infected patients(LEOSS)-Register aufgebaut, welches SARS-CoV-2-Infektionen insgesamt europaweit erfasst [6]. Auf dieser Kooperation basierend, ist aktuell eine Analyse des Verlaufes einer SARS-CoV-2-Infektion bei rheumatologischen Patienten im Vergleich zu Patienten ohne ERE oder anderen Autoimmun-/Tumorerkrankungen geplant.

Analysen aus dem COVID-19-Rheuma Register im ersten Jahr der Pandemie

Im Rahmen der ersten Publikation zum COVID-19-Register erfolgten die Beschreibung des Aufbaus des DGRh-Registers sowie eine erste Analyse der Akzeptanz und Rekrutierung nach einem Dokumentationszeitraum von 4 Wochen [7]. In diesem Zeitraum, welcher v. a. die erste Welle der COVID-19-Pandemie in Deutschland umfasste, wurden 104 Patienten erfolgreich dokumentiert, und der Einsatz von GC kristallisierte sich als ein erster möglicher Risikofaktor für eine Hospitalisierung im Rahmen von COVID-19 heraus [7].

In der Folgepublikation mit zum damaligen Zeitpunkt 468 erfassten Patienten konnten Risikofaktoren hinsichtlich einer Hospitalisierung bei einer SARS-CoV-2-Infektion sehr viel genauer analysiert werden [8]. Hierbei wurden Patientenalter, kardiovaskuläre Komorbiditäten, chronisch interstitielle Lungenerkrankungen bzw. chronisch obstruktive Lungenerkrankungen und der Einsatz von GC als unabhängige Faktoren für die Notwendigkeit einer stationären Behandlung von COVID-19 bei Patienten mit ERE identifiziert. Besonders hervorzuheben war, dass auch die Krankheitsaktivität der ERE als ein unabhängiger Prädiktor für eine Hospitalisierung identifiziert werden konnte [8]. Dies zeigte sich auch in der Analyse der globalen Registerdaten, bei der eine erhöhte Krankheitsaktivität signifikant assoziiert war mit COVID-19-bedingter Mortalität [9]. Hierdurch ließ sich die Empfehlung der DGRh, bestätigen, dass eine adäquat immunmodulatorisch therapierte ERE ein geringeres Risiko für eine Hospitalisierung bzw. einen schweren Krankheitsverlauf bei einer SARS-CoV-2-Infektion haben dürfte [8, 9]. Eine rasch zunehmende Zahl von Publikationen zu COVID-19 generell und speziell bei Patienten mit ERE, hier insbesondere auch aus den Registern, war für die DGRh dann auch Anlass, die ersten Handlungsempfehlungen nach systematischer Literaturrecherche bereits Mitte 2020 zu aktualisieren [10].

Aktueller Stand des Registers

Aktuell sind im Register 2005 Patienten erfasst (Stand: 21.03.2021). Mehrheitlich stammen die eingeschlossenen Patienten aus den Bundesländern Bayern, Baden-Württemberg, Nordrhein-Westfalen und Hessen. Diejenigen Bundesländer, die in der Allgemeinbevölkerung höhere Zahlen von SARS-CoV-2-Infektionen aufweisen, sind im rheumatologischen Register ebenfalls stärker vertreten (◘ **Tab. 1**). Das mittlere Alter der 1348 Frauen, 655 Männer und 2 diversgeschlechtliche Personen beträgt 65 Jahre (Range 19 bis 96 Jahre). Die Haupterkrankungsbilder stellen die rheumatoide Arthritis (RA, 46%), die Spondyloarthritiden (SpA, 27%) einschließlich der Psoriasisarthritis und die Kollagenosen (12%) dar. Des Weiteren weisen 3% der eingeschlossenen Patienten eine ANCA(antineutrophile zytoplasmatische Antikörper)-assoziierte Vaskulitis auf (◘ **Abb. 1**). Mehrheitlich wurden die Patienten mit Methotrexat therapiert, gefolgt von GC und TNF-Inhibitoren (◘ **Abb. 2**). Positiv zu vermerken ist, dass aktuell 1630 Patienten bereits genesen sind, allerdings wurden auch 78 letale Verläufe gemeldet, die mehrheitlich in der zweiten Welle der Pandemie erfasst wurden (◘ **Abb. 3**).

Zusammenfassung · Abstract

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Deutsches Register www.Covid19-Rheuma.de. Statusbericht nach 1 Jahr der Pandemie

Zusammenfassung

Durch das COVID-19-Register (www.covid19-rheuma.de) der Deutschen Gesellschaft für Rheumatologie erfolgte erstmalig die Erfassung und systematische Evaluation einer viralen Infektion bei Patienten mit entzündlich rheumatischen Erkrankungen (ERE). Hierdurch war und ist eine schnelle Generierung von wissenschaftlichen Daten möglich, welche helfen, die Betreuung von Patienten mit ERE im Rahmen der Pandemie zu verbessern. Neben der Bestätigung allgemeiner Risikofaktoren – auch für Patienten mit ERE – wie Patientenalter und Komorbiditäten (z. B. kardiovaskuläre, chronische Lungen- und Nierenerkrankungen) konnten die Einnahme von Glukokortikoiden und die Krankheitsaktivität der rheumatischen Erkrankung als krankheitsspezifische Risikofaktoren für die Notwendigkeit einer stationären Behandlung wegen COVID-19 identifiziert werden. Auswertungen der kontinuierlich wachsenden Kohorte von Patienten mit entzündlich rheumatischen Erkrankungen und einer COVID-19-Infektion erlauben, Handlungsempfehlungen für die Betreuung der Patienten auf eine bessere Evidenz zu stützen. Die Kooperation mit internationalen rheumatologischen Registern (z. B. europäisches COVID-19-Register für ERE) ermöglicht Analysen aggregierter Kohortendaten von Patienten mit entzündlich rheumatischen Erkrankungen und einer SARS-CoV-2-Infektion für internationale Vergleiche und statistisch noch besser abgesicherte Aussagen.

Schlüsselwörter

Entzündlich-rheumatische Erkrankungen · Immunmodulation · SARS-CoV-2 · Glukokortikoide · Risikofaktoren

German registry www.Covid19-Rheuma.de. Status report after 1 year of the pandemic

Abstract

The COVID-19 registry (www.covid19-rheuma.de) of the German Society of Rheumatology was the first registry for the acquisition and systemic evaluation of viral infections in patients with inflammatory rheumatic diseases (IRD). This has enabled rapid generation of scientific data that will help to improve the care of patients with IRD in the context of the pandemic. In addition to confirming general risk factors, such as patient age and comorbidities (e.g. cardiovascular, chronic lung and kidney diseases), the use of glucocorticoids and the disease activity of the rheumatic disease could be identified as disease-specific independent risk factors for the need of hospitalization due to COVID-19. Evaluations of the continuously growing cohort of patients with IRD and COVID-19 enable recommendations for patient care to be based on better evidence. Cooperation with international rheumatology registries (e.g. European COVID-19 registry for IRD) enables analyses of aggregated cohorts of patients with IRD and COVID-19 for international comparisons and statistically even more reliable statements.

Keywords

Inflammatory rheumatic diseases · Immunomodulation · SARS-CoV-2 · Glucocorticoids · Risk factors

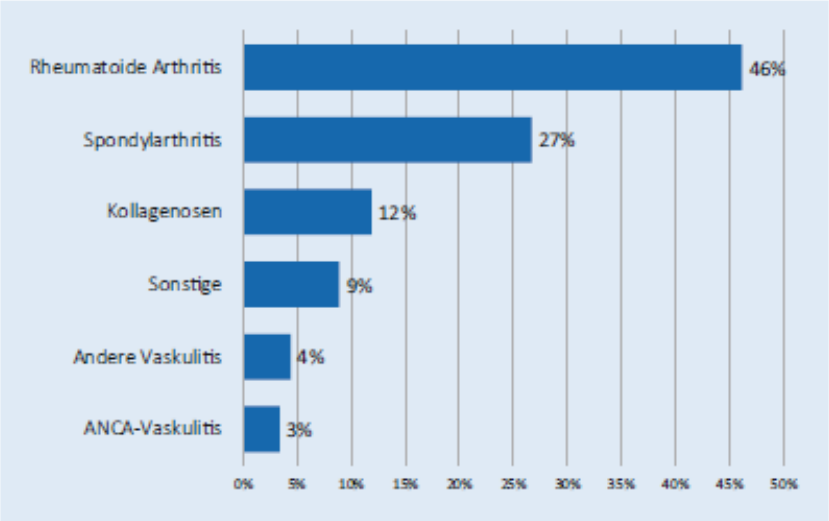

Abb. 1 ▲ Rheumatische Erkrankungen ($n = 2005$). Verteilung der häufigsten Diagnosen/Diagnosegruppen in dem deutschen COVID19-Rheuma Register (Stand 21.03.2021). Doppelnennungen möglich bei Overlap-Syndromen

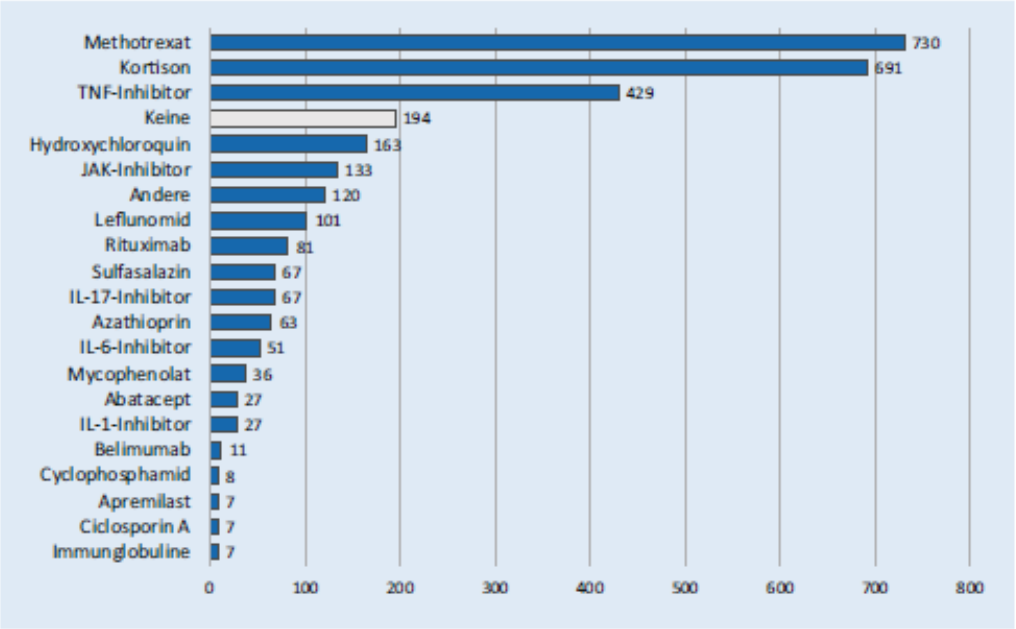

Abb. 2 ◄ Antirheumatische Medikation ($n = 2005$). Immunmodulation zum Zeitpunkt der SARS-CoV-2-Infektion (Stand 21.03.2021). Mehrfachauswahl der immunmodulatorischen Medikamente möglich

Aktuelle Publikationen und weitere Projekte

Zur Frage, inwieweit sich der Verlauf einer SARS-CoV-2-Infektion bei verschiedenen rheumatologischen Diagnosen unterscheidet, erfolgte in der aktuellsten Publikation aus dem Register eine erste Analyse der beiden größten Krankheitsgruppen: rheumatoide Arthritis (RA) und Spondyloarthritis (SpA) [11]. Hierbei wies die Gruppe der SpA eine niedrigere Hospitalisierungsrate (16% vs. 30%) auf. Dies könnte durch den geringeren Einsatz von GC bedingt sein, welche lediglich 13% der SpA-Patienten erhielten gegenüber 40% der RA-Patienten. Bezüglich der letalen Verläufe zeigte sich aber kein signifikanter Unterschied [11].

Flankierend wurde zu dem deutschen COVID-19-Register eine Online-Umfrage zu Auswirkungen der Corona-Pandemie auf Rheumapatientinnen und -patienten aufgesetzt, welche prospektiv über 1 Jahr versucht, die rheumatologische Versorgung und den Umgang der Patienten mit den Problemen, welche die Pandemie für diese mit sich bringt, zu erfassen. Zwischen April und Juli 2020 hatten sich insgesamt 695 Patienten eingeschrieben, sodass dieses Projekt im August 2021 ausgewertet werden kann.

Des Weiteren erfolgte im Februar und März 2021 eine Umfrage unter deutschen Rheumatologen, um deren Einstellung

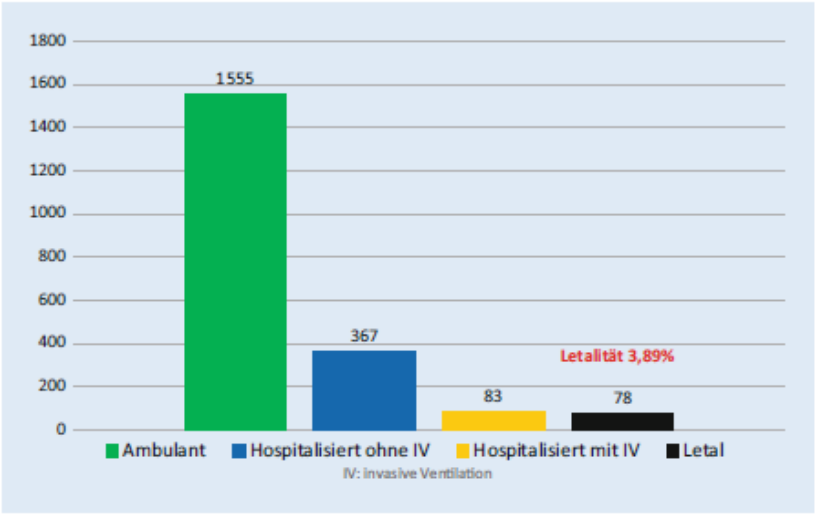

Abb. 3 ▲ Verläufe der SARS-CoV-2-Infektion im Rheumaregister. Letale Verläufe sind in hospitalisierte bzw. ambulante Patienten eingeschlossen

zur Corona-Impfung und zu dem Umgang mit Fragen ihrer Patienten zur Impfproblematik zu analysieren. Die Antworten von insgesamt 214 Ärztinnen und Ärzten werden derzeit ausgewertet.

Im Rahmen der aktuellen Aktivität der Ad-hoc-Kommission COVID-19 der DGRh erfolgt eine Erfassung von Corona-Impfungen bei Patienten mit ERE in einem separaten Impfregister. Darin werden Patienten mit ERE gebeten, Fragen zu Verträglichkeit, Sicherheit und Effektivität der COVID-19-Vakzinierung über einen Zeitraum von 12 Monaten in mehrfachen kurzen Online-Befragungen zu beantworten. Dieses Impfregister wurde Anfang Februar 2021 gestartet und umfasst bislang bereits 106 Patienten (Stand: 21.03.2021). Für Patienten, die nicht selbst an der Online-Impferfassung teilnehmen können, besteht die Möglichkeit einer papierbasierten Erhebung (Download des Formulars unter www.covid19-rheuma.de, **Infobox 1**).

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Danksagung. Die Erfassung der rheumatologischen Patienten mit einer SARS-CoV-2-Infektion im COVID-19-Register ist und war nur durch die Arbeit der dokumentierenden Ärztinnen und Ärzte, der medizinischen Fachangestellten und Studienpersonal möglich. Aktuell dokumentieren 324 Kolleginnen und Kollegen, medizinische Fachangestellte und Studienpersonal aktiv in das COVID19-Register. An dieser Stelle ist es der Ad-hoc-Kommission COVID-19 Register der DGRh ein ganz besonderes Anliegen, einen großen Dank an die Kolleginnen und Kollegen, medizinische Fachangestellten und Studienpersonal für die nicht vergütete Dokumentation der Patienten in das Register auszusprechen. Diese beispielhafte Aktivität der DGRh, durch die bereits wichtige Erkenntnisse aus der Pandemie für unsere Patienten gewonnen werden konnten, wäre ohne das große Interesse und Engagement unserer Kolleginnen und Kollegen nicht möglich gewesen. 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Einhaltung ethischer Richtlinien

Interessenkonflikt. R. Hasseli, A. Pfeil, B.F. Hoyer, H.-M. Lorenz, A.C. Regierer, J.G. Richter, T. Schmeiser, A. Strangfeld, R.E. Voll, A. Krause, H. Schulze-Koops, U. Müller-Ladner und C. Specker geben an, dass in Bezug auf die Arbeit am COVID19-Rheuma.de Register und dieser Publikation kein Interessenkonflikt besteht.

Für die Durchführung der Registerarbeit liegt ein positives Ethikvotum der Justus-Liebig-Universität Gießen (#52-50) vor, und sie wurde im Register für klinische Studien registriert (EuDRACT 2020-001958-21). Die Arbeit erfolgt gemäß der Deklaration von Helsinki.

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3.3 Erhöhtes Risiko für einen schweren Verlauf von COVID-19 unter Therapie mit Rituximab bei ERE – erste Fallberichte weltweit

Originalarbeit 5:

Schulze-Koops H, Krüger K, Vallbracht I, **Hasseli R**, Skapenko A. *Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab.*
Ann Rheum Dis. 2021 May;80(5):e67. doi: 10.1136/annrheumdis-2020-218075

Originalarbeit 6:

Schulze-Koops H, Krüger K, Vallbracht IV, **Hasseli R**, Skapenko A.
Treatment of patients with inflammatory rheumatic diseases with rituximab should be carefully considered during the SARS-CoV-2/COVID-19 pandemic. Response to: 'Persistence of rT-PCR-SARS-CoV-2 infection and delayed serological response, as a possible effect of rituximab according to the hypothesis of Schulze-Koops et al' by Benucci et al.
Ann Rheum Dis Epub ahead of print: downloaded on 06 June 2022, first published as 10.1136/annrheumdis-2020-218686 on 4 August 2020.

Zusammenfassung:

Zu Beginn der COVID-19-Pandemie war noch unbekannt, welchen Einfluss Immunmodulatoren auf das Risiko einer Infektion durch SARS-CoV-2 und deren Krankheitsverlauf nehmen können. Während einerseits u.a. das Robert-Koch-Institut PatientInnen mit ERE zur vulnerablen Gruppe hinsichtlich eines schweren COVID-19-Verlaufs zählte [193], wurden erste Fallberichte beispielsweise aus Italien und New York veröffentlicht, die darauf hindeuteten, dass ERE-PatientInnen unter Therapie mit Biologika kein höheres Risiko für einen schwereren COVID-19-Verlauf aufwiesen [194,195]. Zu diesem Zeitpunkt wurde bereits ein möglicher therapeutischer Effekt von Immunmodulatoren bei COVID-19 diskutiert. Obwohl die Idee einer potenziell schützenden Wirkung von Biologika bei COVID-19 Hoffnung erweckten, waren diese ersten Daten mit Vorsicht zu interpretieren, und vor allem für Rituximab gilt eine Sonderrolle durch seine B-Zell-hemmende Wirkung und lange Wirkdauer.

Aus diesem Grund wurde erstmalig weltweit der Verlauf von COVID-19 bei zwei Patientinnen mit einer rheumatoiden Arthritis unter einer Therapie mit Rituximab beschrieben (Originalarbeit *5*: SARS-CoV-2-Infektion & Rituximab). In beiden Fällen verlief COVID-19 tödlich. Die Patientinnen waren 71 Jahre und 80 Jahre alt, so dass auch das Alter zum schweren Verlauf beigetragen hatte. Trotz der Therapie mit Rituximab lag zuletzt der Immunglobulin G-Spiegel bei beiden PatientInnen im Normbereich. Die Patientinnen befanden sich zudem in Remission bezüglich ihrer Grunderkrankung. In beiden Fällen erfolgte eine stationäre Behandlung der Patientinnen mit der Notwendigkeit einer invasiven Beatmung. In einem der Fälle wurde sogar eine extrakorporale Zytokin-Adsorbtion durchgeführt. Innerhalb von 12 bzw. 17 Tage nach

stationärer Aufnahme verstarben beide Patientinnen an einem Multiorganversagen. Zu diesem Zeitpunkt wiesen PatientInnen im COVID19-Rheuma.de-Register unter Therapie mit Rituximab eine Hospitalisierungsrate von 67% auf [196]. Diese Befunde legen nahe, dass der Verlauf in den beiden beschriebenen Fällen keine unglückliche Ausnahme darstellt.

Basierend auf diesen ersten Daten und den beiden dargestellten Fällen, wurde die Empfehlung ausgesprochen, dass Rituximab bei ERE-PatientInnen nur unter besonderer Abwägung des Nutzen-Risiko-Profils im Kontext der Pandemie eingesetzt werden sollte [94]. Zusätzlich sollte vor Einleitung einer Therapie mit Rituximab bzw. erneuter Gabe von Rituximab eine SARS-CoV-2-Testung erfolgen. Eine Reduktion der begleitenden Glukokortikosteroiddosis zur Risikoreduktion sollte ebenfalls erwogen werden.

Die Veröffentlichung dieser beiden Fälle führte zu weiteren ähnlichen Beobachtungen. Zudem konnte bei ERE-PatientInnen unter Therapie mit Rituximab eine länger anhaltende Virämie nach Infektion durch SARS-CoV-2 nachgewiesen werden (). Obwohl noch weitere Daten zum Risiko von Rituximab während der COVID-19-Pandemie und zu den genauen Mechanismen dringend erforderlich waren, wurde empfohlen, das mögliche Risiko eines schweren COVID-19-Verlaufs unter Therapie mit Rituximab zu beachten und infizierte PatientInnen intensiver zu überwachen.

Die Deutsche Gesellschaft für Rheumatologie (DGRh) sprach basierend auf diesen Daten die Empfehlung aus, im Einzelfall abzuwägen, ob die Verabreichung von Rituximab verschiebbar oder ein Therapiewechsel möglich wäre [197].

Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab

It is currently unknown whether immunosuppressive and/or immunomodulating agents such as biological disease-modifying antirheumatic drugs (bDMARDs) affect the rate and the outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections of patients with inflammatory rheumatic diseases (IRDs). While several national authorities have defined patients under immunosuppressive therapy as at risk for severe COVID-19,[1] accumulating data from individual cases and also from case series, such as a series from Italy published in the *Annals of the Rheumatic Diseases* by Monti *et al*[2] and a report about patients with immune-mediated inflammatory diseases from New York,[3] suggest that baseline use of bDMARDs is not associated with worse COVID-19 outcome. Although the idea of a potentially protective effect of bDMRADs in COVID-19 is intriguing, we feel that extrapolation of these initial data is dangerous and potentially harmful. In particular, some caution may have to be applied when employing rituximab (RTX), a B-cell depleting bDMARD, in patients with immune-mediated disease. This notion may be illustrated by the following observations:

We recently lost two patients with rheumatoid arthritis (RA) treated with RTX to lethal COVID-19. The first patient, a 71-year-old man with rheumatoid factor positive, erosive RA and a history of mild chronic obstructive pulmonary disease was admitted to the hospital with symptoms of severe COVID-19. His RA was well controlled by RTX (2×1000 mg within 14 days every 6 months since 2015) in combination with methotrexate (MTX) 15 mg subcutaneously per week and he has been off daily glucocorticoids since 2017. RTX was well tolerated, no increased infection rate was noted and serum IgG was always within normal limits. As required by label, RTX was always administered with premedication including 50 mg prednisolone. Two weeks after the second RTX infusion in March 2020, the patient presented with a 2-day history of fever (up to 39.5°C), cough and chest pain. SARS-CoV-2 was proven and bilateral COVID-19 pneumonia was diagnosed by clinical examination and chest X-ray. Due to rapidly increasing dyspnoea and renal failure, the patient was transferred to the intensive care unit. Despite antibiotic treatment (piperacillin/tazobactam, followed by meropenem) and nasal high flow therapy, no improvement of the respiratory condition could be achieved. CT scan at that time showed bilateral pneumonia and reticular densifications. Invasive ventilation and increasing inotropic support were subsequently required due to further deterioration. Continuous veno-venous haemofiltration dialysis with cytosorb therapy was initiated. Despite all efforts, the patient died 12 days after admission in multiorgan failure.

The second patient, an 80-year-old woman with erosive RA and a history of mild hypertension and osteoporosis was started on treatment with RTX (2×1000 mg within 14 days) 6 months ago in combination with MTX 10 mg subcutaneously per week and 5 mg/day prednisolone. Her serum IgG was within normal limits. The patient presented to the hospital with sudden onset of fever (up to 39.5°C), dry cough, fatigue and dizziness. SARS-CoV-2 was proven and the patient rapidly deteriorated, requiring invasive ventilation. She developed acute respiratory distress syndrome and passed away despite intensive efforts 17 days after admission in multiorgan failure.

Sustained treatment of IRD with RTX is associated with a decrease in serum IgG and with an increased incidence of certain viral infections. However, COVID-19 has a mild clinically course in patients with agammaglobulinaemia,[4] suggesting that protection from severe COVID-19 may be rather independent of serum IgG. In this regard, our patients' serum IgG always was within normal limits. The lesson from our patients may rather argue that they might have been severely immunocompromised by the depletion of B cells and the application of prednisolone (as part of the premedication in patient 1 and as part of the daily treatment in patient 2). Supportive of this assumption is the aggressive course of COVID-19 in patients with common variable immunodeficiency[4] and the recent observation that glucocorticoids may impose a risk for requiring hospitalisation in patients with IRD infected with SARS-CoV-2.[3]

Our patients are not the unfortunate exceptions in that a substantial proportion of patients with IRD treated with RTX require hospitalisation when infected with SARS-CoV-2 (eg, 67% of the patients in the National Registry for patients with IRD infected with SARS-CoV-2 in Germany) (Hasseli *et al*, submitted for publication, 2020). Although successful treatment of granulomatosis with polyangiitis in a patient with COVID-19 with RTX has been reported,[5] RTX may need to be applied with particular caution in patients with IRD. Consequences for future management of patients with RTX therapy could be to perform a SARS-CoV-2 test before applying RTX, to consider reducing the dose of glucocorticoids during application of RTX (despite the requirement noted in the label) and to instruct the patient to strictly follow the measures in place to avoid contact for several days following RTX application.[1] The fatal outcome of COVID-19 in our patient illustrates the need to be extremely vigilant for the potential of complications associated with immunosuppressive therapy in patients with immune-mediated diseases.

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Treatment of patients with inflammatory rheumatic diseases with rituximab should be carefully considered during the SARS-CoV-2/COVID-19 pandemic. Response to: 'Persistence of rT-PCR-SARS-CoV-2 infection and delayed serological response, as a possible effect of rituximab according to the hypothesis of Schulze-Koops et al' by Benucci *et al*

We thank Dr Benucci *et al* for their comments[1] on our report on fatalities of patients with inflammatory rheumatic diseases (IRDs) treated with rituximab (RTX) during the SARS-CoV-2/COVID-19 pandemic.[2] The authors present a case of COVID-19 in a patient with myositis treated with RTX, who required assisted ventilation and eventually recovered after intensive care including invasive ventilation and medication with remdesivir, dexamethason and tocilizumab. While emphasising the potential of RTX to lead to severe courses of COVID-19, a particularly interesting aspect of the report is the complete absence of antibodies to SARS-CoV-2 even up to 4 weeks after discharge of the patient. The authors therefore conclude that RTX may be hazardous in the present pandemic as it may inhibit the humoral response to SARS-CoV-2 and contribute to secondary worsening of COVID-19.

The case of Dr Benucci reinforces our recommendation for caution and careful vigilance when considering treating patients with IRD with RTX in times of SARS-CoV-2. We had illustrated our concerns on two patients with RTX-treated rheumatoid arthritis who developed fatal COVID-19 and we had hypothesised that persistent B cell depletion and comedication with glucocorticoids may have resulted in severe combined cellular and humoral immunodeficiency. This assumption was based on the well-known association of RTX treatment with an increased risk for the development of viral infections, such as JC virus, hepatitis B virus or cytomegalovirus[3] and the aggressive course of COVID-19 in patients with common variable immunodeficiency.[4] Supporting our hypothesis is a recent publication on persistent SARS-CoV-2 viraemia in two rituximab-treated patients with severe COVID-19 pneumonia until death without any sign of viral clearance.[5] It is intriguing to speculate that a defect in viral clearance may underlie also the unusual course of COVID-19 in patients with IRD treated with RTX that was recently published: Three patients with systemic sclerosis routinely treated with RTX who were affected by COVID-19 and also a patient with granulomatosis with polyangiitis treated with RTX developed atypical late clinical worsening to severe pneumonia.[6 7] Whether these patients and the patients initially reported by us[2] also had a defect in viral clearance or even developed viraemia,[5] a rather unusual situation in viral respiratory diseases, and, if so, whether decreased viral clearance contributed to delayed clinical worsening in the reported clinical cases is unknown. These cases, however, highlight the possibility that rituximab is associated with a specific risk in SARS-CoV-2 infections and in the outcome of COVID-19. Current data from the National Registry for patients with IRD infected with SARS-CoV-2 in Germany support the contention of such a risk as in this registry, 11 out of 18 patients (61.1%) treated with RTX required hospitalisation, with 9 of the 18 patients (50%) required ventilation, whereas only 28 out of 95 patients (28.6%) treated with biological disease modifying anti-rheumatic drugs (bDMARDs) needed hospital care and only 12 (12.2%) required ventilation (Hasseli *et al*, submitted for publication, 2020). While further data on the risk of RTX during the SARS-CoV-2/COVID-19 pandemic and its precise mechanisms are urgently required, physicians should be aware of the potential of RTX-associated severe courses of the infection and remain to be extremely vigilant and cautious when considering RTX treatment.

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Correspondence response

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3.4 Einflussfaktoren für einen schweren COVID-19-Verlauf bei entzündlich-rheumatischen Erkrankungen

Originalarbeit 7:

Hasseli R, Müller-Ladner U, Hoyer BF, Krause A, Lorenz HM, Pfeil A, Richter J, Schäfer M, Schmeiser T, Strangfeld A, Schulze-Koops H, Voll RE, Specker C, Regierer AC.
Older age, comorbidity, glucocorticoid use and disease activity are risk factors for COVID-19 hospitalisation in patients with inflammatory rheumatic and musculoskeletal diseases.
RMD Open. 2021 Jan;7(1):e001464. doi: 10.1136/rmdopen-2020-001464

Originalarbeit 8:

Strangfeld A, Schäfer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, Mateus EF, Richez C, Santos MJ, Schmajuk G, Scirè CA, Sirotich E, Sparks JA, Sufka P, Thomas T, Trupin L, Wallace ZS, Al-Adely S, Bachiller-Corral J, Bhana S, Cacoub P, Carmona L, Costello R, Costello W, Gossec L, Grainger R, Hachulla E, **Hasseli R**, Hausmann JS, Hyrich KL, Izadi Z, Jacobsohn L, Katz P, Kearsley-Fleet L, Robinson PC, Yazdany J, Machado PM; COVID-19 Global Rheumatology Alliance.
Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry.
Ann Rheum Dis. 2021 Jul;80(7):930-942. doi: 10.1136/annrheumdis-2020-219498

Zusammenfassung:

Um die Frage zu beantworten, welchen COVID-19-Verlauf PatientInnen mit ERE aufweisen und ob sich weitere Risikofaktoren identifizieren lassen, erfolgte eine erneute Auswertung der Daten des COVID19-Rheuma.de-Registers (Originalarbeit 7). Bis November 2020 wurden 468 Fälle im Register erfasst. Weiterhin litten die PatientInnen mehrheitlich an einer rheumatoiden Arthritis (48%) gefolgt von PatientInnen mit Spondyloarthritiden (27%). Im Median waren die PatientInnen 57 Jahre alt. Eine COVID-19-assoziierte Hospitalisierung wurde bei 29% der Fälle beschrieben, wovon 5,5% eine invasive Beatmung benötigten. Es wurden 19 letale Fälle berichtet. Eine Monotherapie mit Basismedikamenten, wie z.B. Methotrexat, wurde bei 41% der Fälle berichtet, Biologika waren bei 36% im Einsatz. Eine Therapie mit Glukokortikosteroiden erfolgte bei 39% der PatientInnen, wovon 8% mehr als 5 mg Prednisolon pro Tag erhielten. In der multivariablen Analyse waren das Alter (über 65 Jahre (Odds Ratio (OR) 2,2; 95% Konfidenzintervall (CI) 1,1 – 4,5), kardiovaskuläre Erkrankungen (OR 3,4; 95% CI 1,5 – 7,6), interstitielle Lungenerkrankungen/chronisch obstruktive Atemwegserkrankungen (OR 2,8; 95% CI 1,2 - 6,5), chronische Niereninsuffizienz (OR 3,0; 95% CI 1,2 – 7,5), moderate/hohe Krankheitsaktivität (OR 2,0; 95% CI 1,0 – 3,8) und der Einsatz von Glukokortikosteroiden in einer Dosierung von mehr als 5 mg Prednisolon täglich (OR 3,7; 95% CI 1,5 – 9,1) mit einer vermehrten Hospitalisierung assoziiert. Somit waren neben den Faktoren Alter und Begleiterkrankungen, die auch in der Allgemeinbevölkerung

eine wichtige Rolle für einen schweren COVID-19-Verlauf spielen, die Krankheitsaktivität und der Einsatz von Glukokortikosteroiden mit einer Dosierung > 5 mg Prednisolon täglich mit schweren COVID-19-Verläufen assoziiert. Diese Erkenntnis war bis dahin erstmalig beschrieben worden und untermauerte zusätzlich die Empfehlung der Deutschen Gesellschaft für Rheumatologie, mithilfe der steroidfreien Immunmodulatoren eine Remission der ERE zu erzielen und somit das Risiko für einen schweren Verlauf zu reduzieren.

Da es sich bei der Auswertung um eine überschaubare Patientenanzahl handelte und zudem nur die Lage in Deutschland widerspiegelt, erfolgte ein Datentransfer in das europäische bzw. globale Register. Aufgrund der frühen Anpassung der Datenbank konnte ohne relevanten Datenverlust ein Export der Fälle erfolgen. Der Export erfolgte ebenfalls anonym ohne Rückschlüsse zu den dokumentierenden ÄrztInnen. In dieser internationalen Auswertung wurden während des Zeitraums März bis Juli 2020 3729 Fälle dokumentiert (Originalarbeit *8*). Hierbei lag der Fokus auf der Untersuchung von Parametern, die mit einem tödlichen Verlauf von COVID-19 assoziiert waren. Das Alter lag im Median bei 57 Jahren. Die Letalität war in der gepoolten Analyse höher (10,5%). Faktoren, wie z.B. Alter über 65 Jahre, kardiovaskuläre Erkrankungen und Lungenerkrankungen, waren auch in der gepoolten Analyse mit einem erhöhten Risiko für einen tödlichen COVID-19-Verlauf bei ERE assoziiert.

Eine moderate/hohe Krankheitsaktivität zeigte eine statistische Assoziation mit tödlichen Verläufen auf (OR 1,9; 95% 1,3 – 2,8). Der Einsatz von Rituximab (OR 4,0; 95%CI 2,3 – 7,0), Sulfasalazin (OR 3,6; 95%CI 1,7 – 7,8) und Immunsuppressiva (Azathioprin, Cyclophosphamid, Ciclosporin A, Mycophenolat, Tacrolimus; OR 2,2; 95%CI 1,4 – 3,5) war im Vergleich zu einer Monotherapie mit Methotrexat ebenfalls mit tödlichen Verläufen assoziiert. Interessanterweise war auch eine statistische Assoziation bei ERE-PatientInnen ohne jegliche immunmodulatorische Therapie zum Zeitpunkt der Infektion mit tödlichen Verläufen nachweisbar (OR 2,1; 95%CI 1,5 – 3,0). Bei den übrigen Biologika und Januskinase-Inhibitoren ergab sich zu diesem Zeitpunkt kein Hinweis für eine Einflussnahme auf den Verlauf einer SARS-CoV-2-Infektion bei ERE-PatientInnen, jedoch wurden insgesamt auch nur 141 Personen unter einer Januskinase-Hemmung bis dahin erfasst.
Bezüglich der ERE waren somit die Krankheitsaktivität, sowie bestimmte Therapeutika mit einem tödlichen Verlauf von COVID-19 assoziiert.

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Older age, comorbidity, glucocorticoid use and disease activity are risk factors for COVID-19 hospitalisation in patients with inflammatory rheumatic and musculoskeletal diseases

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ABSTRACT

Introduction Whether patients with inflammatory rheumatic and musculoskeletal diseases (RMD) are at higher risk to develop severe courses of COVID-19 has not been fully elucidated. Aim of this analysis was to describe patients with RMD according to their COVID-19 severity and to identify risk factors for hospitalisation.

Methods Patients with RMD with PCR confirmed SARS-CoV-2 infection reported to the German COVID-19 registry from 30 March to 1 November 2020 were evaluated. Multivariable logistic regression was used to estimate ORs for hospitalisation due to COVID-19.

Results Data from 468 patients with RMD with SARS-CoV-2 infection were reported. Most frequent diagnosis was rheumatoid arthritis, RA (48%). 29% of the patients were hospitalised, 5.5% needed ventilation. 19 patients died. Multivariable analysis showed that age >65 years (OR 2.24; 95% CI 1.12 to 4.47), but even more>75 years (OR 3.94; 95% CI 1.86 to 8.32), cardiovascular disease (CVD; OR 3.36; 95% CI 1.5 to 7.55), interstitial lung disease/chronic obstructive pulmonary disease (ILD/COPD) (OR 2.79; 95% CI 1.2 to 6.49), chronic kidney disease (OR 2.96; 95% CI 1.16 to 7.5), moderate/high RMD disease activity (OR 1.96; 95% CI 1.02 to 3.76) and treatment with glucocorticoids (GCs) in dosages >5 mg/day (OR 3.67; 95% CI 1.49 to 9.05) were associated with higher odds of hospitalisation. Spondyloarthritis patients showed a smaller risk of hospitalisation compared with RA (OR 0.46; 95% CI 0.23 to 0.91).

Conclusion Age was a major risk factor for hospitalisation as well as comorbidities such as CVD, ILD/COPD, chronic kidney disease and current or prior treatment with GCs. Moderate to high RMD disease activity was also an independent risk factor for hospitalisation, underlining the importance of continuing adequate RMD treatment during the pandemic.

Key messages

What is already known about this subject?

- Due to systemic inflammatory conditions and immunomodulating treatment, rheumatic and musculoskeletal disease (RMD) patients might be at increased risk of a more severe course of SARS-CoV-2 infection.
- Only limited data on risk factors for a critical course of COVID-19 in patients with RMD are available.

What does this study add?

- Age, comorbidities (cardiovascular disease, interstitial lung disease/chronic obstructive pulmonary disease and chronic kidney disease), the use of glucocorticoids for the treatment of RMD and RMD disease activity are independent risk factors for COVID-19 hospitalisation.

How might this impact on clinical practice?

- Adequate treatment of RMD with control of disease activity is crucial for the management of our patients during the pandemic.
- Patients with RMD with risk factors identified with this analysis should be closely monitored and receive guidance about infection risk minimising behaviour.

INTRODUCTION

In Germany, the first cases of SARS-CoV-2 infection (COVID-19) were reported at the end of January 2020.[1] Similar to other European countries, SARS-CoV-2 spread rapidly in Germany. The course of infection with SARS-CoV-2 ranges from asymptomatic to fatal. In the general population, higher age, male gender and comorbidities are associated with the severity of SARS-CoV-2 infection.[2 3] Since the outbreak of the pandemic,

concerns have been raised regarding the probability of developing a severe or even life-threatening course in patients with inflammatory rheumatic and musculoskeletal diseases (RMD).[4–6] Patients with RMD are characterised by an overall increase in risk of infection due to the autoimmune disease itself and immunomodulatory drugs.[7–9] The risk of infection is dependent on age, functional capacity, comorbidities and immunomodulatory treatment with biological disease-modifying antirheumatic drugs (bDMARDs) and glucocorticoids (GC).[10] Immunomodulatory drugs with anti-inflammatory action may limit overwhelming immune responses that appear to be responsible for the severe pulmonary complications in COVID-19.[11 12] However, not all immunomodulatory treatments seem to influence the risk for a critical course in the same direction. Whereas registry data had shown a beneficial effect of biological DMARDs regarding the development of sepsis and mortality in patients with rheumatoid arthritis (RA) and serious infections, it had also shown a significantly increased risk conveyed with GCs.[13] Data from the COVID-19 Global Rheumatology Alliance (GRA) physician-reported registry indicate that GC ≥10 mg/day are associated with a higher hospitalisation rate with SARS-CoV-2 infection in patients with RMD,[14] which underlines the importance of controlling disease activity with DMARDs in order to decrease GC dose.

Furthermore, the recommendations from EULAR and DGRh (German Society for Rheumatology) state that immunomodulating therapy should be maintained during the SARS-CoV-2 pandemic to avoid RMD relapse.[15 16]

Limited data are available as for whether and to what extent patients with RMD are at an increased risk for SARS-CoV-2 infection[11 17 18] and for a more severe course of COVID-19. For this reason, a national registry was established allowing a rapid and timely collection of RMD cases with confirmed SARS-CoV-2 infections in Germany in order to analyse the clinical course of COVID-19 in patients with RMD and to develop guidance for the management of patients with RMD during the COVID-19 pandemic.[19] The aim of this analysis was to identify risk factors for hospitalisation, comparing non-hospitalised patients with RMD to hospitalised patients, stratified by the need for invasive ventilation.

METHODS

Data source

In March 2020, the German Society for Rheumatology, together with the Justus-Liebig-University Giessen, founded a national registry for patients with pre-existing inflammatory rheumatic diseases (RMD) and SARS-CoV-2 infection confirmed by PCR test. Rheumatologists voluntarily enter the data into an online database with implemented plausibility checks (URL https://www.covid19-rheuma.de).

The ascertained data include SARS-CoV-2 infection-specific items such as symptoms, duration, treatment and outcome, RMD specific items such as diagnosis, physician assessed disease activity (categorised into remission, low, moderate or high disease activity), and treatment of RMD, and general items such as sociodemographic information and comorbidities. Missing data on diagnosis and treatment of RMD and outcome of COVID-19 can be queried by contacting participating physicians. Data collection was done retrospectively. Participating centres consist of academic and non-academic rheumatology departments and private practices in Germany.

The German registry's content is harmonised with the EULAR COVID-19 database (https://www.eular.org/eular_covid19_database.cfm) to allow joint analysis. The study is registered at EuDRACT 2020-001958-21#.

Statistical analysis

Descriptive statistics were applied to compare non-hospitalised patients with hospitalised patients, either without or with invasive ventilation.

Multivariable logistic regression was used to estimate odds ratios (OR) and 95% CIs for the main outcome parameter of this analysis, which is hospitalisation due to COVID-19 as indicator for severity of the SARS-CoV-2 infection. Simple logistic regressions with one explanatory variable were performed to determine the set of regressors for the multivariable regression. Variables with a $p<0.1$ were included in the final model. Covariates included in the model were age group, rheumatic disease group (RA, spondyloarthritis, connective tissue diseases (CTDs) and vasculitis, other rheumatic diseases), inflammatory activity of the rheumatic disease, specific comorbidities (cardiovascular disease (CVD), hypertension without CVD, interstitial lung diseases (ILD) or chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic kidney disease, cancer), prior and/or current use of GC (none, up to 5 mg/day, over 5 mg/day). Spondyloarthritides included psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) and enteropathic arthritis. CTDs and vasculitis included systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, mixed CTDs, overlap syndromes, polymyalgia rheumatica, granulomatosis with polyangiitis (GPA), eosinophilic GPA, microscopic polyangiitis, large vessel vaculitis, Behçet's disease and other types of vasculitis. For patients belonging to more than one rheumatic disease category, we used the following hierarchy for prioritisation: CTD/vasculitis>RA>spondyloarthritides>other rheumatic diseases. In this way, disjoint categories are created, establishing a clear reference group for interpretation of the regression model and avoiding collinearities. In order to avoid collinearity between CVD and hypertension, hypertension in the model refers to patients who had hypertension but not CVD. Missing values for obesity, disease activity state, GC dose and non-steroidal antirheumatic agents were derived by multiple imputation using full conditional specification.[20] Results of the logistic regression analyses for 10 imputed datasets were pooled by

Table 1 Patient characteristics stratified for non-hospitalisation, hospitalisation without ventilation and hospitalisation with invasive ventilation

Parameter	Non-hospitalised	Hospitalised without invasive ventilation	Hospitalised with invasive ventilation	Total
N	**332 (70.9)**	**110 (23.5)**	**26 (5.5)**	**468**
General				
Age (years)	54 (19)	66 (21)	66.5 (15)	57 (19)
Male sex	111 (33.5)	35 (31.8)	13 (50)	159 (34)
Duration of symptoms (days)	12 (9)	17 (13)	32.5 (12)	14 (13)
Smoking	27 (8.1)	10 (9.1)	3 (11.5)	40 (8.5)
Further outcomes				
Death	1 (0.3)	5 (4.5)	13 (50)	19 (4.1)
ARDS	0	1 (0.9)	15 (57.7)	16 (3.4)
Sepsis	0	1 (0.9)	14 (53.8)	15 (3.2)
RMD				
Moderate/high RMD disease activity	35 (10.5)	29 (25.9)	9 (33.5)	72 (15.4)
RA	146 (44)	62 (56.4)	17 (65.4)	225 (48.1)
Spondyloarthritides	105 (31.6)	15 (13.6)	5 (19.2)	15 (26.7)
Connective tissue diseases/vasculitis	65 (19.6)	31 (28.2)	7 (26.9)	103 (22)
Other RMD diagnoses	26 (7.8)	8 (7.3)	1 (3.8)	35 (7.5)
Comorbidities				
No of comorbidities	0 (1)	1 (2)	2 (2)	1 (2)
Arterial hypertension	92 (27.7)	48 (43.6)	16 (61.5)	156 (33.3)
Cardiovascular disease	16 (4.8)	25 (22.7)	8 (30.8)	49 (10.5)
Interstitial lung disease	6 (1.8)	3 (2.7)	2 (7.7)	11 (2.4)
Chronic obstuctive pulmonary disease	7 (2.1)	12 (10.9)	6 (23.1)	25 (5.3)
Asthma	31 (9.3)	9 (8.2)	1 (3.8)	41 (8.8)
Chronic kidney disease	9 (2.7)	21 (19.1)	2 (7.7)	32 (6.8)
Cancer	11 (3.3)	11 (10)	1 (3.8)	23 (4.9)
Obesity (BMI ≥30 kg/m^2)	59 (17.6)	25 (22.4)	5 (18.5)	88 (18.8)
Diabetes	27 (8.1)	18 (16.4)	3 (11.5)	48 (10.3)
Osteoporosis	19 (5.7)	14 (12.7)	1 (3.9)	34 (7.3)
No comorbidity	154 (46.4)	19 (17.3)	3 (11.5)	176 (37.6)
Therapy				
No DMARD	58 (17.5)	26 (23.6)	5 (19.2)	89 (19)
csDMARD mono	137 (41.3)	49 (44.5)	7 (26.9)	193 (41.2)
tsDMARD	11 (3.3)	6 (5.5)	2 (7.7)	19 (4.1)
bDMARD	126 (38)	29 (26.4)	12 (46.2)	167 (35.7)
TNFi	91 (27.4)	13 (11.8)	2 (7.7)	106 (22.6)
ABA	4 (1.2)	3 (2.7)	1 (3.8)	8 (1.7)
B-cell depletion	10 (3)	7 (6.4)	7 (26.9)	24 (5.1)
IL1i	1 (0.3)	0	0	1 (0.2)
IL6i	6 (1.8)	2 (1.8)	2 (7.7)	10 (2.1)
Other ILi	14 (4.2)	4 (3.6)	0	18 (3.8)
Glucocorticoids	103 (31)	59 (53.6)	18 (69.2)	180 (38.5)
Glucocorticoids ≤5 mg/day	91 (27.3)	42 (38.2)	12 (46.2)	145 (30.9)
Glucocorticoids >5 mg/day	12 (3.7)	17 (15.5)	6 (23.1)	35 (7.6)

Continued

Table 1 Continued

Parameter	Non-hospitalised	Hospitalised without invasive ventilation	Hospitalised with invasive ventilation	Total
N	332 (70.9)	110 (23.5)	26 (5.5)	468
Other RMD medication	6 (1.8)	11 (10)	4 (15.4)	21 (4.5)
NSAID	84 (25.4)	23 (21.3)	3 (11.9)	111 (23.7)
Anti hypertension drugs	67 (20.2)	35 (31.8)	15 (57.7)	117 (25)

For continuous variables, median (IQR) is given, for categorical variables, N (%) is given. The following numbers of missing values exist: 88 (18.8%) for duration of symptoms, 51 (10.9%) for obesity, 31 (6.6%) for disease activity state, 1 for glucocorticoid dose (0.6%, among patients receiving glucocorticoids) and 33 (7.1%) for non-steroidal antirheumatic agents. Absolute numbers may be rounded for some variables due to multiple imputation. Collagenoses include Sjögren syndrome, systemic sclerosis, mixed collagenoses, overlap_collagenoses and polymyositis/dermatomyositis/inclusion body myositis. Other RMD include fibromylagia, sarcoidosis, TRAPS, FMF and adult-onset Still's disease. Other RMD medication include colchicine, mesalazine, and mucofenolate.
ABA, abatacept; ARDS, acute respiratory distress syndrome; bDMARD, biological DMARD; BMI, body mass index; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; RMD, rheumatic and musculoskeletal disease; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic DMARD.

Rubin's rules. Calculations were carried out with the software packages SAS, V.9.4, and R, V.3.6.3.

RESULTS

Patients characteristics

Between March 30 (first patient in) and 1 November 2020 (database lock), 468 patients with RMD and a PCR-confirmed SARS-CoV-2 infection were documented in the German registry, 309 patients were female. Median age was 57 years. Regarding RMD diagnosis, RA was most common with 48%, followed by 14% PsA, and 12% axSpA.

Patient characteristics are shown in table 1, stratified into the three groups: non-hospitalised patients, hospitalised patients without or with need for invasive ventilation. The following numbers of missing values exist: 88 (18.8%) for duration of COVID-19 symptoms, 51 (10.9%) for obesity, 31 (6.6%) for inflammatory activity state, 1 for GC dose (0.6%, among patients receiving GCs) and 33 (7.1%) for non-steroidal antirheumatic drugs. There was no missing data on outcome of SARS-CoV-2 infection, so all patients either fully recovered or died.

Of the 468 patients, 136 (29%) were hospitalised of whom 26 (5.5%) needed invasive ventilation. 19 patients died, resulting in a case fatality rate of 4%. Eighteen of these patients died in the hospital, 13 had received invasive ventilation.

Most patients with RMD had comorbidities; only 38% did not have any other chronic condition. The most frequent comorbidity was arterial hypertension, followed by obesity, CVD and diabetes.

Regarding RMD treatment, 19% of the patients did not receive any DMARD. Thirty-six per cent were on bDMARDs and 41% on conventional synthetic (cs) DMARD monotherapy. Thirty-nine per cent of the patients were on GC treatment, most of them (81%) received low dose GCs of ≤5 mg/day.

Comparison of non-hospitalised patients with hospitalised patients without ventilation and hospitalised patients with invasive ventilation

The percentage of men was larger among hospitalised patients with ventilation (50%) compared with those without ventilation (32%) or non-hospitalised (34%) (table 1).

Forty-four per cent of the non-hospitalised patients suffered from RA, compared with 56% and 65% in the hospitalised groups. According to physicians' assessments, moderate to high RMD disease activity was present in 11% of the non-hospitalised patients, 26% in the hospitalised patients without ventilation and 34% in the ventilated patients.

Regarding RMD treatment, 18% of the non-hospitalised patients did not receive any DMARD compared with 24% and 19% in the hospitalised groups. Tumour necrosis factor inhibitors were documented as RMD treatment in 27% of the non-hospitalised patients, in 12% of the hospitalised group without ventilation and 8% in the ventilated patients. Twenty-seven per cent of the ventilated patients were on B-cell-depletion treatment, whereas only 3% of the non-hospitalised and 6% of the hospitalised patients without ventilation had received B-cell-depleting treatment.

Factors associated with hospitalisation

Results of the univariate analyses comparing non-hospitalised patients with hospitalised patients are shown in table 2.

The results of the multivariable model are shown in figure 1 and online supplemental table 1). Age>65 years (OR 2.24; 95% CI 1.12 to 4.47), but even more>75 years (OR 3.94; 95% CI 1.86 to 8.32), CVD (OR 3.36; 95% CI 1.5 to 7.55), lung disease (ILD/COPD) (OR 2.79; 95% CI 1.2 to 6.49) and chronic kidney disease (OR 2.96; 95% CI 1.16 to 7.5) were associated with higher

Table 2 OR of COVID-19 hospitalisation in univariate analyses of patients with RMD

Variable	OR	95% CI	P value
Age 66–75 years	2.470	1.393 to 4.378	0.0020
Age >75 years	7.269	3.983 to 13.263	<0.0001
Gender, male	1.081	0.711 to 1.644	0.7155
Current smoking	1.194	0.596 to 2.390	0.6167
Moderate to high RMD disease activity	3.203	1.879 to 5.461	<0.0001
RMD diagnosis			
spondyloarthritides (reference: RA)*	0.333	0.185 to 0.599	0.0002
CTDs/vasculitis (reference: RA)*	0.882	1.936 to 1.505	0.6438
other RMDs (reference: RA)*	1.283	0.674 to 2.443	0.4473
Comorbidities			
Cardiovascular disease	6.327	3.346 to 11.966	<0.0001
Art. hypertension	1.508	0.975 to 2.331	0.0647
ILD/COPD	4.994	2.448 to 10.191	<0.0001
Asthma	0.771	0.367 to 1.619	0.4916
Chronic kidney disease	7.305	3.283 to 16.255	<0.0001
Obesity (BMI ≥30 kg/m^2)	1.283	0.767 to 2.145	0.3419
Diabetes	2.063	1.122 to 3.794	0.0198
Cancer	2.568	1.086 to 6.074	0.0318
RMD treatment			
No DMARD (reference: csDMARDs)	1.308	0.765 to 2.234	0.3264
B/tsDMARD (reference: csDMARD)	0.875	0.558 to 1.373	0.5614
Glucocorticoids ≤5 mg/day (reference: no glucocorticoids)†	1.755	1.153 to 2.671	0.0087
Glucocorticoids >5 mg/day (reference: no glucocorticoids)†	5.250	2.533 to 10.881	<0.0001
NSAID	0.710	0.429 to 1.175	0.1825

For each variable, a separate logistic regression analysis was run containing only an intercept term and the variable in question. For disease activity, obesity, glucocorticoid use and NSAID, missing values were imputed 10 times and the analysis was conducted on each imputation stratum. Subsequently, combined results were obtained following Rubin's rules. Variables presenting a p<0.1 were entered into the multivariable model.
*The variable RMD diagnosis is jointly represented by three dummy regressors.
†The variable glucocorticoid use is jointly represented by two dummy variables.
.BMI, body mass index; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DMARD, disease-modifying antirheumatic drug; ILD, interstitial lung disease; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; RMD, rheumatic and musculoskeletal disease.

odds of hospitalisation. Patients with spondyloarthritides showed a lower risk of hospitalisation compared with RA (OR 0.46; 95% CI 0.23 to 0.91). Moderate to high RMD disease activity was furthermore significantly associated with hospitalisation (OR 1.96; 95% CI 1.02 to 3.76), as well as treatment with GC in dosages>5 mg/day (OR 3.67; 95% CI 1.49 to 9.05).

DISCUSSION

In the challenging situation of the SARS-CoV-2 pandemic, physicians and patients need rapid access to the evolving evidence to close the gaps of knowledge which are stressful for patients with chronic conditions. When the pandemic started, it was unclear whether patients with RMD are at an increased risk to get infected or whether they have a higher risk of a severe course of COVID-19. In this analysis, hospitalisation was used as indicator for a more severe course. Older age, CVD, ILD/COPD, chronic kidney disease, treatment with GC at doses of >5 mg/day, and moderate to high RMD disease activity were identified as independent risk factors for hospitalisation.

Our results are in line with the recently published analysis of the GRA.[14] In the GRA analysis, the cases from the German registry had not yet been included, so these two cohorts are independent. Similar results have also been found in a meta-analysis on autoinflammatory diseases including RMDs.[21]

Age seems to be the most important factor associated with a more severe course of COVID19[2 3 22 23] and this

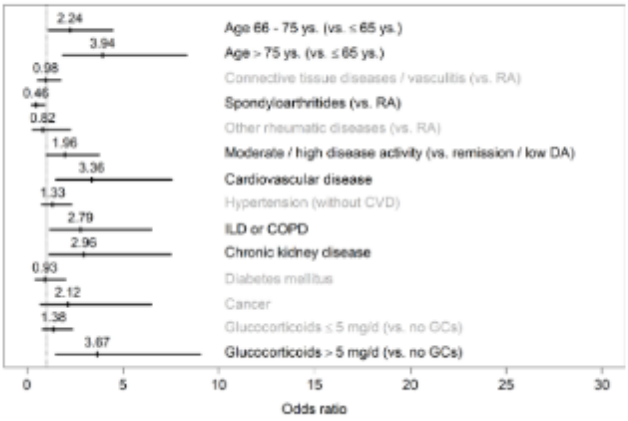

Figure 1 Multivariable logistic regression was used to estimate ORs and 95% CIs for the main outcome parameter of this analysis, hospitalisation due to COVID-19 versus non-hospitalisation as indicator for severity of the SARS-CoV-2 infection. COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DA, disease activity; GC, glucocorticoid; ILD, interstitial lung disease; RA, rheumatoid arthritis.

holds also true for patients with RMD as described in our analysis and other reports.[24–28]

Importantly, moderate to high RMD disease activity was identified as an independent risk factor for hospitalisation. This is an important finding, not only in that this is a risk factor specifically related to RMDs but also with implications for the daily management, reaffirming recent recommendations that state the importance of RMD disease control during the pandemic.[15 16]

The influence of comorbidities is also widely recognised since the first reports of COVID-19.[29] In our cohort, CVD, ILD/COPD and chronic kidney disease were significantly associated with hospitalisation. Interestingly, asthma was not associated with an increased risk as was also described in the UK.[3] This is in accordance with an asthma-specific analysis where the authors did not find an association of asthma with hospitalisation.[30] This effect is in contrast to other pulmonary comorbidities such as ILD and COPD.

In our cohort, prior or current treatment with GC was associated with a high risk of hospitalisation in accordance with the GRA analysis[14] and with previous evidence of an increased infection risk in general.[10]

The interpretation of the influence of GC treatment on hospitalisation has to be performed with caution. There is a probability of confounding by indication since GC are given under certain circumstances which may influence the outcome itself like a high disease activity of the RMD. Since uncontrolled RMD activity also enhances the risk of infections, our results should not encourage stopping GC treatment. However, GC should be administered in the lowest possible dose, as recommended by the recently published guidance for the management of COVID-19 in RMD,[15 16] as already a dose of >5 mg/day was associated with an increased risk of hospitalisation in our study.

Male gender has also been described as an important risk factor for a more severe course and higher mortality.[3 23] In our analysis, male gender was not associated with hospitalisation. This was also the case in the GRA analysis.[14] However, regarding the results of the descriptive analysis (table 1), male gender was much more common in the group of ventilated patients compared with the other patients. As already described in the general population, male gender might therefore be associated with a worse outcome also in patients with RMD.[3 23 31]

Comparing the results from RMD with chronic inflammatory bowel disease (IBD), interesting parallels can be found. In the first analysis of the international registry for patients with IBD and confirmed SARS-Cov-2 infection, similar risk factors associated with worse COVID-19 outcome were identified, namely older age, number of comorbidities and use of systemic GC.[32]

The strengths of our study include the large sample size with PCR confirmed SARS-CoV-2 infections in patients with RMD. As all patients were treated in Germany, both the healthcare system and treatment strategies for COVID-19 were comparable in all cases, reducing confounding due to differences regarding these factors as might be present in analyses including patients from many countries. The completeness of data is high with only a small percentage of missing values. Particularly, the outcome 'hospitalisation' was known in all cases, as all cases were documented after full recovery or death of patient.

A limitation of our study is the observational design, which is prone to confounding by indication. For example, it is possible that patients taking GCs might be hospitalised more often because of the potential risk of a more severe outcome of the infection. Also, a potential influence of the SARS-CoV-2 infection on the course of the RMD cannot be assessed based on our data because of the cross-sectional design. Only few details of the RMD are known, as factors like disease duration, functional capacity or treatment history are not captured in the registry.

Although this is one of the largest RMD COVID-19 cohorts published so far, the number of cases was still too low to include specific RMD treatments into the multivariable analysis. With increasing numbers of patients, these analyses will probably become possible in the near future.

Another limitation is that possibly more severe cases were preferably documented, resulting in a selection bias. However, we believe that the conclusions drawn from our model are robust since there is no indication that the impact of age, disease activity, specific comorbidities or GC treatment is influenced by this bias.

In this large German cohort of patients with RMD with SARS-CoV-2 infection, 29% were hospitalised. Age, RMD disease activity, CVD, ILD/COPD and GC treatment starting at doses of >5 mg/day were independently associated with hospitalisation. These risk factors are similar to those found in general COVID-19 cohorts. However,

to our knowledge, this is the first analysis identifying moderate to high RMD disease activity as independent risk factor for hospitalisation due to COVID-19. It is important to continue the documentation of patients with RMDs and COVID-19 in order to generate more evidence for counselling and to find the best therapeutic management of our patients.

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EPIDEMIOLOGICAL SCIENCE

Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry

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ABSTRACT

Objectives To determine factors associated with COVID-19-related death in people with rheumatic diseases.

Methods Physician-reported registry of adults with rheumatic disease and confirmed or presumptive COVID-19 (from 24 March to 1 July 2020). The primary outcome was COVID-19-related death. Age, sex, smoking status, comorbidities, rheumatic disease diagnosis, disease activity and medications were included as covariates in multivariable logistic regression models. Analyses were further stratified according to rheumatic disease category.

Results Of 3729 patients (mean age 57 years, 68% female), 390 (10.5%) died. Independent factors associated with COVID-19-related death were age (66–75 years: OR 3.00, 95% CI 2.13 to 4.22; >75 years: 6.18, 4.47 to 8.53; both vs ≤65 years), male sex (1.46, 1.11 to 1.91), hypertension combined with cardiovascular disease (1.89, 1.31 to 2.73), chronic lung disease (1.68, 1.26 to 2.25) and prednisolone-equivalent dosage >10 mg/day (1.69, 1.18 to 2.41; vs no glucocorticoid intake). Moderate/high disease activity (vs remission/low disease activity) was associated with higher odds of death (1.87, 1.27 to 2.77). Rituximab (4.04, 2.32 to 7.03), sulfasalazine (3.60, 1.66 to 7.78), immunosuppressants (azathioprine, cyclophosphamide, ciclosporin, mycophenolate or tacrolimus: 2.22, 1.43 to 3.46) and not receiving any disease-modifying anti-rheumatic drug (DMARD) (2.11, 1.48 to 3.01) were associated with higher odds of death, compared with methotrexate monotherapy. Other synthetic/biological DMARDs were not associated with COVID-19-related death.

Conclusion Among people with rheumatic disease, COVID-19-related death was associated with known general factors (older age, male sex and specific comorbidities) and disease-specific factors (disease activity and specific medications). The association with moderate/high disease activity highlights the importance

Key messages

What is already known about this subject?

- To date, most available data on outcomes for people with rheumatic diseases infected with SARS-CoV-2 come from single centre or single country case series or from one large international registry; the COVID-19 Global Rheumatology Alliance (GRA) physician registry.
- The first GRA publication identified factors associated with higher odds of COVID-19 hospitalisation, including older age, presence of comorbidities and higher dosages of glucocorticoids (≥10 mg/day of prednisolone equivalent).
- Clinical outcome information on patients with COVID-19 who have rheumatic disease therefore remains limited, particularly with regard to factors associated with COVID-19-related death.

What does this study add?

- In this analysis of 3729 patients with rheumatic diseases, older age, male sex, and cardiovascular and chronic lung disease were associated with COVID-19-related death.
- Disease-specific factors, namely, moderate/high disease activity and certain medications (rituximab, sulfasalazine and immunosuppressants (as opposed to immunomodulators like disease-modifying anti-rheumatic drugs (DMARDs)) were also associated with COVID-19-related death.

Key messages

How might this impact on clinical practice or future developments?

- There is differential risk of COVID-19-related death according to disease activity and treatments in patients with rheumatic disease, highlighting the need for adequate disease control with DMARDs, preferably without increasing the glucocorticoid dosage.

of adequate disease control with DMARDs, preferably without increasing glucocorticoid dosages. Caution may be required with rituximab, sulfasalazine and some immunosuppressants.

INTRODUCTION

There is a lack of robust data to inform our understanding of outcomes following SARS-CoV-2 infection in patients with inflammatory rheumatic diseases, leading to uncertainties regarding chronic disease management, especially for those taking immunosuppressant or immunomodulatory drugs.[1–3]

Whether people with rheumatic diseases belong to a vulnerable, higher risk population for SARS-CoV-2 infection and have poorer outcomes is unclear.[1–8] In general, this population seems to have similar or only slightly poorer outcomes compared with those without rheumatic disease.[7–9] However, important confounding disease-related factors, such as disease activity or treatments, have previously not been addressed.

Medications commonly used to treat rheumatic diseases have been used or are being tested for the prevention and/or treatment of COVID-19 and its complications,[10] raising questions about the impact of these treatments on the outcomes of SARS-CoV-2 infection. Continuation of immunomodulatory or immunosuppressive therapy is essential for controlling rheumatic disease activity, avoiding disease progression and preventing joint or organ-damage related to sustained inflammation. Withdrawal of effective treatments should be based on sound evidence, even during a pandemic.

To generate more granular data relevant to rheumatic diseases, a global network of rheumatologists, data scientists and patients developed a COVID-19 physician-reported case registry in March 2020.[11 12] Analysis of the first 600 patients revealed that older age and comorbidities were associated with hospitalisation,[13] similar to results in the general population.[8 14] More robust data on the risk of poor outcomes, in particular risk of death, are required.

The aim of this study was to investigate factors associated with COVID-19-related death in patients with rheumatic diseases and to analyse these associations by disease group.

METHODS

Data source

The COVID-19 Global Rheumatology Alliance (C19-GRA) physician-reported registry is an observational registry launched on 24 March 2020. Data are entered voluntarily by rheumatologists or under supervision of rheumatologists; patients are eligible for inclusion if they have a pre-existing rheumatic disease and a COVID-19 diagnosis. Data are entered either directly into the global or European data entry systems or transferred from national registries (France, Germany, Italy, Portugal and Sweden).

We used data collected on or before 1 July 2020. Further details of this registry have been described elsewhere.[11–13] Countries were assigned to the six WHO regions (www.who.int); the 'Americas' was further divided into north and south. Given the registry collects anonymous data, the UK Health Research Authority and the University of California San Francisco Institutional Review Board considered it exempt from patient consent.

Patient stratification into diagnostic groups

Rheumatic diseases differ regarding the disease-modifying antirheumatic drugs (DMARDs) approved for their treatment. To minimise the impact of this heterogeneity on the associations of interest, in addition to the main analysis with all patients, diagnostic categories were defined (figure 1) and stratified analyses were undertaken for patients with (1) inflammatory joint diseases (IJD), (2) rheumatoid arthritis (a subset of the IJD subgroup) and (3) connective tissue diseases (CTD)/vasculitis.

COVID-19 reporting and outcome

Both confirmed and presumptive cases of COVID-19 were reported. The method of COVID-19 diagnosis was specified: PCR, CT scan, metagenomic testing, laboratory assays or based on symptoms only.

For analysis, patients were subsequently categorised into (1) *confirmed* or high likelihood of COVID-19 (chest imaging (CT or chest X-ray) showing bilateral infiltrates and/or symptoms after close contact with a known laboratory-confirmed COVID-19 positive patient) or (2) *presumptive* cases based on symptoms alone.

The primary outcome was COVID-19-related death.

Treatment prior to COVID-19

Antirheumatic medications used prior to COVID-19 diagnosis were categorised into groups shown in figure 1. Immunomodulatory drugs (conventional synthetic (cs)/biological (b)/targeted synthetic (ts) DMARDs) were distinguished from immunosuppressive drugs (azathioprine, cyclophosphamide, ciclosporin, mycophenolate mofetil/mycophenolic acid, tacrolimus) as recommended by Isaacs and Burmester[15]; glucocorticoids are also immunosuppressive but they were examined separately and categorised by prednisolone-equivalent dosage (1–10 mg/day and >10 mg/day). Methotrexate monotherapy was adopted as the medication reference group; methotrexate is the anchor drug in multiple rheumatic diseases[16] and it represents the largest medication category in the registry.

Statistical analyses

Descriptive tables were produced for the whole cohort and then by diagnostic group, country (for the six countries with the highest number of cases: France, Germany, Italy, Spain, UK and USA) and medication. Independent associations between demographic and disease features and COVID-19-related death were estimated using multivariable logistic regression and reported as OR and 95% CI. Covariates included in the model were age, sex, key comorbidities (hypertension alone or cardiovascular disease (CVD) alone, hypertension combined with CVD, chronic lung disease, chronic kidney disease (CKD) and diabetes), smoking status (ever vs never), rheumatic disease diagnostic group, disease activity as per the physician's global assessment (severe/high or moderate disease activity vs minimal/low disease activity or remission), rheumatic disease treatment prior to COVID-19 diagnosis and prednisolone-equivalent glucocorticoid use.

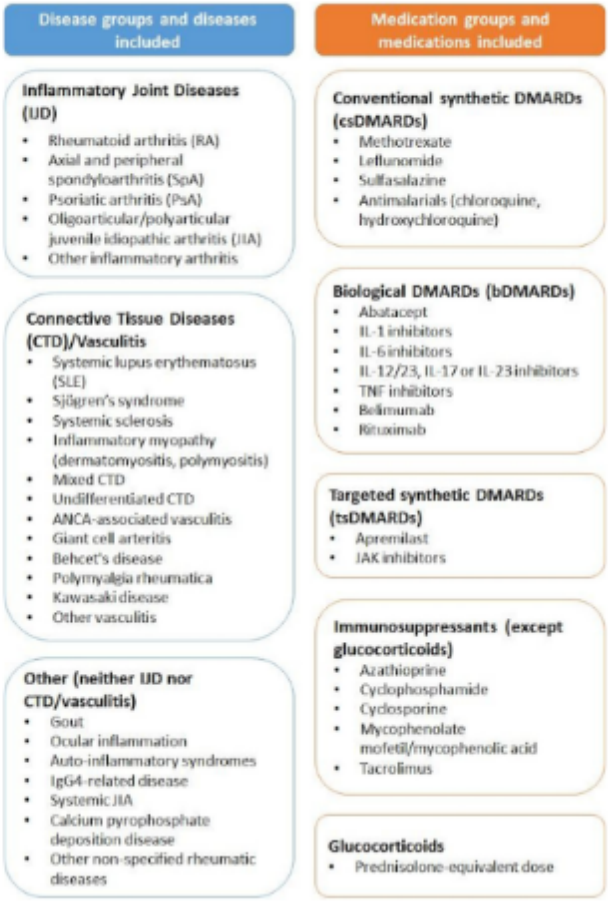

Figure 1 Disease and medication groups. ANCA, anti-neutrophil cytoplasm antibodies; DMARD, disease-modifying antirheumatic drugs; IgG, immunoglobulin; IL, interleukin; JAK, Janus kinase; TNF, tumour necrosis factor.

All patients with confirmed or presumptive COVID-19 were included in the main analyses. Patients with missing primary outcome (N=82) or missing values for age, sex and DMARD (N=19) were excluded from analysis. Missing values for comorbidities, smoking status, glucocorticoid therapy and disease activity were derived by multiple imputation using full conditional specification.[17] Results of the logistic regression analyses for 10 imputed datasets were pooled by Rubin's rules. As disease activity was missing for all French patients, country-level life expectancy was used in the imputation model to explain potential structural differences in disease activity between countries not accounted for in the patient-level data (data from 2018, source: http://hdr.undp.org/).

To account for pronounced heterogeneity between participating countries regarding both healthcare systems and infection dynamics, countries were implicitly considered as data clusters in the regression analysis by assuming that the data arose from a cluster sample design; this was done by applying a Taylor series linearisation in the variance estimation.[18]

For patients listed as having more than one rheumatic disease or being treated with more than one of the medications of interest, we created a hierarchy based on clinical expertise to categorise patients. This process creates disjoint categories, allowing a clear reference group for interpretation of the regression models and avoiding collinearities. Patients with more than one of the following diseases were grouped according to the following hierarchy: systemic lupus erythematosus (SLE)>vasculitis>other CTD>RA>psoriatic arthritis (PsA)>(other) spondyloarthritis (SpA)>other IJD>other non-IJD/non-CTD rheumatic disease. Patients receiving multiple csDMARDs or immunosuppressants (except glucocorticoids) were grouped according to the following hierarchy: immunosuppressants>sulfasalazine>antimalarials>leflunomide>methotrexate. Patients receiving a b/tsDMARD were considered solely in the b/tsDMARD group. Patients treated with more than one b/tsDMARD (N=4), patients receiving IL-1 inhibitors (N=20) and patients receiving DMARDs atypical for their disease subgroup (N=48) were excluded from analysis due to very low numbers (figure 2). Patients were excluded from a particular analysis if the medication they received provided ≤20 patients for that analysis or if there were no deaths reported for that specific medication.

The following sensitivity analyses were performed to examine the robustness of our findings to procedures for handling missing data: (1) excluding patients from France (no disease activity data available); (2) complete case analysis. Further sensitivity analyses were conducted to assess the stability of the results: (1) limited to patients with confirmed or highly likely COVID-19; (2) using the alternative outcome 'death or invasive ventilation'; (3) using a reduced number of covariates to assess the risk of overfitting; (4) analysis explicitly controlling for country, using data from the top six reporting countries; (5) analysis stratified for several binary key variables (age >65 or not, sex, ever smoked vs not, high/moderate/severe disease activity vs remission/low disease activity, CVD, chronic lung disease, glucocorticoid use) to assess the possibility of interactions.

Data were considered statistically significant for p values <0.05. All analyses were conducted in SAS (V.9.4) and R (V.3.6.3).

RESULTS

As of 1 July 2020, 3830 patients were in the registry, of whom 3729 had no missing values for death, age, sex and DMARD therapy (table 1, results for all patients; online supplemental table 1, results stratified by diagnostic subgroup; online supplemental table 2, results stratified by country; online supplemental table 3, results stratified by medication of interest).

Patient characteristics and outcomes of COVID-19

Mean age was 57 (15.7) years and most patients were ≤65 years (2586/3729, 69.3%) and female (2534/3729, 68%). The most common disease was RA (1394/3729, 37.4%), followed by CTDs other than SLE (533/3729, 14.3%), SLE (391/3729, 10.5%), PsA (440/3729, 11.8%) and other SpA (431/3729, 11.6%).

Patients were primarily from Europe (2315/3729, 62.1%) or North America (1105/3729, 29.6%). Nearly half (1309/2758, 47.5%) had minimal or low disease activity and one-third (893/2758, 32.4%) were in remission before COVID-19. One-quarter of all patients (776/3164, 24.5%) were ever smokers.

Most patients had a laboratory-confirmed diagnosis of COVID-19 (2897/3729, 77.7%); 2.4% (91/3729) had a high likelihood of infection based on imaging or confirmed COVID-19 contacts.

Death occurred in 10.5% (390/3729) of patients; 68.7% (268/390) of those who died were >65 years. Nearly half of all patients (1739/3546; 49.0%) were hospitalised. Invasive ventilation was reported in 6.2% (187/2995) of patients, but in 40.8% (120/294) of those who died.

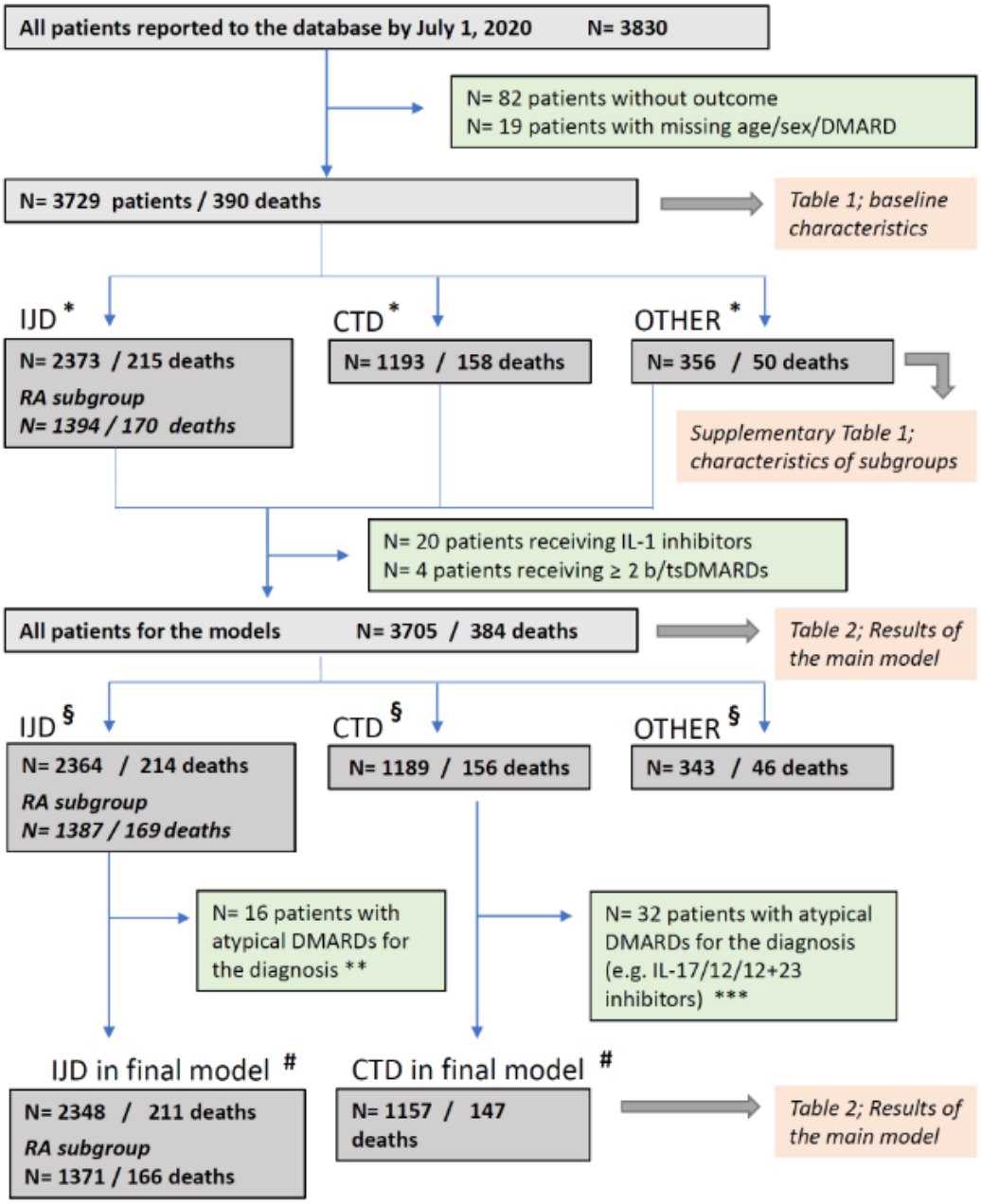

Figure 2 Patient flowchart. Some patients had diagnoses in multiple groups; as a result, the sum of patients in each group is greater than the total number of patients. (*) Patients belonging to more than one diagnosic group: IJD and CTD: N=78 (10 deaths); IJD and other: N=70 (12 deaths); CTD and other: N=50 (13 deaths); IJD and CTD and other: N=5 (2 deaths). (§) Patients belonging to more than one diagnosic group: IJD and CTD: N=77 (10 deaths); IJD and other: N=70 (12 deaths); CTD and other: N=49 (12 deaths); IJD and CTD and other: N=5 (2 deaths). (#) Patients belonging to more than one diagnosic group: IJD and CTD: N=59 (7 deaths). (**) Non-typical DMARDs for IJD and RA: immunosuppressants and belimumab; non-typical DMARDs for RA: IL-17/IL-23/IL-12+23 inhibitors. (***) Non-typical DMARDs for CTD: abatacept, IL-17/IL-23/IL-12+23 inhibitors, sulfasalazine, leflunomide and tsDMARDs. b/tsDMARDs, biological/targeted synthetic disease-modifying antirheumatic drugs; CTD, connective tissue disease/vasculitis; DMARDs, disease-modifying anti-rheumatic drugs; IJD, inflammatory joint disease; IL, interleukin; RA, rheumatoid arthritis.

Comorbidities

Most patients (2582/3700, 69.8%) had at least one comorbidity, and 20.5% (760/3700) had more than three. The most frequent were hypertension (1307/3700, 35.3%), chronic lung disease (719/3700, 19.4%), obesity (BMI ≥30; 597/3700, 16.1%), diabetes (505/3700, 13.6%), other CVD (442/3700, 11.9%) and CKD (258/3700, 7.0%). Among deceased patients, the proportion of those with comorbidities was higher, with 42.7% (165/386) having ≥3 comorbidities, namely, 54.9% (212/386) with hypertension, 35.8% (138/386) with chronic lung disease, 24.6% (95/386) with diabetes, 32.1% (124/386) with other CVD and 19.9% (77/386) with CKD.

Treatments

At the time of COVID-19 diagnosis, 40.6% (1514/3729) of patients were treated only with csDMARDs, immunosuppressants or combinations of these; 35.7% (1331/3729) received

Table 1 Patient demographic and clinical characteristics

Parameter	Not deceased	Deceased	Total
N	3339	390	3729
General			
Age (years)	55.5 (15.2)	69.7 (14.6)	57.0 (15.7)
≤30	197 (5.9)	9 (2.3)	206 (5.5)
31–50	1012 (30.3)	31 (7.9)	1043 (28)
51–65	1255 (37.6)	82 (21)	1337 (35.9)
66–75	536 (16.1)	109 (27.9)	645 (17.3)
>75	339 (10.2)	159 (40.8)	498 (13.4)
Male sex	1031 (30.9)	164 (42.1)	1195 (32)
Ever smoker	664 (23.3) (*N=2854*) (*Missing=485*)	112 (36.1) (*N=310*) (*Missing=80*)	776 (24.5) (*N=3164*) (*Missing=565*)
Regions			
African region	14 (0.4)	2 (0.5)	16 (0.4)
Eastern Mediterranean region	83 (2.5)	11 (2.8)	94 (2.5)
European region	2040 (61.1)	275 (70.5)	2315 (62.1)
North American region	1024 (30.7)	81 (20.8)	1105 (29.6)
South American region	112 (3.4)	10 (2.6)	122 (3.3)
South-East Asian region	11 (0.3)	0	11 (0.3)
Western Pacific region	55 (1.6)	11 (2.8)	66 (1.8)
Inflammatory joint diseases			
Rheumatoid arthritis	1224 (36.7)	170 (43.6)	1394 (37.4)
Spondyloarthritis	416 (12.5)	15 (3.8)	431 (11.6)
Psoriatic arthritis	420 (12.6)	20 (5.1)	440 (11.8)
Juvenile idiopathic arthritis (poly, oligo, not systemic)	21 (0.6)	4 (1)	25 (0.7)
Other inflammatory arthritis	90 (2.7)	8 (2.1)	98 (2.6)
Total inflammatory joint diseases	2158 (64.6)	215 (55.1)	2373 (63.6)
Connective tissue diseases/Vasculitis			
Systemic lupus erythematosus	355 (10.6)	36 (9.2)	391 (10.5)
Connective tissue diseases (other than SLE)	473 (14.2)	60 (15.4)	533 (14.3)
Vasculitis	258 (7.7)	68 (17.4)	326 (8.7)
Total CTD	1035 (31)	158 (40.5)	1193 (32.0)
Other RMDs			
Total	306 (9.2)	50 (12.8)	356 (9.5)
Disease activity	*N=2464* (*Missing=875*)	*N=294* (*Missing=96*)	*N=2758* (*Missing=971*)
Remission	799 (32.4)	94 (32)	893 (32.4)
Minimal/low disease activity	1202 (48.8)	107 (36.4)	1309 (47.5)
Moderate disease activity	388 (15.7)	60 (20.4)	448 (16.2)
Severe/high disease activity	75 (3)	33 (11.2)	108 (3.9)
Other outcomes			
Hospitalised	1368 (43.3) (*N=3162*) (*Missing=177*)	371 (96.6) (*N=384*) (*Missing=6*)	1739 (49) (*N=3546*) (*Missing=183*)
Invasive ventilation	67 (2.5) (*N=2701*) (*Missing=638*)	120 (40.8) (*N=294*) (*Missing=96*)	187 (6.2) (*N=2995*) (*Missing=734*)
Comorbidities	*N=3314* (*Missing=25*)	*N=386* (*Missing=4*)	*N=3700* (*Missing=29*)
Hypertension	1095 (33)	212 (54.9)	1307 (35.3)
Cardiovascular disease	318 (9.6)	124 (32.1)	442 (11.9)
Cerebrovascular disease	89 (2.7)	20 (5.2)	109 (2.9)
Chronic lung disease	581 (17.5)	138 (35.8)	719 (19.4)
Chronic kidney disease	181 (5.5)	77 (19.9)	258 (7)
Obesity (BMI ≥30)	539 (16.3)	58 (15)	597 (16.1)
Morbid obesity (BMI ≥40)	106 (3.2)	16 (4.1)	122 (3.3)
Diabetes	410 (12.4)	95 (24.6)	505 (13.6)
Cancer	165 (5)	49 (12.7)	214 (5.8)
Other comorbidities	771 (23.3)	126 (32.6)	897 (24.2)
Number of comorbities	1.3 (1.3)	2.5 (1.6)	1.4 (1.3)
No comorbidity	1090 (32.9)	28 (7.3)	1118 (30.2)
One comorbidity	1032 (31.1)	83 (21.5)	1115 (30.1)
Two comorbidities	597 (18)	110 (28.5)	707 (19.1)
≥3 comorbidites	595 (18)	165 (42.7)	760 (20.5)
DMARD therapies			
csDMARDs monotherapy	592 (17.7)	59 (15.1)	651 (17.5)
csDMARDs combination therapy	692 (20.7)	61 (15.6)	753 (20.2)
Methotrexate monotherapy	531 (15.9)	47 (12.1)	578 (15.5)
Methotrexate combination therapy	607 (18.2)	52 (13.3)	659 (17.7)
Leflunomide monotherapy	61 (1.8)	12 (3.1)	73 (2)
Leflunomide combination therapy	120 (3.6)	10 (2.6)	130 (3.5)
Sulfasalazine monotherapy	51 (1.5)	16 (4.1)	67 (1.8)
Sulfasalazine combination therapy	129 (3.9)	26 (6.7)	155 (4.2)
Antimalarial monotherapy	287 (8.6)	17 (4.4)	304 (8.2)
Antimalarial combination therapy	322 (9.6)	39 (10)	361 (9.7)
Immunosuppressants monotherapy	149 (4.5)	26 (6.7)	175 (4.7)
Immunosuppressants combination therapy	147 (4.4)	21 (5.4)	168 (4.5)
Mycophenolate mofetil monotherapy	68 (2)	14 (3.6)	82 (2.2)
Mycophenolate mofetil combination therapy	81 (2.4)	15 (3.8)	96 (2.6)
Azathioprine monotherapy	63 (1.9)	7 (1.8)	70 (1.9)
Azathioprine combination therapy	51 (1.5)	3 (0.8)	54 (1.4)
Cyclophosphamide monotherapy	10 (0.3)	3 (0.8)	13 (0.3)
Cyclophosphamide combination therapy	5 (0.1)	5 (1.3)	10 (0.3)
Tacrolimus monotherapy	5 (0.1)	2 (0.5)	7 (0.2)
Tacrolimus combination therapy	11 (0.3)	0	11 (0.3)
Ciclosporin monotherapy	3 (0.1)	0	3 (0.1)
Ciclosporin combination therapy	11 (0.3)	1 (0.3)	12 (0.3)
bDMARDs monotherapy	675 (20.2)	48 (12.3)	723 (19.4)
bDMARDs combination therapy	562 (16.8)	46 (11.8)	608 (16.3)
TNF inhibitors monotherapy	434 (13)	13 (3.3)	447 (12)
TNF inhibitors combination therapy	340 (10.2)	17 (4.4)	357 (9.6)
Abatacept monotherapy	28 (0.8)	4 (1)	32 (0.9)
Abatacept combination therapy	46 (1.4)	5 (1.3)	51 (1.4)
B-cell-targeted bDMARDs monotherapy	71 (2.1)	25 (6.4)	96 (2.6)
B-cell-targeted bDMARDs combination therapy	106 (3.2)	18 (4.6)	124 (3.3)
Rituximab monotherapy	66 (2)	25 (6.4)	91 (2.4)
Rituximab combination therapy	85 (2.5)	17 (4.4)	102 (2.7)
Belimumab monotherapy	5 (0.1)	0	5 (0.1)
Belimumab combination therapy	22 (0.7)	1 (0.3)	23 (0.6)
IL-6 inhibitors monotherapy	51 (1.5)	3 (0.8)	54 (1.4)
IL-6 inhibitors combination therapy	34 (1)	2 (0.5)	36 (1)

Continued

Table 1 Continued

Parameter	Not deceased	Deceased	Total
IL-1 inhibitors monotherapy	10 (0.3)	2 (0.5)	12 (0.3)
IL-1 inhibitors combination therapy	4 (0.1)	4 (1)	8 (0.2)
IL-17, IL-23, IL-12/23 inhibitors monotherapy	79 (2.4)	1 (0.3)	80 (2.1)
IL-17, IL-23, IL-12/23 inhibitors combination therapy	36 (1.1)	0	36 (1)
tsDMARDs monotherapy	61 (1.8)	5 (1.3)	66 (1.8)
tsDMARDs (*) combination therapy	71 (2.1)	10 (2.6)	81 (2.2)
JAK inhibitors monotherapy	54 (1.6)	4 (1)	58 (1.6)
JAK inhibitors combination therapy	67 (2)	9 (2.3)	76 (2)
Apremilast monotherapy	7 (0.2)	1 (0.3)	8 (0.2)
Apremilast combination therapy	3 (0.1)	1 (0.3)	4 (0.1)
No DMARD therapies	615 (18.4)	124 (31.8)	739 (19.8)
Further therapies			
Glucocorticoids (#)	1056 (32) (*N=3302*) (*Missing=37*)	217 (57.1) (*N=380*) (*Missing=10*)	1273 (34.6) (*N=3682*) (*Missing=47*)
Glucocorticoids 1–10 mg/day	833 (25.6) (*N=3254*) (*Missing=85*)	150 (41.3) (*N=363*) (*Missing=27*)	983 (27.2) (*N=3617*) (*Missing=112*)
Glucocorticoids>10 mg/day	171 (5.3) (*N=3254*) (*Missing=85*)	49 (13.5) (*N=363*) (*Missing=27*)	220 (6.1) (*N=3617*) (*Missing=112*)
NSAIDs	600 (19.3) (*N=3103*) (*Missing=236*)	38 (11.0) (*N=345*) (*Missing=45*)	638 (18.5) (*N=3448*) (*Missing=281*)

Data are N (column %) for categorical variables or mean (SD) for continuous variables. The table includes all patients with a non-missing outcome and non-missing values for age, sex and disease-modifying anti-rheumatic drugs (DMARDs) (101 patients excluded). Data refer to patients with non-missing values for the respective variable; total N for patients with non-missing values is given in parentheses for variables with missing values; the total number of missing values is also given in parenthesis, for the applicable variables. (*) Includes one patient on a study medication (Lenabasum). (#) Includes patients with a missing glucocorticoid dosage.
bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTD, connective tissue diseases; DMARD, disease-modifying antirheumatic drug; IL, interleukin; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; N, number; NSAID, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

bDMARDs and 3.9% (147/3729) received tsDMARDs. One-fifth (739/3729, 19.8%) were not receiving any DMARD/immunosuppressive treatment (except glucocorticoids), and this proportion was higher among deceased patients (124/390, 31.8%).

Among the patients not receiving any DMARD/immunosuppressive treatment, 39.8% (290/729) received glucocorticoids, 9.8% (70/712) with a prednisolone-equivalent dosage of >10 mg/day; the most frequent diagnostic categories being other non-specified rheumatic diseases (173/739, 23.4%), vasculitis (161/739, 21.8%), CTD other than SLE (156/739, 21.1%) and RA (110/739, 14.9%).

Country-specific differences

The majority of cases (2993/3729, 80.3%) were reported from six countries with considerable differences in reported percentages of death (online supplemental table 2). Overall, 10.5% (390/3729) of patients died, with highest proportions in the UK (91/435, 20.9%) and Italy (53/315, 16.8%). Death was reported in lower proportions in the USA (70/1005, 7.0%), Germany (15/198, 7.6%), France (62/793, 7.8%) and Spain (21/247, 8.5%). Other major differences between the countries were the distribution of rheumatic diseases and the distribution and frequency of comorbidities.

Factors associated with death

In multivariable analyses (table 2, figure 3), patients between 66 and 75 years of age were more likely to have died (OR 3.00, 95% CI 2.13 to 4.22) than those ≤65 years. The association was even more pronounced in patients over 75 years (6.18, 4.47 to 8.53; vs ≤65 years). Male sex was also associated with higher odds of death (1.46, 1.11 to 1.91). Current or former smoking was only associated with death in the RA subgroup (1.45, 1.02 to 2.04).

Other factors associated with death included chronic lung disease (1.68, 1.26 to 2.25) and CVD combined with hypertension (1.89, 1.31 to 2.73), whereas hypertension or CVD alone did not show a significant association. CKD was significantly associated with death in patients with CTD or vasculitis (2.30, 1.37 to 3.88) but not in other disease subgroups.

Across all diagnostic groups, treatments with leflunomide, antimalarials, TNF inhibitors, abatacept, belimumab, IL-6 inhibitors, IL-17/IL-23/IL-12+23 inhibitors and tsDMARDs were not associated with death, as compared with methotrexate monotherapy. In the overall model, not receiving DMARD treatment was associated with death (2.11, 1.48 to 3.01) compared with methotrexate monotherapy. This was also seen in the IJD, RA and CTD subgroups.

Compared with methotrexate monotherapy, treatments associated with a higher odds of death were rituximab (4.04, 2.32 to 7.03, in the overall model; 5.42, 2.77 to 10.61, in the IJD subgroup; 4.99, 2.43 to 10.26, in the RA subgroup; 3.72, 1.21 to 11.48, in the CTD/vasculitis subgroup), sulfasalazine (3.60, 1.66 to 7.78, in the overall model and consistent across all subgroups) and immunosuppressants (azathioprine, cyclophosphamide, ciclosporin, mycophenolate or tacrolimus: 2.22, 1.43 to 3.46, in the overall model; 2.44, 1.06 to 5.65, in the CTD/vasculitis subgroup; not applicable to other subgroups).

An additional analysis indicated that the association of sulfasalazine with an increased odds for death was mainly driven by the larger group of sulfasalazine monotherapy and persisted even when sulfasalazine combination treatment (plus either antimalarials, leflunomide or methotrexate) was considered separately (data not shown).

Treatment with higher dosages of glucocorticoids (>10 mg/day prednisolone-equivalent dose vs no use) was also found to be associated with death (1.69, 1.18 to 2.41), particularly in the CTD/vasculitis subgroup (1.93, 1.11 to 3.36).

Higher disease activity at COVID-19 diagnosis was consistently associated with death across all disease groups. Patients with high/moderate/severe disease activity had higher odds of death (1.87, 1.27 to 2.77) than patients with low disease activity or in remission (overall model and consistent across all subgroups).

Sensitivity analyses

Results were largely consistent in our sensitivity analyses (online supplemental tables 4–9). In the complete case analysis (online supplemental table 5), the association between sulfasalazine and death was no longer statistically significant. In stratified analyses (online supplemental tables 10–16), sulfasalazine use was not associated with death among patients that never smoked, with the OR among ever smokers being almost threefold than among non-smokers (online supplemental table 12).

DISCUSSION

With global cooperation, the C19-GRA physician-reported registry is the largest collection to date of patients with rheumatic

Table 2 Multivariable logistic regression analysis of factors associated with COVID-19-related death in patients with rheumatic diseases (all patients)

	All			Patients with inflammatory joint diseases (IJDs)			Only patients with rheumatoid arthritis			Patients with connective tissue diseases (CTDs) or vasculitis		
	384/3705 (10.4%)			211/2348 (9.0%)			166/1371 (12.1%)			147/1157 (12.7%)		
N deaths/patients (%)	N deaths/patients	OR	95% CI	N deaths/patients	OR	95% CI	N deaths/ patients	OR	95% CI	N deaths/ patients	OR	95% CI
Age, years												
Age≤65	118/2565	1	Reference	55/1657	1	Reference	40/840	1	Reference	56/779	1	Reference
65 years<Age≤75	109/644	**3**	**2.13 to 4.22**	71/426	**3.63**	**2.55 to 5.15**	55/314	**3.10**	**1.68 to 5.72**	33/187	**2.29**	**1.34 to 3.93**
Age>75	157/496	**6.18**	**4.47 to 8.53**	85/265	**8.21**	**5.54 to 12.18**	71/217	**7.30**	**4.42 to 12.06**	58/191	**4.08**	**2.27 to 7.36**
Male sex (vs female)	161/1188	**1.46**	**1.11 to 1.91**	82/788	1.31	0.95 to 1.8	55/345	1.17	0.78 to 1.76	63/296	1.66	0.96 to 2.86
Ever smoked (vs never)	140/922	1.21	0.94 to 1.57	84/607	1.26	0.93 to 1.72	71/385	**1.45**	**1.02 to 2.04**	42/248	1.11	0.67 to 1.86
Comorbidities												
Hypertension alone or CVD alone	155/1150	1.19	0.89 to 1.59	79/690	1.04	0.74 to 1.46	66/454	1.11	0.74 to 1.67	69/406	**1.56**	**1.06 to 2.29**
Hypertension and CVD	89/301	**1.89**	**1.31 to 2.73**	53/168	**2.29**	**1.25 to 4.23**	38/118	**2.03**	**1.03 to 3.97**	28/106	1.57	0.78 to 3.16
Chronic lung disease	136/721	**1.68**	**1.26 to 2.25**	76/406	**1.52**	**1.04 to 2.21**	63/293	1.44	0.99 to 2.09	54/285	**2.05**	**1.47 to 2.85**
Chronic kidney disease	76/259	1.67	0.99 to 2.8	27/111	1.09	0.54 to 2.21	21/83	1.01	0.46 to 2.24	41/124	**2.30**	**1.37 to 3.88**
Diabetes mellitus	96/508	1.38	0.88 to 2.17	55/313	1.31	0.95 to 1.79	39/213	1.08	0.72 to 1.61	32/154	1.39	0.64 to 3
Rheumatic disease												
Rheumatoid arthritis	160/1326	1	Reference	166/1373	1	Reference		n.a.			n.a.	
Systemic lupus erythematosus	36/391	1.2	0.70 to 2.04		n.a.			n.a.		32/378	1	Reference
Vasculitis	67/325	0.8	0.60 to 1.08		n.a.			n.a.		64/318	0.81	0.49 to 1.33
Other connective tissue diseases	53/473	**0.75**	**0.58 to 0.97**		n.a.			n.a.		51/461	0.78	0.39 to 1.54
Psoriasis arthritis	19/429	0.75	0.53 to 1.07	19/437	0.82	0.55 to 1.22		n.a.			n.a.	
Spondyloarthritis	15/423	0.72	0.34 to 1.54	15/424	0.82	0.4 to 1.69		n.a.			n.a.	
Other inflammatory arthritis or non-systemic JIA	10/109	0.79	0.46 to 1.34	11/114	0.76	0.43 to 1.36		n.a.			n.a.	
Other rheumatic diseases (not IJDs/CTDs/ vasculitis)	24/229	**0.51**	**0.35 to 0.73**		n.a.			n.a.			n.a.	
High/moderate/severe disease activity (DA) vs remission/low DA	109/722	**1.87**	**1.27 to 2.77**	54/453	**1.6**	**1.13 to 2.26**	44/274	**1.60**	**1.03 to 2.47**	51/230	**2.45**	**1.49 to 4.02**
Medication												
Methotrexate	47/595	1	Reference	41/487	1	Reference	34/354	1	Reference	6/94	1	Reference
No DMARD therapy	124/739	**2.11**	**1.48 to 3.01**	38/239	**2.08**	**1.38 to 3.14**	25/110	**2.12**	**1.34 to 3.37**	67/353	**3.18**	**1.61 to 6.27**
Leflunomide	12/90	1.56	0.9 to 2.7	10/83	1.37	0.69 to 2.73	9/68	1.43	0.71 to 2.86		n.a.	
Antimalarials	27/426	0.99	0.66 to 1.48	17/167	1.14	0.65 to 2	17/141	1.24	0.7 to 2.19	11/271	1.38	0.48 to 4.02
Sulfasalazine	33/144	**3.6**	**1.66 to 7.78**	31/137	**3.40**	**1.46 to 7.93**	21/85	**2.62**	**1.21 to 5.68**		n.a.	
Immunosuppressants	38/276	**2.22**	**1.43 to 3.46**		n.a.			n.a.		32/247	**2.44**	**1.06 to 5.65**
TNF inhibitors	30/803	0.85	0.52 to 1.36	26/764	0.77	0.42 to 1.41	16/292	0.82	0.39 to 1.76	4/39	2.00	0.36 to 11.2
Abatacept	9/81	1.20	0.61 to 2.34	9/75	1.3	0.62 to 2.71	9/68	1.4	0.65 to 2.99		n.a.	
Rituximab	42/192	**4.04**	**2.32 to 7.03**	22/90	**5.42**	**2.77 to 10.61**	21/86	**4.99**	**2.43 to 10.26**	22/104	**3.72**	**1.21 to 11.48**
Belimumab	1/27	0.71	0.19 to 2.68		n.a.			n.a.		1/27	1.07	0.21 to 5.37
IL-6 inhibitors	5/90	0.83	0.38 to 1.84	1/68	0.25	0.03 to 2.43	1/63	0.25	0.03 to 2.33	4/23	2.69	0.88 to 8.19
IL-17/IL-23/IL-12+23 inhibitors	1/115	0.25	0.03 to 2.04	1/112	0.26	0.03 to 2.06		n.a.			n.a.	
tsDMARDs	15/145	1.60	0.91 to 2.8	15/142	1.75	0.99 to 3.12	13/118	1.57	0.75 to 3.27		n.a.	
Glucocorticoids (GCs)												
No GCs	165/2417	1	Reference	109/1721	1	Reference	78/863	1	Reference	38/551	1	Reference
GCs 1–10 mg/day	170/1062	1.43	0.98 to 2.09	89/567	1.36	0.76 to 2.45	78/464	1.34	0.66 to 2.74	75/469	**1.69**	**1.11 to 2.57**

Continued

Table 2 Continued

	All			Patients with inflammatory joint diseases (IJDs)			Only patients with rheumatoid arthritis			Patients with connective tissue diseases (CTDs) or vasculitis		
	384/3705 (10.4%)			211/2348 (9.0%)			166/1371 (12.1%)			147/1157 (12.7%)		
N deaths/patients (%)	N deaths/patients	OR	95% CI	N deaths/patients	OR	95% CI	N deaths/patients	OR	95% CI	N deaths/patients	OR	95% CI
GCs>10 mg/day	49/226	1.69	1.18 to 2.41	12/60	1.55	0.67 to 3.57	10/44	1.59	0.6 to 4.18	34/137	1.93	1.11 to 3.36

Missing values were imputed via multiple imputation, patient numbers may thus be rounded. Effects significant at level α=0.05 are marked in bold. Patients were excluded from a particular analysis if the medication they received provided <20 patients for that analysis or if there were no deaths reported for that specific medication.
TNF; tumour necrosis factor; CTD, connective tissue diseases; CVD, cardiovascular disease; DMARD, disease-modifying antirheumatic drugs; GC, glucocorticoids; IL, Interleukin; JIA, Juvenile idiopathic arthritis; N, number; n.a., not applicable; tsDMARD, targeted synthetic disease-modifying antirheumatic drugs.

diseases and COVID-19. We found that moderate/high disease activity was significantly associated with COVID-19-related death, confirming recent recommendations regarding the importance of disease control in rheumatic diseases in the COVID-19 era.[1] Other factors associated with death were older age, male sex and the presence of comorbidities, which is consistent with reports from the general population.[8] Overall, compared with methotrexate monotherapy, most DMARDs were not associated with higher odds of death, although rituximab and sulfasalazine were notable exceptions. Prednisolone-equivalent dosages >10 mg/day and other immunosuppressive drugs (as opposed to immunomodulatory DMARDs) were also associated with COVID-19-related death.

In this cohort of patients with underlying rheumatic diseases, the COVID-19-related death rate was 10.5%, clearly higher than that reported in the general population in most countries. However, this study was not designed to calculate a precise point estimate for mortality. Reporting biases and population-related factors, including COVID-19 testing rates, could explain this figure and, importantly, it should not be taken as an estimate of the overall death rate among patients with rheumatic diseases and COVID-19.

The association of rituximab with poorer COVID-19-related outcomes is a previously unreported finding outside of case reports. Rituximab binds to CD20 on the surface of B-cells, effectively depleting this cell type, and interferes with antibody development. Therefore, B-cell depletion could potentially compromise antiviral immunity, including the development of SARS-CoV-2 antibodies.[19] With our data, it was not possible to determine the exact timing of infection following rituximab infusion, although all patients were clinically judged by their rheumatologist to have been exposed to the immunological effects of the drug at the time of COVID-19 diagnosis. The association between rituximab and COVID-19-related death could have also been influenced by the typical coadministration of methylprednisolone with rituximab.

A finding that merits further research is the higher odds of death found with sulfasalazine treatment. This association has also been reported in results from an international registry of patients with inflammatory bowel disease and COVID-19, where sulfasalazine or 5-aminosalicylate (5-ASA) use was associated with severe COVID-19 (adjusted OR of 3.1 (1.3 to 7.7)).[20] This finding is surprising as sulfasalazine is usually considered to have a low immunosuppressive effect. Prior research supports an immune regulatory effect driven by sulfasalazine or its metabolite 5-ASA against other RNA viruses.[21–24] However, causal interpretation of the association between sulfasalazine and COVID-19-related death should not be made. The perceived low immunosuppressive effect of sulfasalazine may have led rheumatologists to prescribe preferentially sulfasalazine over methotrexate in patients who were perceived to be at higher risk, for example, patients with pulmonary disease, smoking or recurrent chest infections. In an observational study like ours, this could lead to unmeasured confounding. A salient difference in sulfasalazine users in our study was a higher proportion of current or former smokers, compared with non-users. In the stratified analyses for chronic lung disease, the association between death and sulfasalazine was significant in both subgroups with and without chronic lung disease, while in the stratified analyses for smoking, the association between death and sulfasalazine was limited to ever smokers, so the factor 'smoking' could potentially be an effect modifier. Another potential explanation for this finding could be the

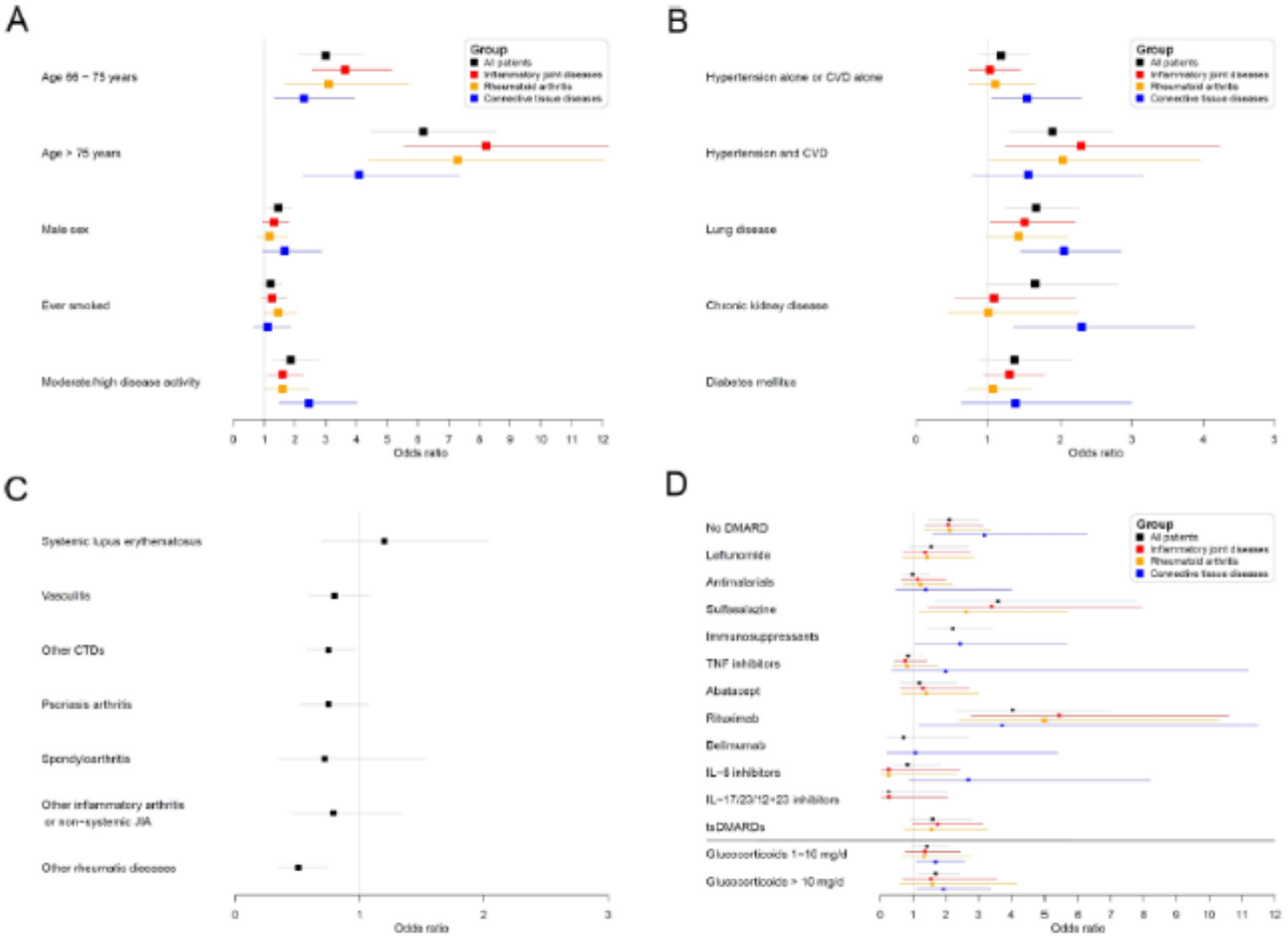

Figure 3 Results of the main logistic regression analysis. Shown are multivariable-adjusted ORs for the outcome COVID-19-related death with 95% CIs, assessing the association with (A) general patient characteristics, (B) comorbidities, (C) rheumatic disease diagnoses (RMD) and (D) rheumatic disease medications. ORs are shown for four groups: all patients (black), patients with inflammatory joint disease (red), patients with rheumatoid arthritis (orange), and patients with a connective tissue disease or vasculitis (blue). For (C), only ORs for all patients are shown. The reference categories are as follows: (A) ≤65 years, females, never smoked, remission or low disease activity; (B) the non-presence of the specific comorbidities (for all effects); (C) rheumatoid arthritis (for all effects); (D) methotrexate monotherapy (for all effects except for glucocorticoids), no glucocorticoids (for glucocorticoid dosage groups). Patients receiving multiple csDMARDs or immunosuppressants (except glucocorticoids) were grouped according to the following hierarchy: immunosuppressants>sulfasalazine>antimalarials>leflunomide>methotrexate; patients receiving a b/tsDMARD were considered solely in the b/tsDMARD group; glucocorticoids were examined separately and categorised by prednisolone-equivalent dosage (1–10 mg/day and >10 mg/day). bDMARD, biological disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTD, connective tissue diseases; CVD, cardiovascular disease; JIA, juvenile idiopathic arthritis; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug.

merging of sulfasalazine combination therapy (with other csDMARDs) with sulfasalazine monotherapy; however, the increased odds for death persisted in the sulfasalazine monotherapy group and was not driven by the combination treatment (data not shown).

Despite the large overall sample size, for some therapies (eg, IL-6 and IL-17/IL-23/IL-12+23 inhibitors) the number of users was low and no firm conclusions could be made. IL-6 inhibitors have been used to counteract the hyperinflammatory state produced by COVID-19, with mostly disappointing randomised trial results.[25 26] Their efficacy is still being investigated in ongoing trials, but it is reassuring that they were not associated with COVID-19-related death in our analyses. Previous studies had shown an association between TNF inhibitors and a decreased risk of sepsis and mortality in patients with RA after serious infection compared with csDMARDs.[27 28] We could not confirm such an association after stratification by disease and adjustment for disease activity. However, the data indicate that some associations may exist among patients diagnosed with IJD other than RA (a subgroup comprising predominantly patients with axial SpA and PsA), in whom male sex and diabetes mellitus were associated with a higher odds of death, and TNF inhibitor use was associated with a lower odds of death (univariable analysis, data not shown). Due to a small number of deceased patients in this subgroup with non-RA subtypes of IJD (n=37 deaths), these effects could not be assessed in a multivariable model and this should be investigated in the future when higher case numbers allow a more stable assessment.

This study has limitations. As a cross-sectional, case-reporting registry, it may be subject to selection bias if more severe cases

are more likely to come to the rheumatologists' attention and therefore to be reported. There is an absence of a population-based comparator, and we are unable to make comparisons between those with and without COVID-19. Moreover, we caution against interpreting our estimates causally. There is likely unmeasured confounding dependent on the particularities of health systems and case reporting differences. We tried to address this by limiting the research questions to those that could be answered with this dataset and by accounting for potential confounders in our analyses. The high number of variables compared with outcome events in the subgroup models may result in biased estimates.[29 30] However, the consistency between the main model and the sensitivity analyses (including using a lower number of variables) do not indicate an issue with overfitting.

In conclusion, people with rheumatic diseases with higher disease activity have higher odds of COVID-19-related death, highlighting the importance of disease control, preferably by managing DMARDs effectively without increasing glucocorticoids. Future studies should address the observed association of rituximab and sulfasalazine with poor outcomes. Finally, as in the general population, older age, male sex and/or the presence of comorbidities increase the odds of COVID-19-related death.

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Correction notice This article has been corrected since it published Online First. The collaborator names have been updated.

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3.5 SARS-CoV-2-Infektionen bei rheumatoider Arthritis

Originalarbeit 9:

Hasseli R, Pfeil A, Hoyer BF, Krause A, Lorenz HM, Richter JG, Schmeiser T, Voll RE, Schulze-Koops H, Specker C, Müller-Ladner U. *Do patients with rheumatoid arthritis show a different course of COVID-19 compared to patients with spondyloarthritis?*
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Originalarbeit 10:

Sparks JA, Wallace ZS, Seet AM, Gianfrancesco MA, Izadi Z, Hyrich KL, Strangfeld A, Gossec L, Carmona L, Mateus EF, Lawson-Tovey S, Trupin L, Rush S, Katz P, Schmajuk G, Jacobsohn L, Wise L, Gilbert EL, Duarte-García A, Valenzuela-Almada MO, Pons-Estel GJ, Isnardi CA, Berbotto GA, Hsu TY, D'Silva KM, Patel NJ, Kearsley-Fleet L, Schäfer M, Ribeiro SLE, Al Emadi S, Tidblad L, Scirè CA, Raffeiner B, Thomas T, Flipo RM, Avouac J, Seror R, Bernardes M, Cunha MM, **Hasseli R**, Schulze-Koops H, Müller-Ladner U, Covid V, Specker C, Souza VA, Mota LMHD, Gomides APM, Dieudé P, Nikiphorou E, Kronzer VL, Singh N, Ugarte-Gil MF, Wallace B, Akpabio A, Thomas R, Bhana S, Costello W, Grainger R, Hausmann JS, Liew JW, Sirotich E, Sufka P, Robinson PC, Machado PM, Yazdany J; COVID-19 Global Rheumatology Alliance. *Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 Global Rheumatology Alliance physician registry.*
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Zusammenfassung:

Die Gruppe der inflammatorischen Arthritiden stellt die größte Krankheitsgruppe bei ERE dar. Die Pathophysiologie der rheumatoiden Arthritis unterscheidet sich deutlich von den Spondyloarthritiden. Die beiden Erkrankungsgruppen weisen ein unterschiedliches Zytokinmuster auf, welches eine wichtige Rolle im Krankheitsgeschehen spielt. Aus diesem Grund sind die Therapieregime unterschiedlich. Bei der rheumatoiden Arthritis spielen Zytokine, wie z.B. Tumornekrose-Faktor-Alpha, Interleukin-1 und 6 eine Rolle, wohingegen bei den Spondyloarthritiden neben Tumornekrose-Faktor-Alpha, Interleukin 12/23 und Interleukin-17 dominieren. Beide Gruppen weisen jedoch auch proinflammatorische Zytokine auf, wie z.B. Tumornekrose-Faktor-Alpha, Interleukin-10, Interleukin-21 oder Interferon γ, die im Rahmen von Infektionen ebenfalls eine wichtige Rolle spielen [198–203]. Auch das Alter der Erstmanifestation unterscheidet sich bei beiden Gruppen. Die rheumatoide Arthritis manifestiert sich häufig zwischen dem 50.-70. Lebensjahr, die Spondyloarthritiden treten bei jüngeren Personen auf. Während vor allem Frauen von der rheumatoiden Arthritis betroffen sind, verteilt sich die Spondyloarthritis in etwa gleich auf beide Geschlechter.

Basierend auf diesen Unterschieden der Pathophysiologie sowie der unterschiedlichen Behandlung lagen bisher keine Daten vor, ob die verschiedenen Formen der

inflammatorischen Arthritiden einen unterschiedlichen COVID-19-Verlauf aufweisen. Aus diesem Grund wurde zunächst der Verlauf von COVID-19 bei PatientInnen mit rheumatoider Arthritis und Spondyloarthritiden untersucht (Originalarbeit *9*).

Hierfür wurden Daten aus dem COVID19-Rheuma.de-Register zwischen März bis November 2020 ausgewertet. In diesem Zeitraum wurden 505 Fälle im Register erfasst, darunter 129 PatientInnen mit Spondyloarthritiden und 229 PatientInnen mit rheumatoider Arthritis. Um den Einfluss des Alters und des Geschlechts auf den Verlauf der Infektion durch SARS-CoV-2 zu beseitigen, erfolgte eine Anpassung beider Gruppen basierend auf Alter und Geschlecht mit einer Verteilung 1:1. Nach der Anpassung standen in beiden Gruppen jeweils 104 Fälle zur Verfügung. Das Alter lag im Median bei 56 Jahren und 63% der PatientInnen waren weiblich. PatientInnen mit Spondyloarthritiden wurden häufiger mit TNF-Hemmern therapiert (45% vs. 19%; p=0,001), wohingegen bei der rheumatoiden Arthritis häufiger Glukokortikosteroide im Einsatz waren (40% vs. 13%; p=0,001).

Der Anteil der hospitalisierten Verläufe war in der Gruppe der rheumatoiden Arthritis signifikant höher (30% vs. 16%; p=0,05), bei der Verteilung der letalen Verläufe zeigten sich jedoch keine signifikanten Unterschiede trotz der unterschiedlichen Pathophysiologie und Unterschiede der Immunmodulation. Bei den Spondyloarthritiden wurden drei letale Verläufe beschrieben und bei der rheumatoiden Arthritis sechs tödliche Fälle. Unter den letalen Verläufen bei PatientInnen mit rheumatoider Arthritis waren auch zwei Personen, die mit Rituximab therapiert wurden, was ebenfalls einen Einflussfaktor auf den Verlauf darstellen könnte.

Für die rheumatoide Arthritis stehen sehr viele unterschiedliche Therapieoptionen zur Verfügung, so dass unabhängig von der Erkrankung die Art und Weise der Immunmodulation den Verlauf von COVID-19 beeinflussen kann. In verschiedenen Arbeiten wurde bereits der negative Einfluss von Rituximab beschrieben, andere Therapieoptionen wurden jedoch bislang nicht ausreichend untersucht. Um dieser Frage nachzugehen, erfolgte eine Auswertung aller weltweit zur Verfügung stehenden Daten aus dem globalen Register (Originalarbeit *10*). Hierfür wurden Daten von März 2020 bis April 2021 ausgewertet. Es wurden spezifisch PatientInnen unter Therapie mit Biologika oder Januskinase-Inhibitoren untersucht. In diesem Zeitraum wurden 2869 PatientInnen mit rheumatoider Arthritis erfasst. Das Alter lag im Median bei 57 Jahre und 81% der PatientInnen waren weiblich. Mit Abatacept wurden 237 Personen therapiert, 364 Personen mit Rituximab, 317 mit IL-6-Inhibitoren, 563 Personen mit einer Januskinase-Hemmung und 1388 Personen mit einer TNF-Hemmern. Eine stationäre Behandlung war bei 21% der Fälle notwendig und die Letalitätsrate lag bei 5,5%. Im Vergleich zur Gruppe der TNF-Hemmern waren die Therapien mit Rituximab (OR 4,2; 95% CI 3,2 – 5,4)

und Januskinase-Hemmern (OR 2,1; 95% CI 1,6 – 2,7) nach Adjustierung für Geschlecht, Alter und relevanten Komorbiditäten mit schwereren COVID-19-Verläufen assoziiert. Die Therapie mit Abatacept und IL-6-Inhibitoren unterschied sich nicht von der mit TNF-Hemmern.

Erstmalig konnte somit in einer großen, internationalen Kohorte von PatientInnen mit rheumatoider Arthritis ein relevanter Unterschied der COVID-19-Verläufe in Abhängigkeit von der Immunmodulation gezeigt werden.

Do patients with rheumatoid arthritis show a different course of COVID-19 compared to patients with spondyloarthritis?

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Abstract

Objective

Rheumatoid arthritis (RA) and spondyloarthritis (SpA) are the most common inflammatory rheumatic diseases (IRD). The aim of this study was to elucidate differences in the outcome of SARS-CoV-2 infection in RA- and SpA-patients.

Methods

Data from the German COVID-19 registry for IRD patients from 30th March to 16th November 2020 were analysed. 208 RA and SpA patients were included in the study, matched for gender and age.

Results

104 SpA patients (40% patients with ankylosing spondylitis, 54% with psoriatic arthritis and 6% with enteropathic arthritis) were compared to 104 RA patients. For both groups, median age was 56 years. TNF-i treatment was reported in 45% of the SpA and in 19% of RA patients (p=0.001). Glucocorticoids were used in 13% of the SpA and in 40% of the RA patients (p=0.001). In both groups, the majority of the patients (97% SpA, 95% RA) recovered from COVID-19. Hospitalisation was needed in 16% of the SpA and in 30% of the RA patients (p=0.05), and oxygen treatment in 10% and 18% respectively (p=ns). Three versus six (p=ns) fatal courses were reported in the SpA versus the RA group.

Conclusion

The study revealed that the hospitalisation rate during COVID-19 infection, but not the mortality, was significantly higher in RA as compared to SpA patients. This could be explained either by different treatment strategies or by different susceptibilities of the two diseases.

Key words

rheumatoid arthritis, spondyloarthritis, SARS-CoV-2 infection, glucocorticoid, DMARD

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Introduction

The outbreak of the new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became a worldwide pandemic (1). Spondyloarthritis (SpA), which includes psoriatic arthritis (PsA), ankylosing spondylitis (AS) and enteropathic arthritis (EA), and rheumatoid arthritis (RA) present the most common inflammatory rheumatic diseases (IRD) (2, 3). Divergences in the cytokine networks driving the individual pathologies might contribute to the distinct clinical manifestations and are the basis for the respective treatment options (4). Said divergences might also confer to different susceptibility to SARS-CoV-2. RA is characterised by the secretion of proinflammatory cytokines, *e.g.* tumour necrosis factor alpha (TNF-α), interleukin (IL) 1 and 6 (5), whereas in SpA, TNF-α, and interleukins 12/23 and -17 appear to play a dominant role (6). Moreover, some pathogenic pathways appear to be shared between IRD and infectious diseases (Fig. 1) (7).

The treatment algorithms of both entities are mainly based on the same immunosuppressants, although personalised treatment is becoming increasingly important (8, 9). For example, traditional immunomodulatory drugs such as methotrexate, leflunomide and sulfasalazine are effective in peripheral arthritis, but not in axial involvement (9). TNF-inhibitors are effective in both SpA and RA, blockage of IL-6 receptors instead only in RA, and IL-12/23 and IL-17 inhibitors only in SpA. Systemic glucocorticoids are usually used to treat disease flares in case of peripheral arthritis which however leads to an increased risk of infection. Since infections are also favoured by uncontrolled rheumatic activity the correct balance between immunosuppression on the one hand and high disease activity on the other, is still an unsolved issue (7, 8, 10). RA is characterised by autoimmune processes while SpA seems to have an autoinflammatory rather than autoimmune origin of inflammation (11, 12). Extra-articular manifestations can occur in both diseases. The manifestations differ in the eye (keratoconjunctivitis sicca and scleritis in RA, *versus* anterior uveitis in AS), heart (pericarditis in RA, conduction disturbances in SpA), lungs (pleural effusions or nodules in RA and fibrosis in SpA) and gastrointestinal tract (peptic ulcers in RA and colitis in SpA) (13). To our knowledge no data exist regarding the comparison of the course and mortality of COVID-19 in SpA and RA patients. Patients with rheumatoid arthritis, systemic lupus erythematosus or psoriasis, when analysed as a combined group, might have a slightly increased risk of death from COVID-19 compared to those with other inflammatory rheumatic diseases, although the role of disease activity and treatment in this risk estimation was not taken into account (14, 15). The aim of this study was to evaluate differences for the outcome of SARS-CoV-2 infection in RA compared to SpA patients.

Patients and methods

Study setting

Data from the German COVID-19 registry for IRD patients (www.COVID19-rheuma.de) obtained between 30th March till 16th November 2020 were evaluated (16). Patients with a known IRD and SARS-CoV-2 infection are included in this ongoing registry by their rheumatologists. Participating centres include both academic and non-academic rheumatology clinics, and private practices throughout Germany.

The German COVID-19 registry

The inclusion criteria in the registry are defined as follows: I. IRD and II. positive laboratory tests for SARS-CoV- 2 (polymerase chain reaction swabs or antibody test). The database includes the following items: federal state, age, weight, height, detailed rheumatological diagnosis, comorbidities, global disease activity, antirheumatic medication at time of study and its changes due to the infection. In addition, the course and outcome of the SARS-CoV-2 infection and COVID-19 related symptoms are documented. In case of missing data for diagnosis, outcome and medication, the respective rheumatologist could be queried directly. The disease activity from the last rheumatological visit was also reported and categorised

into four groups: controlled, low, moderate and high disease activity.

All patients with diagnoses of SpA (PsA, EA and AS) and RA were included for evaluation. Patients with overlapping syndromes were excluded. Matching of SpA and RA patients was performed with respect to age and gender in that age did not differ more than 2 years.

Statistical analysis

Completed cases were reviewed and queried in case of missing or inconsistent data. Analysis was performed descriptively using SPSS Statistics (IBM SPSS Statistics, v. 24.0 Chicago, Illinois, USA, for Windows). Median was calculated for age and body mass index (BMI) of SpA and RA patients. The group differences were tested by the Mann-Whitney U-test, Pearson Chi-Square test and Fisher's exact test. p-values <0.05 were considered as statistically significant.

Data of both groups were numerically compared and are shown in the figures in percentages using GraphPad Prism 6 (GraphPad Software).

Ethical approval

The study was approved by the ethics committee of the Justus-Liebig-University Giessen (#52-50) and registered (EuDRACT 2020-001958-21). Data handling did not involve revealing the identity of any patients. This study was conducted according to the Declaration of Helsinki.

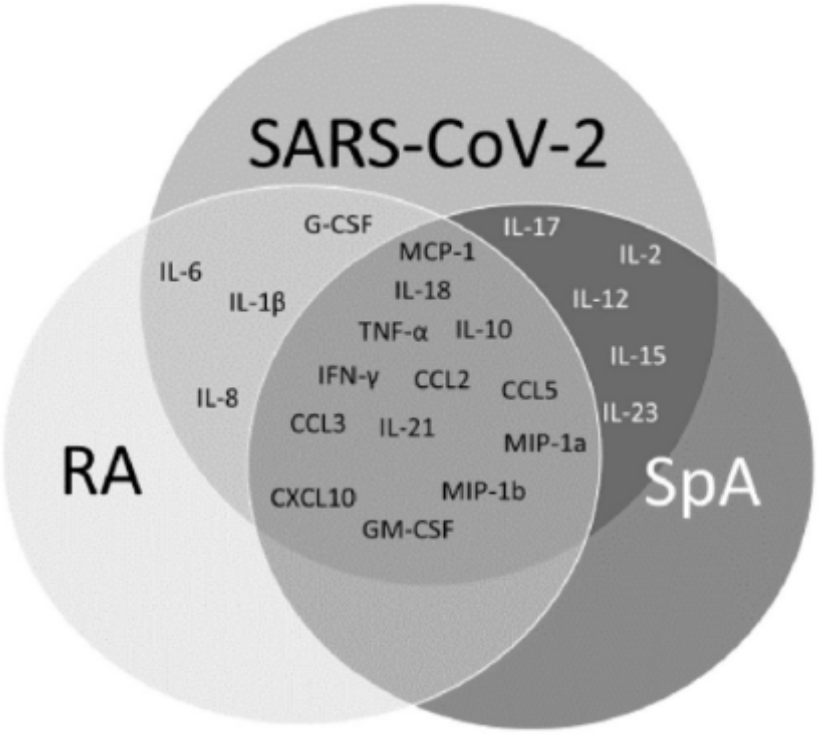


Fig. 1. Relevant cytokines/chemokines in SARS-CoV-2, RA and SpA.
Proinflammatory cytokines and chemokines seem to be shared in the pathophysiology of SARS-CoV-2, RA and SpA. G-CSF, IL-6, IL-1β and IL-8 are crucial in RA and SARS-COV-2. MCP-1, IL-18, TNF-α, IL-10, IFN-γ, CCL2, CCL5, CCL3, IL-21, MIP-1a, MIP-1b, CXCL10, GM-CSF are shared cytokines and chemokines in RA, SpA and SARS-CoV-2. IL-2, IL-17, IL-15 and IL-23 are relevant cytokines in SpA and SARS-CoV-2.
IL-6: interleukin 6; G-CSF: granulocyte colony-stimulating factor; IL-1β: interleukin 1β; IL-8: interleukin 8; IL-18: interleukin 18; IL-21: interleukin 21; IL-17: interleukin 17; IL-12: interleukin 12; IL-2: interleukin 2; IL-15: interleukin 15; IL-23: interleukin 23; IL-2: interleukin 2; MCP-1: monocyte chemoattractant protein-1; TNF-α: tumour necrosis factor α; IFN: interferon; CCL2: CC-chemokine ligand 2; CCL5: CC-chemokine ligand 5; CCL3: CC-chemokine ligand 3; CXCL10: C-X-C motif chemokine ligand 10; GM-CSF: granulocyte macrophage colony stimulating factor; MIP-1a: macrophage inflammatory protein-1a; MIP-1b: macrophage inflammatory protein-1b.

Results

Baseline characteristics

From 30th March till 16th November, in total 505 cases of IRD and SARS-CoV-2 were reported in our registry, which included 129 cases of patients with SpA and 229 cases of patients with RA (Supplementary Fig. S1). For the present analysis, 104 patients from both groups were selected after matching for gender and age (Table I). SpA patients consisted of 42 AS patients (40%), 56 PsA patients (54%) and 6 EA patients (6%). The median age was 56 years (SpA range: 20–87; RA range: 21–86). In both groups 63% (n=65) of the patients were female. The BMI in SpA patients was 26.4 kg/m^2, and 25.0 kg/m^2 in RA patients, respectively.

Disease activity

In the majority of patients, a stable disease activity was reported from the last rheumatological visit (RA: 48% and SpA: 43%, p=n.s.) (Fig. 2, Table I). Low disease activity was reported in 29% of RA and 36% of SpA patients (p=n.s.), moderate disease activity in 13% of RA and 11% of SpA patients (p=n.s.), and high disease activity in 4% and 1% respectively (p=n.s.) (Fig. 2). The rate of moderate and high disease activity was numerically higher in RA patients, whereas stable and low disease activity were equally distributed.

Immunomodulatory drugs

In 40% of the RA patients, glucocorticoids (GC) were used, which was significantly more frequent than in SpA patients with 13% (p=0.001) (Fig. 3). Of these patients, 86% (36/42) of the RA and 93% (13/14) SpA patients were treated with maximum of 5 mg prednisolone per day. In contrast, 45% of SPA patients were treated with TNF-i compared to only 19% of RA patients (p=0.001) (Fig. 3). Conventional synthetic (cs) disease-modifying anti-rheumatic drugs (csDMARDs) as monotherapy were used in 26% of RA patients and in 14% of SpA patients (Fig. 3). 11% of the SpA and 5% of the RA patients did not receive any immunomodulatory drug. Other biological and target synthetic DMARDs were reported in 26% of RA patients (Janus kinase inhibitors (JAK-i (12%)), IL-6-i (5%), abatacept (1%) and rituximab

(9%) and in 19% of the SpA patients (IL-17-i (15%), IL-12/23-i (2%), apremilast (1%), JAK-i (1%)) (Fig. 3). For more detailed information on medication, see Table I.

Comorbidities

The distribution of comorbidities was similar in both groups (median number of comorbidities: 1; Fig. 4). Arterial hypertension, as the major comorbidity, was reported in 34% of the cases in both groups. In more than 40% of the patients (SpA: 41% and RA: 46%; p=ns) no relevant comorbidity was reported (Fig. 4). In 29% of the RA and 26% of the SpA patients more than two comorbidities were documented.

Symptoms of COVID-19

More RA patients (22%) reported loss of appetite compared to SpA patients (13%, p=0.049) as well as vertigo was reported more frequently in RA patients (17%) compared to SpA patients (5%, p=0.003). No further relevant differences in reported COVID-19 symptoms were detected in both groups (Fig. 5). Most of the patients had fever (RA: 50% *vs.* SpA: 61%; p=ns), dry cough (RA: 68% and SpA: 57%; p=ns) and fatigue (RA: 48% *vs.* SpA: 45%; p=n.s.) (Fig. 5).

The median duration of COVID-19 related symptoms was 14 days (0–90 days) in the RA patients and 12 days (0–42 days) in the SpA patients (p=ns). In both groups, the majority of the patients recovered (SpA: 97% *vs.* RA: 95%) and 8% of the patients did not show any COVID-19 related symptoms.

Course of COVID-19:

Hospitalisation was necessary in 30% of the RA patients compared to 16% of the SpA patients (p=0.05), and numerically more RA patients received non-invasive and invasive oxygen treatment (RA: 18% *vs.* SpA: 10%; p=ns) (Fig. 6, Table I). Only one RA patient was supported by an extracorporeal membrane oxygenation. Complications, such as acute respiratory distress syndrome, occurred more often in RA (12%) compared to SpA (6%); p=ns). The rate of mortality was 6% in RA and 3% in SpA patients (p=ns, Table I). Further details of fatal courses are included in Table I.

Table I. Comparison of the SpA and RA patients regarding disease activity, immunomodulatory drugs, comorbidities, COVID-19 symptoms, COVID-19 course and characteristics of hospitalisation.

	SpA (104)	RA (104)	p-value (difference)
Baseline characteristics			
Female	63% (65)	63% (65)	p=1.000
Male	37% (39)	37% (39)	
Age (median) in years	56 (20-87)	56 (21-86)	p=0.999
BMI (median)	26.4	25.0	p=0.402
Disease activity (DA)			
Stable	43% (45)	48% (50)	p=0.289
Low	36% (37)	29% (30)	p=0.185
Moderate	10% (11)	12% (13)	p=0.414
High	1% (1)	4% (4)	p=0.184
Unknown	10% (10)	7% (7)	p=0.307
Immunomodulatory drugs			
GC (all)	13% (14)	40% (42)	**p=0.001**
GC (only)	3% (3)	2% (2)	p=0.500
GC (≤5 mg prednisolone per day)	93% (13/14)	86% (36/42)	
Prednisolone daily dose (median)	5 mg	5 mg	p=0.140
csDMARD (only)	14% (15)	26% (27)	p=0.028
GC + csDMARD	4% (4)	20% (21)	**p=0.001**
TNF-i (all)	45% (46)	19% (20)	**p=0.001**
TNF-i (only)	33% (34)	6% (6)	**p=0.001**
TNF-i + csDMARD/GC	12% (12)	13% (14)	p=0.417
JAK-i	1% (1)	12% (12)	**p=0.001**
IL-6-i	–	5% (5)	–
ABA	–	1% (1)	–
RTX	–	9% (9)	–
IL-17-i	15% (16)	–	–
IL-12/23-i	2% (2)	–	–
APR	1% (1)	–	–
No	11% (11)	5% (5)	p=0.096
Comorbidities			
CVD	9% (9)	6% (6)	p=0.197
AHT	34% (35)	34% (35)	p=0.558
Bronchial asthma	11% (11)	7% (7)	p=0.250
COPD	3% (3)	5% (5)	p=0.361
ILD	2% (2)	1% (1)	p=0.500
CRF	5% (5)	8% (8)	p=0.284
OST	5% (5)	4% (4)	p=0.500
DM	8% (8)	9% (9)	p=0.500
Cancer	8% (8)	4% (4)	p=0.187
Other	20% (21)	19% (20)	p=0.500
No	41% (43)	46% (48)	p=0.288
≥2	26% (27)	29% (30)	p=0.378
COVID-19 symptoms			
Duration (median) in days	12 (range: 0–42)	14 (range: 0–90)	p=0.297
Recovered	97% (101)	95% (98)	p=0.249
Fever	61% (63)	50% (52)	p=0.081
Cough	57% (59)	68% (71)	p=0.057
Expectoration	8% (8)	10% (10)	p=0.403
Rhinitis	20% (21)	20% (21)	p=0.568
Myalgia	38% (39)	26% (27)	p=0.050
Fatigue	45% (47)	48% (50)	p=0.391
Headache	38% (39)	29% (30)	p=0.093
Dyspnea	26% (27)	32% (33)	p=0.222
Vertigo	5% (5)	17% (18)	**p=0.003**
Abdominal pain	3% (3)	3% (3)	p=0.659
Diarrhoea	10% (10)	10% (10)	p=0.593
Vomiting	1% (1)	4% (4)	p=0.184
Loss of appetite	13% (13)	22% (23)	**p=0.049**
Loss of odour	26% (27)	32% (33)	p=0.222
Loss of taste	32% (33)	33% (34)	p=0.500
Other	18% (19)	15% (16)	p=0.365
No	8% (8)	8% (8)	p=0.602

	SpA (104)	RA (104)	*p*-value (difference)
COVID-19 course			
Hospitalisation	16% (17)	30% (32)	***p*=0.011**
Oxygen treatment	10% (11)	18% (19)	*p*=0.083
Invasive ventilation	3% (3)	8% (8)	*p*=0.107
Complications	6% (6)	12% (12)	*p*=0.080
Fatal courses	3% (3)	6% (6)	*p*=0.249
Characteristics of hospitalised patients			
Female	59% (10)	63% (20)	p=0.520
GC	18% (3)	47% (15)	***p*=0.041**
TNF-i	18% (3)	6% (2)	*p*=0.220
Fatal courses	18% (3)	16% (5)	*p*=0.577
Details of fatal courses			
Gender	1 male; 2 females	4 males, 2 females	
Age (years)	59 64 82	52 62 66 72 74 86	
BMI	27.8 40.6 unknown	28.7 32.0 33.6 unknown (3)	
Disease activity	Low: 1 Unknown: 2	Stable: 1 Low: 3 Moderate: 1 High: 1	
≥2 comorbidities	3	4	
Immunomodulatory drugs	GC: 2 (≤5 mg prednisolone/day) Sulfasalazine: 1 None: 1	GC: 4 (≤5 mg prednisolone/day) MTX: 1 LEF: 1 HCQ: 1 RTX: 2	

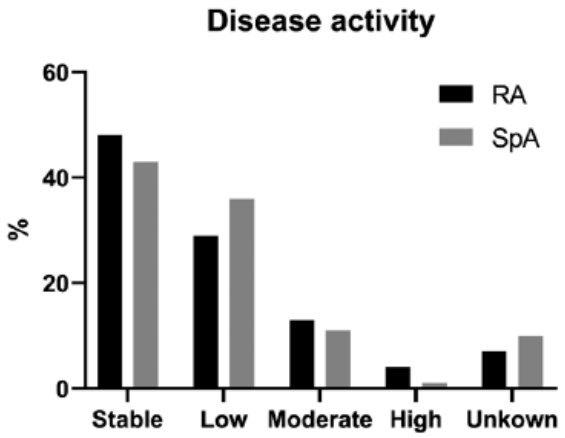


Fig. 2. Distribution of disease activity in RA and SpA patients. In 48% of the RA patients and 43% of the SpA patients, stable disease activity was reported. Low disease activity was reported in 29% of the RA and 36% of the SpA patients. Moderate disease activity could be detected in 13% of the RA and 11% of the SpA patients. Only 4% of the RA and 1% of the SpA patients were reported with high disease activity. Unknown disease activity was reported 10% of the SpA and 7% of the RA patients.

Characteristics of hospitalised patients

Regarding hospitalised cases, the median age of SpA patients was 64.0 (range: 41–87) years compared to 62.0 (range: 21–86) in RA patients. The rate of hospitalised patients treated with GC was again significantly higher in RA patients compared to SpA patients (47% *vs.* 18%; $p<0.05$). The median prednisolone dose was 5 mg per day in RA patients and 2.5 mg per day in SpA. Three RA patients received even 10–20 mg prednisolone per day. TNF-i treatment was reported in 18% of hospitalised SpA patients and 6% of RA-patients (*p*=ns) Of note, the majority of RA patients (6 out of 9 patients) treated with rituximab were treated as inpatients. On the other hand, 4 of these 6 patients received in addition ≤5 mg prednisolone/day and 3 patients additionally methotrexate. The median age of hospitalised rituximab patients was 61.0 years (range: 21–86) and the patients had at least one other comorbidity. Two of these patients needed invasive ventilation.

Discussion

The infection risk of IRD patients depends on the disease activity, on comorbidities, and on the type and dosage of immunomodulatory treatment (17, 18). Patients affected by IRD are at an overall increased risk of infections compared to the general population (18-20), but only few data exist, whether specific types of IRD or the respective immunomodulation might be associated with an increased risk for viral infections of the respiratory tract, including development of a severe course of COVID-19.

To our knowledge this is the first comparison of the most common types of IRD, RA and SpA, regarding the outcome of SARS-CoV-2 infection, and in this gender- and age-matched comparison we found a significantly lower rate of hospitalisation in SpA patients (16%) compared to RA patients (30%). In addition, the number of SpA patients who needed oxygen treatment was also lower (10%) compared to RA patients (18%). Fatalities were twice as high in RA compared to SpA (6 *vs.* 3), due to the low numbers however, this was not statistically significant. Noteworthy, RA-patients (40%) were significantly more often treated with GC compared to SpA-patients (13%). As GC seem to be associated with worse outcome (21), this could be one of the reasons for the higher hospitalisation rate and mortality in RA patients. Another potential reason could be treatment with rituximab (RTX) in the RA group. Six of nine RA patients treated with RTX

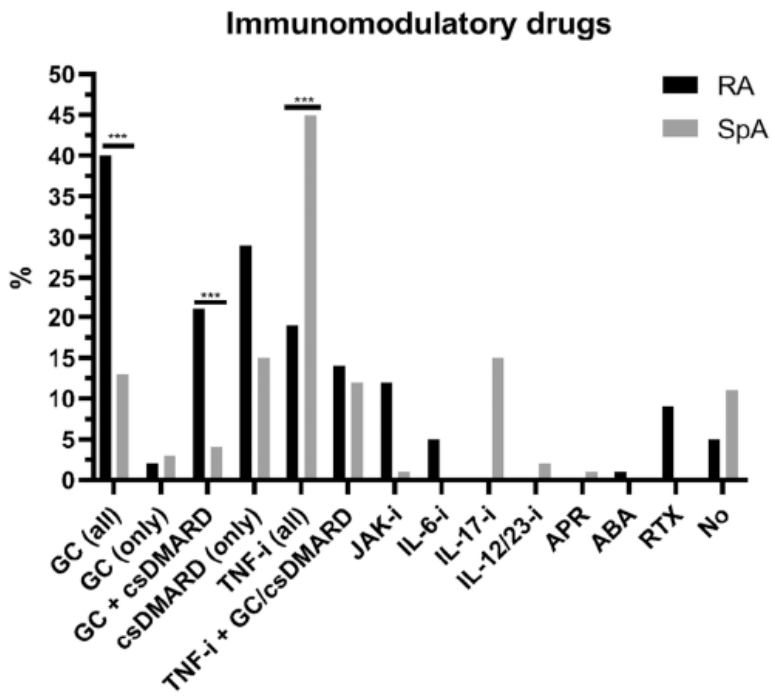


Fig. 3. Distribution of immunomodulatory drugs in RA and SpA patients.
The majority of the RA patients (40%) were treated with GC, which was the case in only 13% of the SpA patients (p=0.001). Single use of GC was reported in 2% of the RA and 3% of the SpA patients. 20% of the RA and 4% of the SpA patients were treated with a combination of GC and csDMARD (p=0.001). 26% of the RA and 14% of the SpA patients were treated with only csDMARD (p=0.028). The use of TNF-i was reported in 19% of the RA and 45% of the SpA patients (p=0.001). Combined TNF-i and GC/csDMARD were used in 13% of the RA and 12% of the SpA patients. JAK-i was reported in 12% of the RA and 1% of the SpA patients. 5% of the RA patients were treated with IL-6-i, 1% with ABA and 9% with rituximab. 15% of the SpA patients were treated with IL-17-i, 2% with IL-12/23-i and 1% with APR. In 5% of the RA and 11 of the SpA patients no immunomodulatory drug was used.
GC: glucocorticoids; csDMARD: conventional synthetic disease-modifying drug; TNF-i: tumour necrosis factor α inhibitor; JAK-i: Janus kinase inhibitor; IL-6-i: interleukin 6 inhibitor; IL-17-i: interleukin 17 inhibitor; IL-12/23-i: interleukin 12/23 inhibitor; APR: apremilast; ABA: abatacept; RTX: rituximab.

needed hospitalisation, of whom two were reported as fatal. Some studies described also a higher risk for hospitalisation in patients treated with rituximab (22-25), potentially based on a decrease in serum IgG resulting in a generally increased incidence of certain viral infections (22). During the COVID-19 pandemic, a higher incidence of severe COVID-19 in patients on RTX compared to infliximab was described (26). In contrast, in psoriasis patients receiving biologic treatment, no adverse impact of biologics on COVID-19 outcome could be observed (27). PsA and RA share similarities, such as synovitis, but show differences in the pathophysiology (Fig. 1) and in treatment strategies. With regard to these two entities, Rituximab is exclusively used in RA in the case of chronic inflammatory arthritis, while IL-17-inhibitors are used in PsA and AS. This could be an explanation for the differences in the hospitalisation rates in these two diseases.

Despite all of the efforts to investigate the influence of SARS-CoV-2 on IRD patients, still limited data are available how COVID-19 affects IRD patients and how immunomodulatory drugs might influence the course of COVID-19. SARS-CoV-2 can lead to a massive immune response with a "cytokine storm" and an often fatal outcome (28, 29). Cytokines play also a crucial role in the pathophysiology of COVID-19 (30). An infection with SARS-CoV-2 can lead to an activation of the innate immune cells, which is especially the case in severe COVID-19 courses (30). Due to this activation, elevated levels of TNF, IL-1β, IL-6, IL-8, IL-17, G-CSF and GM-CSF and chemokines, *e.g.* C-C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 10 (CXCL10) and macrophage inflammatory protein 1 alpha (MIP-1α), MIP-1β are detectable (30, 31). Inhibiting the cytokine storm by targeting cytokines, such as TNF-α, might have a positive influence on the course of COVID-19 (32, 33). These cytokines and chemokines do also play a crucial role in the pathophysiology of RA and SpA (Fig. 1). This could be a further reason for the lower hospitalisation rate of SpA patients compared to RA patients, since the proportion of TNF-i use was significantly higher in SpA than in RA (p=0.001). Although in patients hospitalised with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone (34), in IRD patients, long-term 'antirheumatic' therapy with prednisolone exposure starting already with a dose of 5 mg/day was associated with a higher risk for hospitalisation (21, 35, 36).

The limitations of our study, due to the fortunately low number of severe courses, are the lack of analysis of interaction between variables associated with mortality, such as specific immunomodulatory drugs. However, as mostly symptomatic patients were tested and included in our registry, the prevalence of asymptomatic infections may even have been higher. Another limitation could be that due to the matching process, the SpA study population increased in age (53 years → 56 years), while RA patients decreased (72 years → 56 years). In addition, both groups were matched for gender, which led to a change of the rate of male/female patients in both groups (SpA: 50% → 63% female; RA: 72% → 63% female). As more male and younger patients are affected by SpA, this could have an impact on the course of COVID-19 in these patients.

Conclusions

In this study comparing gender- and age-matched RA and SpA patients, a significantly higher hospitalisation rate in RA patients could be observed, which could be due to the use of GC, lower rate of TNF-i treatment or spe-

Fig. 4. Distribution of comorbidities in RA and SpA patients.
CVD was reported in 9% of SpA and 6% of the RA patients. In both groups, AHT was reported in 34% of the cases,11% of the SpA and 5% of the RA patients suffered from bronchial asthma, 5% of the RA patients and 3% of the SpA patients from COPD, 2% of the SpA patients and 1% of the RA patients from ILD. CRF was reported in 8% of the RA and 5% of the SpA patients, OST in 4% of the RA and 5% of the SpA patients, DM in 9% of the RA and 8% of the SpA patients and cancer/history of cancer in 4% of the RA and 8% of the SpA patients. 46% of the RA and 41% of the SpA patients had no comorbidities, 29% of the RA and 26% of the SpA patients had more than two comorbidities.
CVD: cardiovascular diseases; AHT: arterial hypertension; AB: bronchial asthma; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; CRF: chronic renal failure; OST: osteoporosis; DM: diabetes mellitus; >2: more than 2 comorbidities.

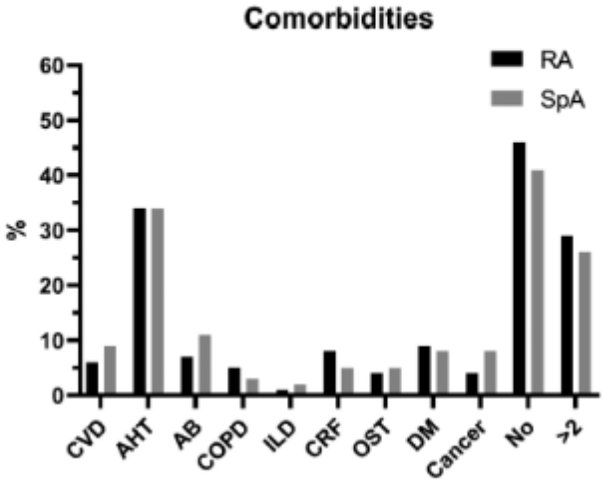
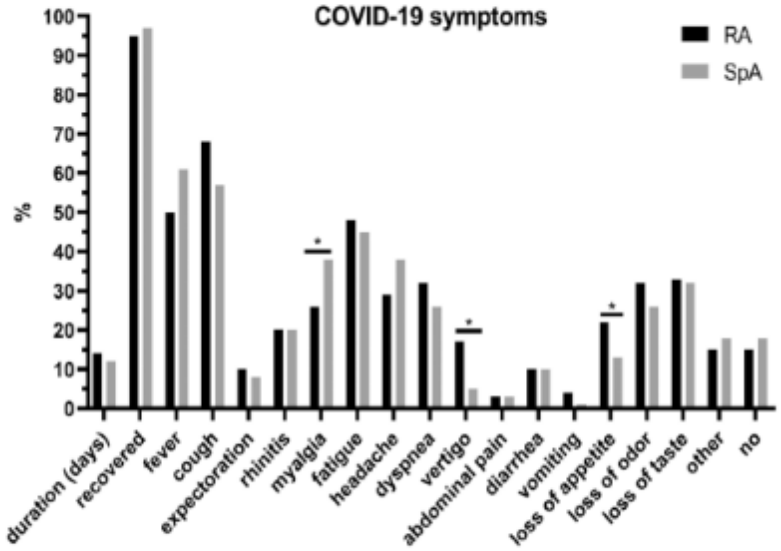


Fig. 5. Distribution of COVID-19 duration, rate of recovery and COVID-19 symptoms in RA and SpA patients.
COVID-19 duration was in RA patients 14 days and in SpA patients 12 days in median. In both groups, the majority of the patients (97% SpA, 95% RA) recovered from COVID-19. 50% of the RA and 61% of the SpA patients reported fever, 68% of the RA and 57% of the SpA patients cough, 10% of the RA and 8% of the SpA patients expectoration, 20% of each group rhinitis, 26% of the RA and 38% of the SpA patients myalgia (p=0.05), 48% of the RA and 45% of the SpA patients fatigue, 29% of the RA and 38% of the SpA patients headache, 32% of the RA and 26% of the SpA patients dyspnea, 17% of the RA and 5% of the SpA patients vertigo (p=0.003), 3% of each group abdominal pain, 10% of each group diarrhoea, 4% of the RA and 1% of the SpA patients vomiting, 22% of the RA and 13% of the SpA patients loss of appetite (p<0.05), 32% of the RA and 26% of the SpA patients loss of odour, 33% of the RA and 32% of the SpA patients loss of taste, 15% of the RA and 18% of the SpA patients other relevant symptoms. In 8% of the RA and SpA patients no COVID-19 related symptoms occurred.

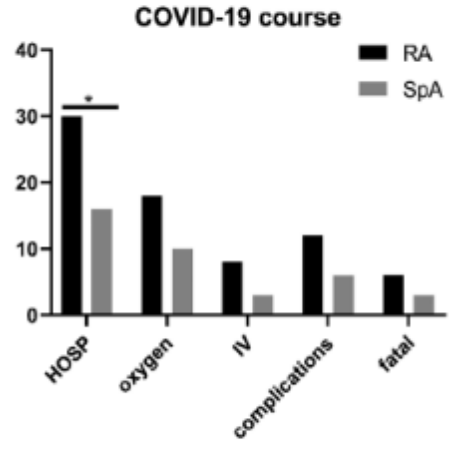


cific pathophysiology of the disease. We did not find any relevant differences in the frequency of COVID-19-related mortality.

Key messages

- RA patients were treated more often with glucocorticoids
- SpA patients received more frequently bDMARDs, especially TNF-inhibitors
- The number of patients, who did not develop any COVID-19 related symptoms after infection, was similar in both groups
- SpA patients show a lower hospitalisation rate (16% *vs*. 30% RA patients), but COVID-19 affected SpA patients do not differ significantly in mortality

Fig. 6. Distribution of COVID-19 courses in RA and SpA patients.
30% of the RA and 16% of the SpA patients needed to be hospitalised (p=0.011), 18% of the RA and 10% of the SpA patients were treated with oxygen non-invasively and invasively. 8% of the RA and 3% of the SpA patients needed an IV. In 6% of the RA and 3% of the SpA cases deadly courses were reported.
HOSP: hospitalisation; oxygen: oxygen treatment IV: invasive ventilation



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EPIDEMIOLOGICAL SCIENCE

Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 Global Rheumatology Alliance physician registry

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ABSTRACT

Objective To investigate baseline use of biologic or targeted synthetic (b/ts) disease-modifying antirheumatic drugs (DMARDs) and COVID-19 outcomes in rheumatoid arthritis (RA).

Methods We analysed the COVID-19 Global Rheumatology Alliance physician registry (from 24 March 2020 to 12 April 2021). We investigated b/tsDMARD use for RA at the clinical onset of COVID-19 (baseline): abatacept (ABA), rituximab (RTX), Janus kinase inhibitors (JAKi), interleukin 6 inhibitors (IL-6i) or tumour necrosis factor inhibitors (TNFi, reference group). The ordinal COVID-19 severity outcome was (1) no hospitalisation, (2) hospitalisation without oxygen, (3) hospitalisation with oxygen/ventilation or (4) death. We used ordinal logistic regression to estimate the OR (odds of being one level higher on the ordinal outcome) for each drug class compared with TNFi, adjusting for potential baseline confounders.

Results Of 2869 people with RA (mean age 56.7 years, 80.8% female) on b/tsDMARD at the onset of COVID-19, there were 237 on ABA, 364 on RTX, 317 on IL-6i, 563 on JAKi and 1388 on TNFi. Overall, 613 (21%) were hospitalised and 157 (5.5%) died. RTX (OR 4.15, 95% CI 3.16 to 5.44) and JAKi (OR 2.06, 95% CI 1.60 to 2.65) were each associated with worse COVID-19 severity compared with TNFi. There were no associations between ABA or IL6i and COVID-19 severity.

Conclusions People with RA treated with RTX or JAKi had worse COVID-19 severity than those on TNFi. The strong association of RTX and JAKi use with poor COVID-19 outcomes highlights prioritisation of risk mitigation strategies for these people.

INTRODUCTION

The ongoing COVID-19 pandemic has had a significant impact on people with rheumatoid arthritis (RA), many of whom are treated with biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs).[1] While b/tsDMARDs are important for controlling RA disease activity, their influence on COVID-19 outcomes in people with RA remains unclear. This uncertainty has led to anxiety, social isolation due to shielding practices and b/tsDMARD discontinuation, which may contribute to RA flares.[2–4] Addressing the knowledge gaps around the influence of b/tsDMARDs on COVID-19 outcomes is a priority for people with RA and their providers.

Key messages

What is already known about this subject?

- A previous international registry study of the COVID-19 Global Rheumatology Alliance (C19-GRA) suggested that people with systemic rheumatic diseases on biologic or targeted synthetic (b/ts) disease-modifying antirheumatic drugs (DMARDs) had lower odds of hospitalisation than those not using DMARDs.
- Previous studies reported that people with systemic rheumatic diseases using rituximab had higher odds of COVID-19-related mortality than those using alternative DMARDs such as methotrexate.

What does this study add?

- Using the C19-GRA, we analysed people with rheumatoid arthritis (RA) using b/tsDMARD (to limit the potential for confounding) at the time of COVID-19 onset and investigated an ordinal outcome that encompassed a range of COVID-19 outcomes.
- People with RA using rituximab or Janus kinase (JAK) inhibitors at COVID-19 onset were more likely to experience poor COVID-19 outcomes, ranging from hospitalisation to death, compared with use of tumour necrosis factor inhibitors.

How might this impact on clinical practice or future developments?

- People using rituximab or JAK inhibitors for RA are more likely to experience poor COVID-19 outcomes and should be prioritised for risk mitigation strategies.

The impact of b/tsDMARDs on COVID-19 outcomes is of particular interest since some of these medications, such as tocilizumab and baricitinib, have been studied as repurposed treatments for COVID-19. Some evidence suggests that baseline use of certain b/tsDMARDs, like tumour necrosis factor inhibitors (TNFi), for inflammatory disorders may be associated with less severe COVID-19 outcomes.[5] In addition, among patients with COVID-19, treatment with interleukin 6 inhibitors (IL-6i) and baricitinib led to improved outcomes in some clinical trials.[6–9] However, there are also concerns that baseline use of certain b/tsDMARDs, such as rituximab or abatacept, may be associated with worse COVID-19 outcomes due to impaired viral immune defences.[10 11]

Due to sample size limitations, previous studies of b/tsDMARD use and COVID-19 outcomes have combined heterogeneous rheumatic diseases and medications and/or investigated a single outcome, such as hospitalisation.[5 12] Therefore, we used the COVID-19 Global Rheumatology Alliance (C19-GRA) physician registry to evaluate the associations of different classes of b/tsDMARDs with a range of COVID-19 outcomes in people with RA.

METHODS

Data source and study sample assembly

People with rheumatic disease and COVID-19 from the C19-GRA registry and the European Alliance of Associations for Rheumatology (EULAR) COVID-19 database were included in the analyses. We included cases entered between 24 March 2020 and 12 April 2021. The C19-GRA and EULAR databases include people with rheumatic diseases diagnosed with COVID-19, as reported by rheumatology providers via two international data entry portals. The details of these registries have been previously reported.[5 12–17] We analysed people with RA on b/tsDMARD at the time of COVID-19 clinical onset. As of 12 April 2021, a total of 15 127 people with rheumatic diseases and COVID-19 have been reported. We included people with RA who were taking one of the following medication classes: Cytotoxic T lymphocyte-associated antigen immunoglobulin (CTLA4-Ig: abatacept), anti-CD20 (rituximab), IL-6i (tocilizumab, sarilumab), Janus kinase inhibitors (JAKi: tofacitinib, baricitinib or upadacitinib) or TNFi (infliximab, etanercept, adalimumab, certolizumab pegol and golimumab). The drug class of b/tsDMARD was collected, rather than individual drugs. We did not include IL-1 inhibitors since these were infrequently used for RA. Prior studies using the C19-GRA and EULAR databases have included some patients also reported in this study, but the analyses included in this study and observations reported are novel. In addition, follow-up for this study is more current than previous publications using these data.

Data quality was assessed by the University of California, San Francisco and the University of Manchester, UK, which both confirmed that there were no duplicates in the data entries.

Baseline b/tsDMARD exposures

The exposure of interest was baseline use of a b/tsDMARD at the time of COVID-19 clinical onset. As in previous C19-GRA investigations, we included confirmed and presumptive cases of COVID-19.[5 12 14] We limited this analysis to users of abatacept, rituximab, IL-6i, JAKi or TNFi to limit the cohort to people with similar RA disease severity and minimise the impact of confounding by indication. We included b/tsDMARD users regardless of whether they also used a conventional synthetic (cs) DMARD or glucocorticoids, but did not include people on csDMARDs (eg, hydroxychloroquine, methotrexate, sulfasalazine, leflunomide) monotherapy, as monotherapy may indicate less severe RA or be due to care access barriers or socioeconomic factors. TNFi users were the reference group since TNFis are the most frequently used b/tsDMARD in RA. People with RA who were reported to be on more than one b/tsDMARD were excluded from the analysis.

COVID-19 outcomes

The primary outcome of interest was a mutually exclusive ordinal COVID-19 severity outcome: (1) no hospitalisation, (2) hospitalisation with no oxygenation, (3) hospitalisation with any oxygenation or mechanical ventilation, and (4) death. We chose this primary outcome to estimate the association of b/tsDMARD exposure with general odds of worse COVID-19 severity rather than a single outcome. A similar outcome was developed by the WHO to capture the spectrum of disease and is used in clinical trials evaluating COVID-19 therapeutics.[18] If a patient met multiple levels of the outcome, they were only included at the highest level. At the time of analysis, all patients were required to have a resolved clinical course.

Covariates

Details regarding demographics, including age, race/ethnicity and continent, and patient characteristics, including obesity, smoking, comorbidities (interstitial lung disease (ILD), history of cancer, hypertension, cardiovascular disease, chronic kidney disease/end-stage kidney disease, diabetes, non-ILD pulmonary disease), RA disease activity (as judged by the reporting physician), glucocorticoid dose for RA at the time of COVID-19 onset

and use of concomitant csDMARD (methotrexate, sulfasalazine, hydroxychloroquine), were by physician report. For glucocorticoid dose, the amount of prednisone-equivalent glucocorticoid prescribed was treated as a categorical variable (none, >0–5 mg/day, 6–9 mg/day and ≥10 mg/day). Hypertension and cardiovascular disease were collapsed as a single comorbidity due to collinearity.

Statistical analysis

We reported baseline characteristics and outcomes across the exposure categories of baseline b/tsDMARD use with descriptive statistics.

Ordinal logistic regression models were used to assess the association between each b/tsDMARD compared with TNFi use and the severity of COVID-19 on an ordinal scale in unadjusted and multivariable analyses to estimate ORs and 95% CIs. The effect size of the ordinal outcome can be interpreted as the odds of being one level higher on the ordinal COVID-19 severity scale than the reference group. We assessed the proportional odds assumption for the ordinal regression model using the Brant test.[19] Models in which the proportional odds assumption was not met were refitted using the partial proportional odds model which relaxes the assumption of proportionality for offending predictors.[20] We considered potential confounders known to be associated with either b/tsDMARD use or COVID-19 severity. Covariates included in multivariable models included sociodemographic features (age, sex), obesity, smoking status (ever vs never), concomitant csDMARD use (methotrexate, hydroxychloroquine, sulfasalazine, or leflunomide), categorical glucocorticoid use/dose, categorical comorbidity count (0, 1, 2 of the following: chronic kidney insufficiency/end-stage kidney disease, diabetes, non-ILD pulmonary disease), other key comorbidities as individual variables (hypertension/cardiovascular disease, ILD and cancer), disease activity (moderate/high vs remission/low), continent (Europe, North America, South America, other) and calendar time (January–15 June 2020 vs 16 June 2020–12 April 2021).[21] These time periods were selected based on the initial publication of the RECOVERY trial, which reported a survival benefit associated with dexamethasone and influenced subsequent practice.[22] We assumed that missing data were 'missing at random'. We then performed multiple imputation five times to get pooled estimates to impute missing values for disease activity, race/ethnicity, glucocorticoid dose, smoking, hypertension/cardiovascular disease and comorbidity count. After imputation, we compared the distribution of imputed values with the distribution of variables before imputation to confirm that distributions were similar before and after imputation.

To confirm the robustness of our findings, we performed several sensitivity analyses. First, we excluded patients with ILD or cancer from the analysis since rituximab is commonly used in these patients, who may also be susceptible to poor COVID-19 outcomes. Second, given data showing a strong association between race/ethnicity and COVID-19 outcomes in the USA, we performed an analysis adjusting for this variable among US patients in the registry. The race/ethnicity variable was categorised as white, black, Hispanic, Asian or other/mixed race. However, for the model with IL-6i, there were few outcomes within the race/ethnicity variable so we were unable to perform the model. Third, we used propensity score matching to further address potential confounding by indication. We estimated propensity scores for b/tsDMARD use based on age, sex, obesity, smoking, concomitant csDMARDs, glucocorticoid use/dose, number of comorbidities, disease activity, region and calendar time. Covariate balance between each b/tsDMARD drug class and TNFi was assessed using Love plots (online supplemental figures 1–4), which showed that most of the covariates were matched with an absolute standardised mean difference less than 0.1, denoting sufficient matching performance.[23] Ordinal logistic regression was then performed after matching. Fourth, we repeated our primary analysis after excluding patients with a presumptive diagnosis of COVID-19. Presumptive cases were those that lacked one of the following: positive PCR or antigen test for SARS-CoV-2 or typical chest imaging findings. Fifth, we repeated the analysis but stratified by calendar time (before or after 15 June 2020 when RECOVERY trial's results were announced) and by continent (North America or Europe) in case calendar time and geography may have influenced the results. Sixth, we used a revised version of the ordinal COVID-19 severity outcome that considered mechanical ventilation as its own category.

We then repeated our primary analyses using dichotomised outcomes rather than the ordinal COVID-19 severity scale to investigate whether there were particular outcomes driving the associations we observed. For example, we investigated whether each b/tsDMARD was associated with hospitalisation (yes/no) compared with TNFi use.

We used the Brant test to assess whether the observed deviations from the ordinal logistic regression are larger than what could be attributed to chance alone. If the p values are greater than the alpha level of 0.05, then the covariates satisfy the proportional odds assumption. This assumption states that the estimate between each pair of outcomes across the response levels regardless of the partition that we consider. For abatacept and JAKis, both age and glucocorticoid dose violated the assumption, and for IL-6is and rituximab, age, gender and glucocorticoid dose violated the assumption. In order to address the lack of proportionality for these covariates, partial proportional odds models were run to relax this assumption for the respective covariates for each medication category (online supplemental table 1). We found that the estimates were similar when comparing the proportional odds models and the non-proportional odds model, so we reported the model without relaxing the assumption.

Results were considered statistically significant at two-sided $p<0.05$. Analyses were conducted in R V.4.0.2.

RESULTS

Study sample and baseline characteristics

From a total of 6132 RA cases reported to the registry, we identified 2869 who were on abatacept (n=237), rituximab (n=364), IL-6i (n=317), JAKi (n=563) or TNFi (n=1388) at the time of clinical COVID-19 onset. The baseline clinical characteristics are shown in table 1. The sample was predominantly female (80.8%) and the mean age was 56.7 years (SD 13.4). Most patients were from Europe (51.8%) and North America (35.0%). Overall, 354 (12.3%) were obese, 582 (20.3%) were ever smokers, 810 (28.2%) were on glucocorticoids, 1409 (49.1%) were on concomitant csDMARDs, and 510 (17.8%) had moderate/high RA disease activity. Among b/tsDMARD users, rituximab users were more likely than TNFi users to have ILD (11.0% vs 1.4%) or a history of cancer (7.4% vs 0.9%); JAKi users were slightly more likely than TNFi users to be obese (15.1% vs 10.3%).

Table 1 Baseline characteristics according to use of biologic or targeted synthetic disease-modifying antirheumatic drugs for rheumatoid arthritis at the time of COVID-19 onset

	Overall N=2869	Abatacept n=237	Rituximab n=364	IL-6 inhibitors n=317	JAK inhibitors n=563	TNF inhibitors n=1388
Demographics						
Mean age (years), SD	56.7 (13.4)	61.4 (14.0)	58.0 (12.9)	56.4 (12.0)	58.0 (12.3)	55.2 (14.0)
Female	2316 (80.8)	188 (79.3)	299 (82.1)	257 (81.3)	470 (83.5)	1102 (79.4)
Race/ethnicity						
White	1670 (69.0)	78 (69.5)	187 (64.5)	169 (67.9)	360 (73.2)	829 (69.3)
Black	113 (4.7)	5 (3.2)	14 (4.8)	11 (4.4)	22 (4.5)	60 (5.0)
Hispanic	472 (19.5)	32 (20.8)	66 (22.8)	46 (18.5)	79 (16.1)	233 (19.5)
East Asian	81 (3.3)	8 (5.2)	10 (3.4)	12 (4.8)	10 (2.0)	37 (3.1)
Other	85 (3.3)	2 (1.3)	13 (4.5)	11 (4.4)	21 (4.3)	38 (3.2)
Continent						
Europe	1486 (51.8)	103 (43.5)	218 (59.9)	183 (57.7)	283 (50.3)	699 (50.4)
North America	1005 (35.0)	105 (44.3)	111 (30.5)	83 (26.2)	208 (36.9)	498 (35.9)
South America	276 (9.6)	20 (8.4)	23 (6.3)	33 (10.4)	55 (9.8)	145 (10.4)
Other	302 (10.5)	9 (3.8)	12 (3.3)	18 (5.7)	17 (3.0)	46 (3.3)
Comorbidity count*						
0	1494 (52.1)	113 (47.7)	161 (44.2)	161 (50.8)	270 (48.0)	789 (56.8)
1	837 (29.2)	70 (29.5)	119 (32.7)	99 (31.2)	176 (31.3)	373 (26.9)
2	538 (18.8)	54 (22.8)	84 (23.1)	57 (18.0)	117 (20.8)	226 (16.3)
Individual comorbidities						
Hypertension	983 (34.3)	91 (38.4)	121 (33.2)	108 (34.1)	221 (39.3)	442 (31.8)
Cardiovascular disease	247 (8.6)	29 (12.2)	36 (9.9)	32 (10.1)	51 (9.1)	99 (7.1)
Diabetes	356 (12.5)	30 (12.8)	54 (14.9)	43 (13.6)	74 (13.2)	155 (11.3)
Chronic kidney disease	98 (3.4)	11 (4.7)	11 (3.0)	14 (4.4)	22 (3.9)	40 (2.9)
Lung disease†	432 (15.2)	41 (17.4)	87 (24.0)	44 (13.9)	92 (16.4)	168 (12.3)
Interstitial lung disease	103 (3.6)	15 (6.3)	40 (11.0)	15 (4.7)	13 (2.3)	20 (1.4)
Cancer	40 (1.5)	5 (2.5)	27 (7.4)	6 (2.2)	5 (1.0)	11 (0.9)
Obesity	354 (12.3)	31 (13.1)	52 (14.3)	43 (13.6)	85 (15.1)	143 (10.3)
Smoking status						
Ever	582 (20.3)	104 (43.9)	70 (19.2)	57 (18.0)	99 (17.6)	300 (21.6)
Never	1369 (47.7)	56 (23.6)	142 (39.0)	152 (47.9)	262 (46.5)	694 (50.)
Missing	918 (32.0)	77 (32.5)	137 (37.6)	107 (33.8)	202 (35.9)	394 (28.4)
Concomitant RA medications						
Any conventional synthetic DMARD	1409 (49.1)	118 (49.8)	194 (53.3)	102 (32.2)	228 (40.5)	767 (55.3)
Methotrexate	1188 (41.4)	92 (38.8)	146 (40.1)	91 (28.7)	188 (33.4)	671 (48.3)
Sulfasalazine	136 (4.7)	9 (3.8)	26 (7.1)	8 (2.5)	18 (3.2)	75 (5.4)
Hydroxychloroquine	260 (9.1)	25 (10.5)	58 (15.9)	18 (5.7)	43 (7.6)	116 (8.4)
Leflunomide	176 (10.5)	26 (11.0)	49 (13.5)	20 (6.3)	29 (5.2)	117 (8.4)
Glucocorticoid dose, median (IQR)	5.0 (4.0–6.0)	5.0 (4.0–5.5)	5.0 (5.0–7.5)	5.0 (4.5–7.0)	5.0 (3.0–5.0)	5.0 (5.0–7.0)
Categorical glucocorticoid use/dose						
No glucocorticoid use	1756 (61.2)	120 (56.9)	186 (51.1)	173 (54.6)	320 (63.5)	957 (76.1)
Glucocorticoid >0–5 mg/day prednisone equivalent	600 (20.9)	68 (32.2)	93 (25.5)	69 (21.8)	149 (29.6)	221 (17.6)
Glucocorticoid 6–9 mg/day prednisone equivalent	68 (2.4)	8 (3.8)	10 (2.7)	15 (4.7)	12 (2.4)	23 (1.8)
Glucocorticoid ≥10 mg/day prednisone equivalent	142 (4.9)	15 (7.1)	28 (7.7)	19 (6.0)	23 (4.6)	57 (4.5)
Missing	303 (10.6)	26 (11.0)	47 (12.9)	41 (12.9)	59 (10.5)	130 (9.4)
RA disease activity by global physician assessment						
Remission or low	1949 (67.9)	147 (74.2)	226 (76.1)	198 (77.3)	388 (78.7)	990 (81.5)
Moderate or high	510 (17.8)	51 (25.8)	71 (23.9)	58 (22.7)	105 (21.3)	225 (18.5)
Missing	410 (14.3)	39 (16.5)	67 (18.4)	61 (19.2)	70 (12.4)	173 (12.5)
Confirmed COVID-19	2333 (81.3)	201 (84.8)	304 (83.5)	244 (77.0)	475 (84.4)	1109 (79.9)

n (%) presented unless otherwise specified.
*Comorbidity count included diabetes, lung disease and chronic kidney disease.
†Interstitial lung disease, chronic obstructive pulmonary disease, asthma or other lung disease.
DMARDs, disease-modifying antirheumatic drugs; IL-6, interleukin 6; JAK, Janus kinase; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

COVID-19 outcomes

Outcomes according to the COVID-19 severity scale are shown in table 2. The majority of patients (78.6%) were not hospitalised, 137 (4.8%) were hospitalised without oxygenation, 319 (11.1%) were hospitalised with any oxygen or ventilation requirement, and 157 (5.5%) died. Among rituximab users, 80 (22.0%) required hospitalisation with any oxygen or ventilation and 54 (14.8%) died compared with 103 (7.4%)

Table 2 Frequencies and proportions of outcomes in the ordinal COVID-19 severity scale according to baseline use of biologic or targeted synthetic disease-modifying antirheumatic drug for patients with rheumatoid arthritis at the time of COVID-19 onset (N=2869)

COVID-19 severity scale	Overall N=2869 n (%)	Abatacept n=237 n (%)	Rituximab n=364 n (%)	IL-6 inhibitors n=317 n (%)	JAK inhibitors n=563 n (%)	TNF inhibitors n=1388 n (%)
Not hospitalised	2256 (78.6)	181 (76.4)	210 (57.7)	271 (85.5)	409 (72.6)	1185 (85.4)
Hospitalised without oxygenation	137 (4.8)	12 (5.1)	20 (5.5)	13 (4.1)	28 (5.0)	64 (4.6)
Hospitalised with any oxygen or ventilation	319 (11.1)	26 (11.0)	80 (22.0)	24 (7.6)	86 (15.3)	103 (7.4)
Death	157 (5.5)	18 (7.6)	54 (14.8)	9 (2.8)	40 (7.1)	36 (2.6)

IL-6, interleukin 6; JAK, Janus kinase; TNF, tumour necrosis factor.

and 36 (2.6%) TNFi users, respectively. Among JAKi users, 86 (15.3%) were hospitalised with oxygen/ventilation and 40 (7.1%) died. Only 9 (2.8%) patients on baseline IL-6i died.

Associations of b/tsDMARDs with COVID-19 severity

The multivariable ordinal logistic regression model is shown in table 3. Compared with TNFi users, rituximab users had 4.15 (95% CI 3.40 to 3.80) greater odds of worse COVID-19 severity as compared with patients taking TNFi, while JAKi users had 2.06 (95% CI 1.60 to 2.65) greater odds of worse COVID-19 severity. No significant associations were found with respect to abatacept or IL-6i compared with TNFi in the primary analysis.

Sensitivity analyses

Sensitivity analyses of the drug class comparisons are shown in table 3. After excluding patients with ILD or cancer, the association between rituximab with poor COVID-19 outcomes when compared with TNFi use remained strong (OR 4.34, 95% CI 3.23 to 5.82). Among patients with RA in the USA, results were also similar when additionally adjusting for race/ethnicity. We also performed a propensity score-matched analysis instead of multivariable ordinal logistic regression. The sample for each propensity score-matched analysis is illustrated in online supplemental figure 5. Rituximab users (OR 3.36, 95% CI 2.11 to 5.34) and JAKi users (OR 1.56, 95% CI 1.01 to 2.42) had increased COVID-19 severity compared with TNFi users in this analysis. In the propensity score-matched analysis, abatacept had an OR of 1.60 (95% CI 1.02 to 2.51) for the ordinal COVID-19 severity outcome compared with TNFi. IL-6i use was not associated with COVID-19 severity in any of the analyses. Brant tests indicated that the proportional odds assumption did not hold for propensity score models; therefore, partial proportional odds models were used and confirmed that the effect estimates remained consistent (data not shown).

When stratified by calendar time (before or after 15 June 2020) and restricted to Europe or North America, the results were similar (online supplemental table 2).

Individual COVID-19 outcomes

We also performed analyses for each binary level of the COVID-19 severity scale (table 4). Rituximab and JAKi use were each associated with increased odds for each COVID-19 outcome compared with TNFi use. For example, rituximab use had increased odds for hospitalisation (OR 4.53, 95% CI 3.32 to 6.18) as well as death (OR 4.57, 95% CI 3.32 to 9.01) compared with TNFi use. JAKi use was associated with all outcomes considered, including hospitalisation requiring any oxygen or ventilation or death (OR 1.55, 95% CI 1.04 to 2.18) and death (OR 2.04, 95% CI 1.58 to 2.65) compared with TNFi. In these analyses, there were no statistically significant associations between abatacept or IL-6i use and the dichotomised outcomes when compared with TNFi use.

We considered a revised version of the ordinal outcome that included mechanical ventilation as a separate level. There were relatively few patients who survived after requiring mechanical ventilation (online supplemental table 2). Results were similar using this revised ordinal outcome (online supplemental tables 3 and 4).

DISCUSSION

Among patients with RA on b/tsDMARDs at the onset of COVID-19, rituximab and JAKi users were at increased odds for worse COVID-19 outcomes compared with TNFi users. In contrast, we did not find an association between abatacept or IL-6i use with worse COVID-19 outcomes when compared with TNFi users. These observations can inform decision making for providers and patients during the ongoing COVID-19 pandemic. Given the association between rituximab and JAKi use with poor outcomes, vaccination and public health measures such as mask wearing and social distancing for COVID-19 risk mitigation remain paramount. In addition, other specific interventions (eg, monoclonal antibody treatment) might be considered in these patients with COVID-19 exposure or early infection.[24]

Our observations, which use the largest sample of individuals with RA and COVID-19 assembled to date, regarding rituximab exposure confirm findings from prior studies suggesting an association between baseline use of B cell depleting therapies and worse COVID-19 outcomes in people with rheumatic diseases[12 25 26] and multiple sclerosis.[27] We also expand on prior observations using the C19-GRA and EULAR databases by evaluating the association of rituximab with COVID-19 severity rather than only mortality and by using an alternative reference group (TNFi rather than methotrexate) and performing propensity score analyses to further address confounding by indication. By focusing on a single disease, we also were able to identify a novel association of JAKis with COVID-19 severity. Mechanistically, the impact of B cell depletion on antibody production would be expected to impair the immune system's normal response to a viral infection. Indeed, the antibody response to COVID-19 is critical for controlling the initial infection and preventing reinfection.[28] We lacked details regarding the timing of rituximab exposure in relation to the COVID-19 infection or the duration of B cell depletion at the time of infection, which may be particularly relevant when considering the risk of a poor outcome following rituximab exposure. It is also possible that glucocorticoids given as a premedication to rituximab infusions may have contributed to the increased risk of poor COVID-19 outcomes in patients with RA on rituximab. While the results were robust to several sensitivity analyses, it is possible that the result could be confounded by factors such as unrecognised ILD.

Table 3 Results of primary and sensitivity analyses investigating the associations of baseline use of biologic or targeted synthetic disease-modifying antirheumatic drugs with COVID-19 severity (N=2869)

	Abatacept		Rituximab		IL-6i		JAKi		TNFi
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	Ref
Unadjusted	1.88 (1.35 to 2.63)	<0.01	4.63 (3.60 to 5.96)	<0.01	1.00 (0.71 to 1.41)	0.99	2.28 (1.80 to 2.88)	<0.01	Ref
Age-adjusted and sex-adjusted	1.40 (0.99 to 1.99)	0.06	4.45 (3.43 to 5.77)	<0.01	1.06 (0.68 to 1.37)	0.84	2.10 (1.64 to 2.68)	<0.01	Ref
Multivariable-adjusted (primary analysis)	1.26 (0.88 to 1.80)	0.21	4.15 (3.16 to 5.44)	<0.01	0.81 (0.56 to 1.18)	0.55	2.06 (1.60 to 2.65)	<0.01	Ref
Confirmed cases only*	1.14 (0.77 to 1.68)	0.52	4.25 (3.17 to 5.69)	<0.01	0.74 (0.49 to 1.11)	0.15	2.05 (1.57 to 2.69)	<0.01	Ref
Excluding patients with ILD or cancer†	1.18 (0.79 to 1.76)	0.43	4.34 (3.23 to 5.82)	<0.01	0.81 (0.54 to 1.21)	0.30	2.14 (1.64 to 2.79)	<0.01	Ref
Restricted to USA and additionally adjusted for race‡	1.16 (0.79 to 1.69)	0.45	4.77 (3.57 to 6.38)	<0.01†	¶	¶	2.86 (1.76 to 4.65)	<0.01†	Ref
Propensity score-matched§	1.60 (1.02 to 2.51)	0.04	4.70 (3.31 to 6.65)	<0.01	0.76 (0.46 to 1.23)	0.26	2.09 (1.50 to 2.90)	<0.01	Ref

The effect size is the odds of being one level higher on the ordinal COVID-19 severity scale than the reference group (TNFi users).
Adjusted for age, sex, region, calendar time, obesity, smoking, concomitant csDMARD use, glucocorticoid use/dose, comorbidity count, hypertension/cardiovascular disease, interstitial lung disease, cancer and rheumatoid arthritis disease activity except as otherwise indicated.
*n=2333 in the analysis analysing only confirmed COVID-19 cases.
†n=2704 in the analysis excluding ILD and cancer.
‡n=868 in the USA-only analysis.
§n for each pair of propensity score-matched analyses: abatacept: 236, TNFi: 1376; rituximab: 364, TNFi: 1382; IL-6i: 313, TNFi: 1387; JAKi: 560, TNFi: 1379.
¶Due to the small number of events in the covariate of race, the IL-6i model could not be analysed.
csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ILD, interstitial lung disease; IL6i, interleukin 6 inhibitor; JAKi, Janus kinase inhibitor; Ref, reference; TNFi, tumour necrosis factor inhibitors.

Table 4 Multivariable* OR of biologic or targeted synthetic disease-modifying antirheumatic drugs at each binary level of the COVID-19 severity scale (N=2869)

	Abatacept		Rituximab		IL-6 inhibitors		JAK inhibitors		
COVID-19 outcome	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	TNF inhibitors
Hospitalised	1.18 (0.76 to 1.82)	0.47	4.53 (3.32 to 6.18)	<0.01	0.84 (0.53 to 1.33)	0.45	2.40 (1.78 to 3.24)	<0.01	Ref
Hospitalised with oxygenation/ventilation or death	1.12 (0.70 to 1.81)	0.63	2.87 (2.03 to 4.06)	<0.01	0.72 (0.43 to 1.20)	0.20	1.55 (1.04 to 2.18)	0.01	Ref
Death	1.46 (0.72 to 2.89)	0.30	4.57 (3.32 to 9.01)	<0.01	1.13 (0.50 to 2.59)	0.77	2.04 (1.58 to 2.65)	<0.01	Ref
Mechanical ventilation (restricted to only hospitalised patients, n=613)	1.41 (0.94 to 2.10)	0.09	4.05 (3.08 to 5.33)	<0.01	0.75 (0.51 to 1.10)	0.14	2.03 (1.56 to 2.62)	<0.01	Ref
Mechanical ventilation or death	1.14 (0.78 to 1.66)	0.50	4.44 (3.39 to 5.82)	<0.01	0.74 (0.50 to 1.09)	0.12	2.02 (1.56 to 2.61)	<0.01	Ref

*Adjusted for age, sex, region, calendar time, obesity, smoking, concomitant csDMARD use, glucocorticoid use/dose, comorbidity count, hypertension/cardiovascular disease, interstitial lung disease, cancer and rheumatoid arthritis disease activity.
csDMARD, conventional synthetic disease-modifying antirheumatic drug; IL-6, interleukin 6; JAK, Janus kinase; Ref, reference; TNF, tumour necrosis factor.

Our findings are of particular interest given recent clinical trials and observational studies suggesting that IL-6i[6–8 29–32] and JAKi[9] may improve outcomes for patients in the general population with COVID-19. We found no association of baseline IL-6i use in RA with COVID-19 severity compared with TNFi use. In contrast, while baricitinib treatment may have some benefit on time to recovery for patients with more severe COVID-19,[9] we observed worse outcomes associated with baseline use of JAKi. This was also suggested in a recent population-based study investigating RA and other inflammatory joint diseases in Sweden.[25] Glucocorticoids are known to have benefits when initiated for moderate-to-severe COVID-19, but are also associated with worse outcomes among those on baseline glucocorticoids at the time of infection,[5 12] although this may be explained by residual disease activity.[33] Therefore, the timing of JAKi use relative to the COVID-19 disease course may explain our findings. Similar to glucocorticoids, baseline use of JAKi at the time of SARS-CoV-2 infection may enhance viral reproduction and dampen a healthy immune response, while JAKi initiation at clinical deterioration may dampen an aberrant systemic inflammatory response. Alternatively, there may be relevant differences in COVID-19 outcomes depending on the type of JAKi used given that JAKis like tofacitinib, baricitinib and upadacitinib target different Janus kinases. We were unable to perform analyses of each individual JAKi since these were collected as a class. While the primary analysis found no association of abatacept with COVID-19 severity, there was a statistical association in the propensity score-matched analysis. Further research is needed on the safety of abatacept for infection risk and severity since its mechanism of action may impair adaptive immune response.

Our study has a number of strengths, including the international nature of the registry and the large sample size. Additionally, we used an active comparator (TNFi), which was also a b/tsDMARD in a single rheumatic disease, as well as two different modelling approaches (multivariable logistic regression and propensity score matching) among other sensitivity analyses to account for confounding by indication and to confirm the robustness of our findings. Our observations expand on prior general population and RA cohort studies that identified older age, greater comorbidity burden and other factors associated with worse COVID-19 and must also be considered when assessing an individual's risk.

Our study also has certain limitations. First, the Global Rheumatology Alliance and EULAR registries are voluntary and require a provider to submit the details of a case, perhaps biasing our sample towards more severe cases. As such, the proportion of events reported across exposure groups may be an overestimate of that observed among all patients with RA in real-world practice and should be interpreted in that context. However, the effect size estimates do have clinical interpretation in potentially identifying patients with RA who could be susceptible to poor COVID-19 outcomes. While we designed the study to limit the potential impact of selection bias and confounding by indication by examining advanced therapies in a single rheumatic disease, it is possible that selective reporting could have varied across different b/tsDMARD classes as the exposure of interest. This potential bias may have caused an upward deflection in the effect size estimate if more severe cases of a particular b/tsDMARD class were systematically reported compared with others, and this could contribute to the findings that we report. We further mitigated this possibility by adjusting for differences in concomitant medication use, disease activity and comorbidities, as well as performing an analysis removing patients with ILD or cancer. Our findings remained when we excluded presumptive cases of COVID-19. Second, although we were able to adjust for a number of potential confounders of our observed associations, there is the potential for residual unmeasured confounding. Analysing only patients on b/tsDMARD may have helped minimise some unmeasured confounding related to access to care since all analysed patients with RA were able to receive these targeted medications. In addition, the consistent results observed in sensitivity analyses excluding patients with ILD or cancer who may be more likely to receive rituximab support the robustness of our results. However, we did not have data available on RA duration or previous RA medications (eg, previous TNFi use in patients on other classes of b/tsDMARDs), which may have affected the results. Medications were collected by DMARD class, so we were unable to compare individual medications within the same class. However, the goal of the study was to compare different biologic mechanisms of action for COVID-19 severity. Additionally, it is also possible that TNFi use may protect against severe COVID-19 outcomes. Thus, these results should be interpreted cautiously and additional studies are needed to confirm our observed associations. Third, while we leveraged the largest cohort of patients with rheumatic disease with COVID-19, a somewhat small number of outcomes of interest occurred in some subgroups, which may have limited our power to detect significant differences among abatacept users, in particular. In addition, we were unable to investigate individual JAKi or TNFi. Finally, we did not examine medication changes after COVID-19 onset since this occurred after baseline and may have mediated the relationship we report. Most of the drugs have lengthy biologic effects (especially rituximab), while JAKis have short half-lives. Some clinicians may have chosen to continue IL-6is after COVID-19 onset, as suggested by the American College of Rheumatology.[34] Future studies are needed to investigate the association of medication changes with COVID-19 outcomes.

In conclusion, use of rituximab or JAKi, but not abatacept or IL-6i, at the time of COVID-19 infection was associated with worse COVID-19 outcomes compared with TNFi among patients with RA. Additional studies are warranted to confirm these observations. Strategies are needed to improve outcomes following COVID-19 RA on rituximab or JAKis.

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3.6 Die Rolle der Tumor-Nekrose-Faktor-Blockade bei immunvermittelten-entzündlichen Erkrankungen im Kontext von SARS-CoV-2

Originalarbeit 11:

Izadi Z, Brenner EJ, Mahil SK, Dand N, Yiu ZZN, Yates M, Ungaro RC, Zhang X, Agrawal M, Colombel JF, Gianfrancesco MA, Hyrich KL, Strangfeld A, Carmona L, Mateus EF, Lawson-Tovey S, Klingberg E, Cuomo G, Caprioli M, Cruz-Machado AR, Mazeda Pereira AC, **Hasseli R**, Pfeil A, Lorenz HM, Hoyer BF, Trupin L, Rush S, Katz P, Schmajuk G, Jacobsohn L, Seet AM, Al Emadi S, Wise L, Gilbert EL, Duarte-García A, Valenzuela-Almada MO, Isnardi CA, Quintana R, Soriano ER, Hsu TY, D'Silva KM, Sparks JA, Patel NJ, Xavier RM, Marques CDL, Kakehasi AM, Flipo RM, Claudepierre P, Cantagrel A, Goupille P, Wallace ZS, Bhana S, Costello W, Grainger R, Hausmann JS, Liew JW, Sirotich E, Sufka P, Robinson PC, Machado PM, Griffiths CEM, Barker JN, Smith CH, Yazdany J, Kappelman MD; Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection (PsoProtect); the Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD); and the COVID-19 Global Rheumatology Allianc; Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection (PsoProtect); the Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD); and the COVID-19 Global Rheumatology Alliance (GRA). *Association Between Tumor Necrosis Factor Inhibitors and the Risk of Hospitalization or Death Among Patients With Immune-Mediated Inflammatory Disease and COVID-19.*
JAMA Netw Open. 2021 Oct 1;4(10):e2129639. doi: 10.1001/jamanetworkopen.2021.29639

Originalarbeit 12:

Hasseli R*, Regierer AC*, Schäfer M, Hoyer BF, Krause A, Lorenz HM, Pfeil A, Richter J, Schmeiser T, Schulze-Koops H, Strangfeld A, Voll RE, Specker C, Mueller-Ladner U. *TNFi is associated with positive outcome, but JAKi and rituximab are associated with negative outcome of SARS-CoV-2 infection in patients with RMD.*
RMD Open. 2021 Oct;7(3):e001896. doi: 10.1136/rmdopen-2021-001896
*geteilte Erstautorenschaft

Zusammenfassung:

TNF-Hemmer werden nicht nur bei entzündlich-rheumatischen Erkrankungen eingesetzt sondern auch bei chronisch-entzündlichen Darmerkrankungen und der Psoriasis [204,205]. Zwar sind TNF-Hemmer insgesamt mit einer höheren Infektneigung assoziiert [166], im Kontext von COVID-19 war bislang jedoch kein schwerer Verlauf unter dieser Therapie zu beobachten. Da in der ersten großen Auswertung des globalen Registers sogar eine Reduktion der schweren COVID-19-Verläufe unter TNF-Hemmern gezeigt werden konnte [206], stellte sich somit die Frage, ob TNF-Hemmer im Kontext von COVID-19 protektiv wirken könnten. In einer weiteren Studie wurden von Februar bis April 2020 bei 213 PatientInnen mit immunvermittelten

Erkrankungen in 36% der Fälle eine SARS-CoV-2-Infektion nachgewiesen [20]. Im Vergleich zur Allgemeinbevölkerung wiesen diese PatientInnen keine vermehrte Assoziation einer COVID-19-bedingten Hospitalisierung oder Notwendigkeit einer Beatmung auf. Unter der Therapie mit TNF-Hemmern konnte zudem eine reduzierte Assoziation der COVID-19-bedingten Hospitalisierung nachgewiesen werden [20].

Aus diesem Grund wurden Daten aus dem globalen Register für entzündlich-rheumatische Erkrankungen, Daten aus dem Register für chronisch-entzündliche Darmerkrankungen (*Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD))* und Daten aus dem Register für Psoriasis *(Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection (PsoProtect))* gemeinsam analysiert (Originalarbeit *11*). Insgesamt wurden 6077 PatientInnen mit der Diagnose einer inflammatorischen Arthritis, einer chronisch-entzündlichen Darmerkrankung oder Psoriasis aus 77 Ländern ausgewertet. Es flossen Daten in die Auswertung ein, die bis zum 01. Februar 2021 erfasst wurden.

Das Alter lag im Durchschnitt bei 49 Jahren und 59% der PatientInnen waren weiblich. In 35% der Fälle litten die PatientInnen an einer rheumatoiden Arthritis, gefolgt von 25% mit einem Morbus Crohn. Die Rate der COVID-19-assoziierten Hospitalisierung lag bei 25% und die Letalitätsrate betrug 3,1%. In der gepoolten Analyse war die Therapie mit TNF-Hemmern in Kombination mit Azathioprin/Mercaptopurin im Vergleich zur Monotherapie mit TNF-Hemmern häufiger mit schweren Verläufen assoziiert (OR 1,7; 95% CI 1,2 – 2,6; $p = 0{,}006$). Auch der Einsatz von Azathioprin/Mercaptopurin als Monotherapie (OR 1,8; 95% CI 1,3 – 2,6; p = 0,001), Methotrexat-Monotherapie (OR 2,0; 95%CI 1.6 – 2.6; p<0,001) und Januskinase-Inhibitoren in Monotherapie schnitten schlechter ab. Dagegen zeigte sich kein relevanter Unterschied bei Personen, die TNF-Hemmer in Kombination mit Methotrexat im Vergleich zur TNF-Hemmern als Monotherapie erhielten.

Ein ähnliches Bild zeigte sich auch in der Gesamtauswertung des COVID19-Rheuma.de-Registers (Originalarbeit *12*). Während des Untersuchungszeitraums von März 2020 bis April 2021 wurden 2274 PatientInnen im Register erfasst. Es wurde eine Ordinalskala für den Schweregrad der SARS-CoV-2-Infektion definiert:

1) weder hospitalisiert, noch beatmet oder verstorben
2) hospitalisiert ohne invasive Beatmung und nicht verstorben
3) invasive Beatmung oder verstorben

Unabhängig von der Diagnose und Therapie der ERE waren weiterhin das Alter, das männliche Geschlecht, kardiovaskuläre Begleiterkrankungen, Lungenerkrankungen und chronische Niereninsuffizienz mit schwerwiegenderen Verläufen der SARS-CoV-2-Infektion assoziiert. Die COVID-19-assoziierte Letalität betrug 3,6%. Erstmalig konnte gezeigt werden, dass es einen relevanten Unterschied innerhalb der ERE bezüglich des Infektionsverlaufs gab.

In der multivariablen Regressionsanalyse zeigte sich bei PatientInnen mit einer Psoriasisarthritis eine Assoziation mit milderen Verläufen einer SARS-CoV-2-Infektion im Vergleich zu Personen mit einer rheumatoiden Arthritis (OR 0,5; 95% CI 0.3 – 0.7). Da die Krankheitsaktivität mit der Dosierung und Notwendigkeit einer Glukokortikosteroidtherapie korreliert, wurden diese beiden Parameter für die weitere Auswertung gemeinsam untersucht. PatientInnen die eine sehr geringe Entzündungsaktivität zum Zeitpunkt der SARS-CoV-2-Infektion aufwiesen, jedoch mit bis zu 10 mg/Tag Prednisolon therapiert wurden, wiesen einen schwerwiegenderen Verlauf der SARS-CoV-2-Infektion auf als PatientInnen mit derselben Krankheitsaktivität und ohne eine zusätzliche Glukokortikosteroidtherapie (OR 1,6; 95%CI 1,2 – 2,0). Die Assoziation mit dem Schweregrad von COVID-19 nahm weiter schrittweise mit steigender Krankheitsaktivität und höheren Glukokortikosteroiddosen zu.

Da Methotrexat mehrheitlich bei ERE (außer bei entzündlicher Aktivität an der Wirbelsäule) als Erstlinientherapie eingesetzt wird, wurde für den Einfluss der Immunmodulation auf den Verlauf der SARS-CoV-2-Infektion die Methotrexat-Monotherapie als Referenzgruppe definiert. Die Therapie mit JAKi war hierbei mit einem schwerwiegenderen COVID-19-Verlauf assoziiert (OR 1,8; 95%CI 1,1 – 2,7), noch deutlicher war das Ergebnis unter Therapie mit Rituximab (OR 5,4; 95%CI 3,3 – 8,8). TNF-Hemmer wiesen dagegen eine signifikante Assoziation mit milderen Verläufen der SARS-CoV-2-Infektion auf (OR 0,6; 95%CI 0,4 – 0,9). Immunsuppressiva (Mycophenolat, Azathioprin, Cyclophosphamid und Ciclosporin) waren ebenfalls mit schwereren COVID-19-Verläufen assoziiert (OR 2,2; 95%CI 1,3 – 3,9). Dies bestätigte die Ergebnisse aus der internationalen Auswertung auch mit Gesundheitsdaten aus Deutschland.

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Original Investigation | Infectious Diseases

Association Between Tumor Necrosis Factor Inhibitors and the Risk of Hospitalization or Death Among Patients With Immune-Mediated Inflammatory Disease and COVID-19

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Abstract

IMPORTANCE Although tumor necrosis factor (TNF) inhibitors are widely prescribed globally because of their ability to ameliorate shared immune pathways across immune-mediated inflammatory diseases (IMIDs), the impact of COVID-19 among individuals with IMIDs who are receiving TNF inhibitors remains insufficiently understood.

OBJECTIVE To examine the association between the receipt of TNF inhibitor monotherapy and the risk of COVID-19–associated hospitalization or death compared with other commonly prescribed immunomodulatory treatment regimens among adult patients with IMIDs.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was a pooled analysis of data from 3 international COVID-19 registries comprising individuals with rheumatic diseases, inflammatory bowel disease, and psoriasis from March 12, 2020, to February 1, 2021. Clinicians directly reported COVID-19 outcomes as well as demographic and clinical characteristics of individuals with IMIDs and confirmed or suspected COVID-19 using online data entry portals. Adults (age ≥18 years) with a diagnosis of inflammatory arthritis, inflammatory bowel disease, or psoriasis were included.

EXPOSURES Treatment exposure categories included TNF inhibitor monotherapy (reference treatment), TNF inhibitors in combination with methotrexate therapy, TNF inhibitors in combination with azathioprine/6-mercaptopurine therapy, methotrexate monotherapy, azathioprine/6-mercaptopurine monotherapy, and Janus kinase (Jak) inhibitor monotherapy.

MAIN OUTCOMES AND MEASURES The main outcome was COVID-19–associated hospitalization or death. Registry-level analyses and a pooled analysis of data across the 3 registries were conducted using multilevel multivariable logistic regression models, adjusting for demographic and clinical characteristics and accounting for country, calendar month, and registry-level correlations.

RESULTS A total of 6077 patients from 74 countries were included in the analyses; of those, 3215 individuals (52.9%) were from Europe, 3563 individuals (58.6%) were female, and the mean (SD) age

(continued)

Key Points

Question Is receipt of tumor necrosis factor (TNF) inhibitor monotherapy at the time of COVID-19 diagnosis associated with adverse COVID-19 outcomes compared with other treatment regimens among patients with immune-mediated inflammatory diseases (IMIDs)?

Findings In this cohort study of 6077 patients with IMIDs and COVID-19, TNF inhibitors in combination with azathioprine/6-mercaptopurine therapy, methotrexate monotherapy, azathioprine/6-mercaptopurine monotherapy, or Janus kinase inhibitor monotherapy were each associated with significantly higher odds of hospitalization or death compared with TNF inhibitor monotherapy.

Meaning This study's findings support the continued use of TNF inhibitor monotherapy among individuals with IMIDs during the pandemic.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

was 48.8 (16.5) years. The most common IMID diagnoses were rheumatoid arthritis (2146 patients [35.3%]) and Crohn disease (1537 patients [25.3%]). A total of 1297 patients (21.3%) were hospitalized, and 189 patients (3.1%) died. In the pooled analysis, compared with patients who received TNF inhibitor monotherapy, higher odds of hospitalization or death were observed among those who received a TNF inhibitor in combination with azathioprine/6-mercaptopurine therapy (odds ratio [OR], 1.74; 95% CI, 1.17-2.58; *P* = .006), azathioprine/6-mercaptopurine monotherapy (OR, 1.84; 95% CI, 1.30-2.61; *P* = .001), methotrexate monotherapy (OR, 2.00; 95% CI, 1.57-2.56; *P* < .001), and Jak inhibitor monotherapy (OR, 1.82; 95% CI, 1.21-2.73; *P* = .004) but not among those who received a TNF inhibitor in combination with methotrexate therapy (OR, 1.18; 95% CI, 0.85-1.63; *P* = .33). Similar findings were obtained in analyses that accounted for potential reporting bias and sensitivity analyses that excluded patients with a COVID-19 diagnosis based on symptoms alone.

CONCLUSIONS AND RELEVANCE In this cohort study, TNF inhibitor monotherapy was associated with a lower risk of adverse COVID-19 outcomes compared with other commonly prescribed immunomodulatory treatment regimens among individuals with IMIDs.

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Introduction

Patients with COVID-19, caused by SARS-CoV-2, can have mild symptoms or experience a severe and/or life-threatening infection.[1] Comorbidities, such as lung disease, diabetes, and obesity, increase the risk of adverse COVID-19 outcomes.[2] Any benefits of treatments for immune-mediated inflammatory diseases (IMIDs) for COVID-19 outcomes remain a topic of interest. These treatments impact the immune system and are associated with a higher risk of infections overall.[3] This association raises concern about impaired immune response to SARS-CoV-2 among patients currently receiving treatment for IMIDs. However, many damaging consequences of SARS-CoV-2 infection are produced by a hyperinflammatory response.[4] Therefore, treatments that target an overactive immune response may have protective benefits against adverse COVID-19 outcomes.[1,4]

Tumor necrosis factor (TNF) inhibitors, a class of biologic therapies that target the proinflammatory cytokine TNF, are first- or second-line treatments for many IMIDs. International registries of patients with IMIDs have provided initial information regarding COVID-19 outcomes among individuals who received TNF inhibitor therapies during the pandemic. An analysis of data from the Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) registry, which includes patients with inflammatory bowel disease (IBD) who were diagnosed with COVID-19, found that prevalent use compared with no use of TNF inhibitors at COVID-19 diagnosis was not associated with severe COVID-19 (odds ratio [OR], 0.9; 95% CI, 0.4-2.2).[5] A study of data from the Global Rheumatology Alliance (GRA) physician-reported registry of COVID-19 outcomes among people with rheumatic diseases found that prevalent use compared with no use of TNF inhibitors at COVID-19 diagnosis was associated with lower odds of COVID-19–associated hospitalization (OR, 0.40; 95% CI, 0.19-0.81).[6] An analysis of data from the Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection (PsoProtect) also found higher odds of hospitalization among patients treated with nonbiologic systemic therapies compared with biologic therapies, including TNF inhibitors (OR, 2.84; 95% CI, 1.31-6.18).[7] Although studies of individual registries have provided initial information, they were often underpowered to perform more granular analyses of commonly used medications, such as monotherapy vs combination therapy with immunomodulatory drugs, or analyses of medications that are used less frequently.

Pooling data across registries offers an opportunity to rapidly assess any association between TNF inhibitor therapies and COVID-19 outcomes among individuals with IMIDs and to evaluate the

consistency of findings across studies and diseases. We pooled data from these 3 international registries of patients with IBD, psoriasis, and rheumatic diseases to evaluate the association between TNF inhibitor monotherapy and COVID-19–associated hospitalization or death compared with other commonly prescribed immunomodulatory regimens among individuals with IMIDs.

Methods

Registry Designs and Approvals

Details of the design of the GRA, SECURE-IBD, and PsoProtect registries have been described previously.[7-10] In brief, clinicians and trained staff directly report COVID-19 outcomes as well as demographic and clinical characteristics of individuals with IMIDs who have confirmed or suspected COVID-19 using online data entry portals. Quality is assessed by registry-specific data validation teams who remove all known or potential duplicates and address erroneous or ineligible reports. The GRA and PsoProtect registries contain only limited data; no personal identifiers, with the exception of COVID-19 diagnosis dates, are included. The SECURE-IBD registry follows the safe harbor deidentification standards of the Health Insurance Portability and Accountability Act. The GRA registry was determined to be nonhuman subjects research by the United Kingdom Health Research Authority, the University of Manchester (United Kingdom), and the University of California, San Francisco, and informed consent was therefore not required. For the SECURE-IBD registry, the Office for Human Research Ethics at the University of North Carolina at Chapel Hill determined that storage and analysis of deidentified data did not constitute human subjects research and did not require institutional review board approval or informed consent. Voluntary ethical approval was sought by the PsoProtect registry and granted by the Leeds Research Ethics Committee (United Kingdom), who determined that informed consent was not required because of the use of deidentified data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

COVID-19 Diagnosis

Among patients with rheumatic disease, a COVID-19 diagnosis was based on polymerase chain reaction (PCR), antibody serology testing, or metagenomic testing; computed tomographic scans; laboratory assays; or symptoms alone. Among patients with IBD, a COVID-19 diagnosis was based on PCR testing, symptoms with confirmatory antibody serology testing, or rapid antigen testing. Among patients with psoriasis, both confirmed and suspected COVID-19 diagnoses were reported; however, information regarding the type of diagnostic testing used was not collected.

Exposures and Outcome

To obtain sufficient statistical power, each exposure category was required to have more than 250 patients in the pooled analysis. Exposure was defined as a categorical variable that comprised the following categories: TNF inhibitor (including adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) monotherapy (reference category), TNF inhibitors in combination with methotrexate therapy, TNF inhibitors in combination with azathioprine/6-mercaptopurine therapy, methotrexate monotherapy, azathioprine/6-mercaptopurine monotherapy, and Janus kinase (Jak) inhibitor (including tofacitinib, baricitinib, and upadacitinib) monotherapy. The outcome of interest was hospitalization or death associated with COVID-19.

Inclusion and Exclusion Criteria

We included adults (age ≥18 years) with a diagnosis of inflammatory arthritis, IBD, or psoriasis who were reported to the GRA, SECURE-IBD, or PsoProtect registries, respectively, from March 12, 2020, to February 1, 2021. Our analysis included reconciled patients only. For the GRA registry, reconciled patients were defined as those with at least 1 of the following recorded outcomes: death, symptoms resolved at the time of data entry, not hospitalized more than 30 days after the initial diagnosis date,

hospitalized and discharged, or not at risk of further interventions or death. For the SECURE-IBD and PsoProtect registries, patients were defined as reconciled after a minimum of 7 days or 14 days, respectively, or if sufficient time had passed to observe the disease course through the resolution of acute illness or death.

To limit confounding from other immunomodulatory medications, we excluded patients who received an exposure treatment regimen as well as concomitant immunomodulatory drugs, except when sulfasalazine, mesalamine, hydroxychloroquine or chloroquine, leflunomide, oral budesonide, or glucocorticoids were used as concomitant medications.

Statistical Analysis

We used descriptive statistics to summarize the demographic and clinical characteristics of the study population. Continuous variables were reported as means with SDs or medians with 25th and 75th percentiles, as appropriate. Categorical variables were reported as numbers with percentages. We performed registry-level analyses and a pooled analysis of data across the 3 registries to estimate independent associations between exposure categories and COVID-19 outcomes. Registry-level effect estimates were reported for exposure categories that included 10 or more patients. Associations were estimated using multilevel multivariable mixed-effects logistic regression analysis and reported as odds ratios (ORs) with 95% CIs. We chose mixed-effects regression analysis for its ability to handle missing data using maximum-likelihood estimation and to fit nested random effects to account for multilevel clustering.[11]

Covariates included in all models were age, sex, current smoking, IMID activity (remission vs active disease, as reported by the clinician), important comorbidities (cardiovascular disease [including coronary artery disease, heart failure, and arrhythmia], diabetes, hypertension, obstructive lung disease [including chronic obstructive pulmonary disease and asthma], interstitial or other chronic lung disease, kidney disease [including chronic kidney insufficiency and end-stage kidney disease], obesity [defined as body mass index ≥30; calculated as weight in kilograms divided by height in meters squared], and cancer, each included as a dichotomous variable), and prednisone-equivalent glucocorticoid dose (included as a continuous variable). For the registry-level analyses, we included the following concomitant medications: sulfasalazine, hydroxychloroquine or chloroquine, and leflunomide for the GRA analysis and mesalamine, sulfasalazine, and oral budesonide for the SECURE-IBD analysis. If any of these concomitant medications were significant confounders ($P < .05$) in the registry-level analyses, they were also included as covariates in the pooled analysis; patients from registries that did not include the respective concomitant medications were assigned to the category of individuals with nonuse of these medications. Registry-level analyses also controlled for disease diagnosis; diagnoses in the GRA registry included rheumatoid arthritis (reference category), psoriatic arthritis, spondyloarthritis, and other inflammatory arthritis or more than 1 type of inflammatory arthritis, and diagnoses in the SECURE-IBD registry included Crohn disease (reference category), ulcerative colitis, and unspecified IBD.

We fitted country-level random effects to account for within-country correlations. To account for changes in COVID-19 treatment and health service use over time, we also fitted random effects for the calendar month of symptom onset (PsoProtect registry) or the calendar month during which the patient was diagnosed (GRA registry) or reported (SECURE-IBD registry). The pooled model also included registry-level random effects accounting for within-registry correlations. The hierarchical order of nested random effects in the pooled model was country followed by time and registry. To improve model fit, we removed influential statistical outliers identified in continuous variables (ie, age and glucocorticoid dose) from the analyses. As a result, 2 patients were removed who received a daily prednisone dose greater than 70 mg.

All analyses were conducted using Stata software, version 16.0 (StataCorp). The threshold for statistical significance was 2-sided $P < .05$.

Rheumatology clinics from 2 large health care systems (Mass General Brigham in Massachusetts and Mayo Clinic in Minnesota and Florida) had processes in place to systematically report all patients

with COVID-19 to the GRA registry. To assess the extent of potential reporting bias arising from convenience sampling, ORs were derived after reweighting the covariate distribution of patients in the GRA registry to those of the 2 health care systems using the inverse odds of sampling weights technique,[12] and those values were compared with the original ORs using standardized difference.[13] In addition, to assess the robustness of results, a pooled sensitivity analysis was performed after excluding patients with a COVID-19 diagnosis that was based on symptoms alone.

Results

As of February 1, 2021, 8268 patients were reported to have received an exposure treatment regimen at COVID-19 diagnosis. Of those, 5220 patients were from the GRA registry, 2720 patients were from the SECURE-IBD registry, and 328 patients were from the PsoProtect registry. A total of 6077 patients from 74 countries met study eligibility criteria and were included in the analyses; of those, 3441 patients (56.6%) were from the GRA registry, 2336 patients (38.4%) were from the SECURE-IBD registry, and 300 patients (4.9%) were from the PsoProtect registry. Of the 2191 patients excluded from the analyses, most were excluded because they had a rheumatic disease diagnosis other than inflammatory arthritis (827 patients), were patients who were nonreconciled (581 patients), or received concomitant medications that were listed in the exclusion criteria (551 patients) (**Table 1**).

The demographic and clinical characteristics of the 6077 patients included in the analysis are shown in **Table 2**. Most patients were from Europe (3215 individuals [52.9%]) and North America (2015 individuals [33.2%]), and the mean (SD) age was 48.8 (16.5) years; 3563 patients (58.6%) were female, and 2468 patients (40.6%) were male. Race and ethnicity were not addressed in these analyses because information on race was not recorded in the PsoProtect registry, and information on race and ethnicity was not available for all countries in the GRA registry. The most common

Table 1. Reasons for Study Exclusion

	No.			
	All patients	GRA registry	SECURE-IBD registry	PsoProtect registry
Total patients using an exposure treatment regimen as of February 1, 2021[a]	8268	5220	2720	328
Patients excluded	2191	1779	384	28
Reason for exclusion				
Age missing or <18 y	230	0	226	4
Nonreconciled[b]	581	581	0	0
Noninflammatory arthritis diagnosis	827	827	NA	NA
Receipt of concomitant medication listed in exclusion criteria[c]	551	370	157	24
Influential statistical outliers[d]	2	1	1	0

Abbreviations: GRA, COVID-19 Global Rheumatology Alliance; PsoProtect, Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection; SECURE-IBD, Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease.

[a] Exposure treatment regimens included tumor necrosis factor (TNF) inhibitor monotherapy, TNF inhibitors in combination with methotrexate therapy, TNF inhibitors in combination with azathioprine/6-mercaptopurine therapy, methotrexate monotherapy, azathioprine/6-mercaptopurine monotherapy, and Janus kinase inhibitor monotherapy.

[b] In the GRA registry, a patient was defined as reconciled if at least 1 of the following criteria were present: deceased, symptoms resolved at the time of data entry, not hospitalized >30 days after the initial diagnosis date, hospitalized and discharged, or not at risk of further interventions or death. In the SECURE-IBD and PsoProtect registries, a patient was defined as reconciled after a minimum of 7 days or 14 days, respectively, or if sufficient time had passed to observe the disease course through resolution of acute illness or death.

[c] Excluded concomitant medications included any medication with the exception of sulfasalazine, mesalamine, hydroxychloroquine or chloroquine, leflunomide, oral budesonide, or glucocorticoids.

[d] To improve model fit, influential statistical outliers identified in continuous variables were removed. Two patients were removed who received a daily prednisone dose >70 mg.

Table 2. Patient Characteristics and COVID-19 Outcomes

Characteristic or outcome	No. (%)			
	Pooled (N = 6077)	GRA (n = 3441)	SECURE-IBD (n = 2336)	PsoProtect (n = 300)
Age, mean (SD), y	48.8 (16.5)	55.0 (14.4)	39.4 (15.4)	49.9 (12.6)
Sex[a]				
Female	3563 (58.6)	2295 (66.7)	1153 (49.4)	115 (38.3)
Male	2468 (40.6)	1144 (33.2)	1139 (48.8)	185 (61.7)
Unknown	46 (0.8)	2 (0.1)	44 (1.9)	0
Region[a]				
Africa	24 (0.4)	16 (0.5)	7 (0.3)	1 (0.3)
Eastern Mediterranean	191 (3.1)	120 (3.5)	68 (2.9)	3 (1.0)
Europe	3215 (52.9)	1800 (52.3)	1143 (48.9)	272 (90.7)
North America	2015 (33.2)	1066 (31.0)	942 (40.3)	7 (2.3)
South America	502 (8.3)	375 (10.9)	111 (4.8)	16 (5.3)
Southeast Asia	22 (0.4)	8 (0.2)	13 (0.6)	1 (0.3)
Western Pacific	85 (1.4)	56 (1.6)	29 (1.2)	0
Unknown	23 (0.4)	0	23 (1.0)	0
Diagnosis[a]				
Rheumatoid arthritis only	2146 (35.3)	2146 (62.4)	NA	NA
Spondyloarthritis only	624 (10.3)	624 (18.1)	NA	NA
Psoriatic arthritis only	566 (9.3)	566 (16.4)	NA	NA
Other inflammatory arthritis or >1 type of inflammatory arthritis	105 (1.7)	105 (3.1)	NA	NA
Crohn disease	1537 (25.3)	NA	1537 (65.8)	NA
Unspecified inflammatory bowel disease	37 (0.6)	NA	37 (1.6)	NA
Ulcerative colitis	762 (12.5)	NA	762 (32.6)	NA
Psoriasis	300 (4.9)	NA	NA	300 (100)
Disease activity[a]				
Remission	2511 (41.3)	1067 (31.0)	1369 (58.6)	75 (25.0)
Active	2918 (48.0)	1829 (53.2)	864 (37.0)	225 (75.0)
Unknown	648 (10.7)	545 (15.8)	103 (4.4)	0
Exposure treatment regimen[a]				
TNF inhibitor monotherapy	2844 (46.8)	1183 (34.4)	1445 (61.9)	216 (72.0)
TNF inhibitor plus methotrexate	669 (11.0)	575 (16.7)	87 (3.7)	7 (2.3)
TNF inhibitor plus azathioprine/6-mercaptopurine	334 (5.5)	7 (0.2)	327 (14.0)	0
Methotrexate monotherapy	1546 (25.4)	1438 (41.8)	31 (1.3)	77 (25.7)
Azathioprine/6-mercaptopurine monotherapy	398 (6.5)	19 (0.6)	379 (16.2)	0
Jak inhibitor monotherapy	286 (4.7)	219 (6.4)	67 (2.9)	0
Concomitant medication				
Sulfasalazine	294 (4.8)	246 (7.1)	48 (2.1)	NA
Mesalamine	384 (6.3)	NA	384 (16.4)	NA
Oral budesonide	39 (0.6)	NA	39 (1.7)	NA
Leflunomide	212 (3.5)	212 (6.2)	NA	NA
Chloroquine or hydroxychloroquine	316 (5.2)	316 (9.2)	NA	NA
Daily glucocorticoid[a]				
No	114 (1.9)	2650 (77.0)	2212 (94.7)	300 (100)
Yes	5162 (84.9)	683 (19.8)	118 (5.1)	0
Unknown	801 (13.2)	108 (3.1)	6 (0.3)	0
Daily prednisone-equivalent glucocorticoid, median (25th percentile-75th percentile), mg	5 (5.0-10.0)	5 (5.0-7.5)	20.0 (5.0-36.0)	NA

(continued)

Table 2. Patient Characteristics and COVID-19 Outcomes (continued)

Characteristic or outcome	No. (%)			
	Pooled (N = 6077)	GRA (n = 3441)	SECURE-IBD (n = 2336)	PsoProtect (n = 300)
Smoking status[a]				
Never or past	4791 (78.8)	2358 (68.5)	2236 (95.7)	197 (65.7)
Current	295 (4.9)	153 (4.4)	100 (4.3)	42 (14.0)
Unknown	991 (16.3)	930 (27.0)	0	61 (20.3)
BMI[a]				
<30	4877 (80.3)	2768 (80.4)	1951 (83.5)	158 (52.7)
≥30	1150 (18.9)	673 (19.6)	385 (16.5)	92 (30.7)
Unknown	50 (0.8)	0	0	50 (16.7)
Lung disease				
Interstitial	164 (2.7)	134 (3.9)	26 (1.1)	4 (1.3)
Obstructive	430 (7.1)	317 (9.2)	99 (4.2)	14 (4.7)
Cardiovascular disease	388 (6.4)	274 (8.0)	90 (3.9)	24 (8.0)
Diabetes	541 (8.9)	401 (11.7)	80 (3.4)	57 (19.0)
Hypertension	1360 (22.4)	1088 (31.6)	193 (8.3)	79 (26.3)
Kidney disease	120 (2.0)	93 (2.7)	24 (1.0)	3 (1.0)
Cancer	117 (1.9)	91 (2.6)	18 (0.8)	8 (2.7)
Hospitalization status[a]				
Not hospitalized	4649 (76.5)	2396 (69.6)	1996 (85.4)	257 (85.7)
Hospitalized	1297 (21.3)	939 (27.3)	316 (13.5)	42 (14.0)
Unknown	131 (2.2)	106 (3.1)	24 (1.0)	1 (0.3)
Death[a]				
Alive	5845 (96.2)	3266 (94.9)	2282 (97.7)	297 (99.0)
Dead	189 (3.1)	166 (4.8)	20 (0.9)	3 (1.0)
Unknown	43 (0.7)	9 (0.3)	34 (1.5)	0
Presumptive COVID-19 diagnosis[b]	864 (14.2)	752 (21.9)	0	112 (37.3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GRA, COVID-19 Global Rheumatology Alliance; Jak, Janus kinase; NA, not applicable; PsoProtect, Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection; SECURE-IBD, Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease; TNF, tumor necrosis factor.

[a] Subcategories are mutually exclusive.

[b] Presumptive diagnosis based on symptoms alone.

disease diagnoses were rheumatoid arthritis (2146 patients [35.3%]), Crohn disease (1537 patients [25.3%]), ulcerative colitis (762 patients [12.5%]), and spondyloarthritis (624 patients [10.3%]). The most common comorbidities were hypertension (1360 patients [22.4%]), diabetes (541 patients [8.9%]), obstructive lung disease (430 patients [7.1%]), and cardiovascular disease (388 patients [6.4%]). Current smoking and obesity were substantially more prevalent among patients in the PsoProtect registry (42 patients [14.0%] and 92 patients [30.7%], respectively) compared with those in the GRA registry (153 patients [4.4%] and 673 patients [19.6%]) or the SECURE-IBD registry (100 patients [4.3%] and 385 patients [16.5%]).

The receipt of TNF inhibitor monotherapy was reported in 1183 patients (34.4%) from the GRA registry, 1445 patients (61.9%) from the SECURE-IBD registry, and 216 patients (72.0%) from the PsoProtect registry (Table 2). Methotrexate monotherapy was the most prevalent treatment regimen at COVID-19 diagnosis among patients from the GRA registry (1438 individuals [41.8%]). The receipt of azathioprine/6-mercaptopurine, alone or in combination with a TNF inhibitor, was reported in a small proportion of patients from the GRA registry (26 individuals [0.8%]) and in 0 patients from the PsoProtect registry. The receipt of Jak inhibitor monotherapy was reported in 219 patients (6.4%) from the GRA registry, 67 patients (2.9%) from the SECURE-IBD registry, and 0 patients from the PsoProtect registry. A total of 1297 patients (21.3%) were hospitalized, and 189 patients (3.1%) died (Table 2). Both hospitalizations and deaths were more common among patients from the GRA registry (939 patients [27.3%] and 166 patients [4.8%], respectively) than the SECURE-IBD registry (316 patients [13.5%] and 20 patients [0.9%]) or the PsoProtect registry (42 patients [14.0%] and 3 patients [1.0%]).

Along with the prespecified covariates, the concomitant medications sulfasalazine, leflunomide, and oral budesonide were included in the pooled multivariable model because these medications were significantly associated with hospitalization or death in the GRA (sulfasalazine: OR, 1.55 [95% CI, 1.03-2.35; *P* = .04]; leflunomide: OR, 1.97 [95% CI, 1.22-3.18; *P* = .005]) or the SECURE-IBD (oral budesonide: OR, 2.71; 95% CI, 1.11-6.60; *P* = .03) registry-level analyses. In the pooled analysis, compared with TNF inhibitor monotherapy, higher odds of hospitalization or death were observed among those who received a TNF inhibitor in combination with azathioprine/6-mercaptopurine therapy (OR, 1.74; 95% CI, 1.17-2.58; *P* = .006). Differences in the odds of hospitalization or death among those who received TNF inhibitor monotherapy vs a TNF inhibitor in combination with methotrexate therapy were not statistically significant in the registry-specific analyses (GRA: OR, 1.20 [95% CI, 0.80-1.79; *P* = .38]; SECURE-IBD: OR, 1.59 [95% CI, 0.76-3.34; *P* = .22]) or the pooled analysis (OR, 1.18; 95% CI, 0.85-1.63; *P* = .33). Compared with those who received TNF inhibitor monotherapy, higher odds of hospitalization or death were observed among those who received methotrexate monotherapy (OR, 2.00; 95% CI, 1.57-2.56; *P* < .001), azathioprine/6-mercaptopurine monotherapy (OR, 1.84; 95% CI, 1.30-2.61; *P* = .001), and Jak inhibitor monotherapy (OR, 1.82; 95% CI, 1.21-2.73; *P* = .004) in the pooled analysis.

Although ORs obtained from registry-specific analyses were generally in the same direction and of similar extent as those obtained from the pooled analysis, we observed some notable differences (**Figure** and eTable in Supplement 1). Odds ratios for methotrexate monotherapy compared with TNF inhibitor monotherapy were larger among patients in the PsoProtect registry than patients in the SECURE-IBD or the GRA registries. Odds ratios for azathioprine/6-marcaptopurine monotherapy compared with TNF inhibitor monotherapy were larger among patients in the GRA registry than patients in the SECURE-IBD registry. In addition, the receipt of Jak inhibitor monotherapy was not associated with higher odds of hospitalization or death compared with TNF inhibitor monotherapy (OR, 0.60; 95% CI, 0.22-1.64; *P* = .32) among patients in the SECURE-IBD registry.

Other factors associated with higher odds of hospitalization or death in the pooled analysis included older age (OR per 1 year increase in age, 1.04; 95% CI, 1.04-1.05; *P* < .001); active IMID at COVID-19 diagnosis (OR, 1.27; 95% CI, 1.04-1.55; *P* = .02); obesity (OR, 1.39; 95% CI, 1.10-1.75; *P* = .005); lung disease (interstitial: OR, 1.81 [95% CI, 1.12-2.95; *P* = .02]; obstructive: OR, 2.34 [95% CI, 1.69-3.24; *P* < .001]); cardiovascular disease (OR, 1.58; 95% CI, 1.13-2.21; *P* = .007); diabetes (OR, 1.54; 95% CI, 1.16-2.05; *P* = .003); chronic kidney disease (OR, 3.10; 95% CI, 1.70-5.66; *P* < .001); concomitant use of sulfasalazine (OR, 1.62; 95% CI, 1.13-2.34; *P* = .009), leflunomide (OR, 1.89; 95% CI, 1.20-2.99; *P* = .006), or oral budesonide (OR, 2.86; 95% CI, 1.20-6.84; *P* = .02); and higher daily prednisone-equivalent glucocorticoid dose (OR per 1 mg increase in dose, 1.07; 95% CI, 1.05-1.08; *P* < .001) (**Table 3**). Female sex was associated with a protective benefit (OR, 0.79; 95% CI, 0.66-0.96; *P* = .02). The intraclass correlation coefficient was 0.27 (95% CI, 0.20-0.36), suggesting that clustering of patients within country, calendar month, and registry explained 27% of the variation in the odds of hospitalization or death. Complete results from registry-specific analyses are shown in the eTable in Supplement 1.

We compared GRA registry-specific results with results obtained after reweighting the covariate distribution of the GRA population to match those of rheumatology clinics that systematically reported all patients diagnosed with COVID-19. Standardized differences between the reweighted and original estimates were in the acceptable range of less than 0.1[14] (0.035 for log OR corresponding to TNF inhibitor in combination with methotrexate therapy compared with TNF inhibitor monotherapy; 0.002 for log OR corresponding to methotrexate monotherapy compared with TNF inhibitor monotherapy; 0.072 for log OR corresponding to Jak inhibitor monotherapy compared with TNF inhibitor monotherapy), suggesting that reporting bias was minimal in the GRA registry (**Table 4**).

A total of 864 patients (14.2%; 112 patients [37.3%] from the PsoProtect registry, 752 patients [21.9%] from the GRA registry, and 0 patients from the SECURE-IBD registry) received a COVID-19

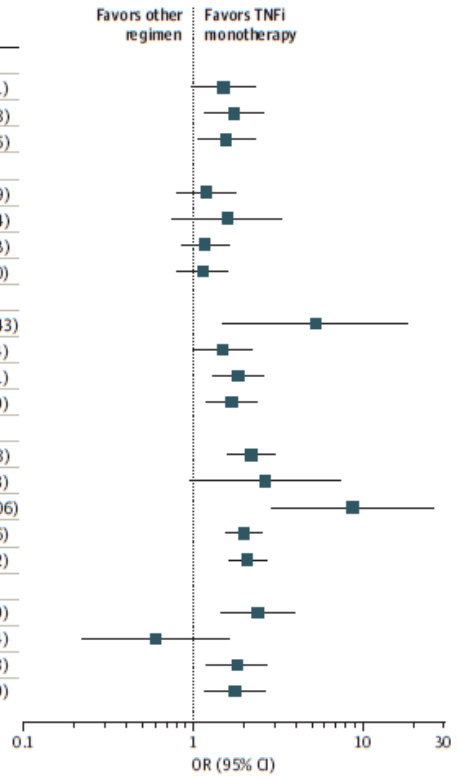
diagnosis based on symptoms alone. Our pooled results remained consistent in a sensitivity analysis that excluded these patients (Figure).

Discussion

This cohort study found that TNF inhibitor monotherapy was associated with a lower risk of COVID-19–associated hospitalization or death among patients with IMIDs compared with other commonly used treatment regimens, including methotrexate, azathioprine/6-mercaptopurine, and Jak inhibitors. After controlling for active disease and common comorbidities, the odds of hospitalization or death among those who received TNF inhibitor combination therapies vs TNF inhibitor monotherapy depended on the type of additional medication used in the combination regimen. Patients receiving TNF inhibitors in combination with azathioprine/6-mercaptopurine therapy had higher odds of hospitalization or death compared with those receiving TNF inhibitor monotherapy,

Figure. Adjusted Odd Ratios (ORs) of COVID-19–Associated Hospitalization or Death Among Patients Receiving Immunomodulatory Treatment Regimens vs Tumor Necrosis Factor Inhibitor (TNFi) Monotherapy

Treatment regimen	OR (95% CI)
TNFi plus AZA/6MP vs TNFi monotherapy	
SECURE-IBD registry	1.51 (0.98-2.31)
Pooled estimate (primary analysis)	1.74 (1.17-2.58)
Pooled estimate (sensitivity analysis)	1.57 (1.06-2.35)
TNFi plus MTX vs TNFi monotherapy	
GRA registry	1.20 (0.80-1.79)
SECURE-IBD registry	1.59 (0.76-3.34)
Pooled estimate (primary analysis)	1.18 (0.85-1.63)
Pooled estimate (sensitivity analysis)	1.14 (0.81-1.60)
AZA/6MP monotherapy vs TNFi monotherapy	
GRA registry	5.28 (1.51-18.43)
SECURE-IBD registry	1.50 (1.00-2.24)
Pooled estimate (primary analysis)	1.84 (1.30-2.61)
Pooled estimate (sensitivity analysis)	1.69 (1.19-2.39)
MTX monotherapy vs TNFi monotherapy	
GRA registry	2.21 (1.59-3.08)
SECURE-IBD registry	2.66 (0.95-7.43)
PsoProtect registry	8.76 (2.94-26.06)
Pooled estimate (primary analysis)	2.00 (1.57-2.56)
Pooled estimate (sensitivity analysis)	2.10 (1.62-2.72)
JAKi monotherapy vs TNFi monotherapy	
GRA registry	2.41 (1.46-3.99)
SECURE-IBD registry	0.60 (0.22-1.64)
Pooled estimate (primary analysis)	1.82 (1.21-2.73)
Pooled estimate (sensitivity analysis)	1.77 (1.16-2.69)



Registry-specific and pooled analyses, with TNFi monotherapy used as the reference category. Pooled estimates were obtained using hierarchical multivariable mixed-effects logistic regression analysis with registry and calendar month random effects nested within country. Pooled sensitivity analysis (n = 5213) excludes patients with a presumptive COVID-19 diagnosis (defined as a diagnosis based on symptoms alone). All ORs were adjusted for age, sex, current smoking, immune-mediated disease activity (remission vs active), important comorbidities (cardiovascular disease, diabetes, hypertension, obstructive lung disease, interstitial or other chronic lung disease, kidney disease, obesity [body mass index ≥30; calculated as weight in kilograms divided by height in meters squared], and cancer), and prednisone-equivalent glucocorticoid dose. The pooled sensitivity analysis was also adjusted for concomitant receipt of leflunomide and oral budesonide. The pooled analysis (N = 6077) was additionally adjusted for concomitant receipt of sulfasalazine. The COVID-19 Global Rheumatology Alliance (GRA) registry-level analysis included 3441 patients and was adjusted for immune-mediated disease diagnosis and concomitant receipt of sulfasalazine, hydroxychloroquine or chloroquine, and leflunomide medications. The Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection (PsoProtect) registry-level analysis included 300 patients. The Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) registry-level analysis included 2336 patients and was adjusted for immune-mediated disease diagnosis and concomitant receipt of mesalamine, sulfasalazine, and oral budesonide medications. AZA/6MP indicates azathioprine/6-mercaptopurine; JAKi, Janus kinase inhibitor; and MTX, methotrexate.

whereas individuals receiving TNF inhibitors in combination with methotrexate therapy had similar odds of hospitalization or death compared with those receiving TNF inhibitors alone.

The lower odds of unfavorable COVID-19 outcomes among patients receiving TNF inhibitors before SARS-CoV-2 infection has several possible explanations. Although the exact mechanism of SARS-CoV-2–associated hyperinflammation remains uncertain, high serum TNF concentrations at the time of COVID-19 admission have been associated with organ damage and worse COVID-19 outcomes.[15] Therefore, blocking TNF could inhibit this detrimental immune response. Multiple case series reporting favorable outcomes among patients receiving TNF inhibitor therapy support this assertion.[1,16,17] Upcoming results from clinical trials investigating the use of TNF inhibitors will enable further evaluation of the association between TNF inhibitor therapy and COVID-19 outcomes.[18,19]

Other possible explanations for our findings include the consequences of non-TNF inhibitor immunosuppressive medications for COVID-19 outcomes. Thiopurine medications are associated with a higher risk of opportunistic viral infections.[20-22] A study examining data from a large registry of patients with IBD found that the receipt of thiopurines, including azathioprine and 6-mercaptopurine, was associated with a higher risk of serious viral infection, specifically infection from species of the Herpesviridae.[23] Although data regarding other viruses cannot be directly extrapolated to COVID-19, this higher risk highlights the potential for an association between thiopurine use and an increased risk of unfavorable outcomes after SARS-CoV-2 infection. Moreover, a recent study of data from the SECURE-IBD registry reported that thiopurine monotherapy and thiopurines in combination with TNF inhibitor therapy were associated with worse COVID-19 outcomes compared with TNF inhibitor monotherapy.[24] In contrast, researchers have postulated that methotrexate therapy may decrease the cytokine storm associated with COVID-19.[25,26]

Table 3. Adjusted Pooled Odds of COVID-19–Associated Hospitalization or Death Among Patients in the 3 Registries[a]

Variable	OR (95% CI)	*P* value
Exposure treatment regimen[b]		
TNF inhibitor monotherapy	1 [Reference]	NA
TNF inhibitor plus methotrexate	1.18 (0.85-1.63)	.33
TNF inhibitor plus azathioprine/6-mercaptopurine	1.74 (1.17-2.58)	.006
Methotrexate monotherapy	2.00 (1.57-2.56)	<.001
Azathioprine/6-mercaptopurine monotherapy	1.84 (1.30-2.61)	.001
Jak inhibitor monotherapy	1.82 (1.21-2.73)	.004
Concomitant medication		
Sulfasalazine	1.62 (1.13-2.34)	.009
Leflunomide	1.89 (1.20-2.99)	.006
Oral budesonide	2.86 (1.20-6.84)	.02
Daily prednisone-equivalent dose per 1 mg increase	1.07 (1.05-1.08)	<.001
Demographic characteristic		
Female sex	0.79 (0.66-0.96)	.02
Age per year	1.04 (1.04-1.05)	<.001
Obesity (BMI ≥30)	1.39 (1.10-1.75)	.005
Current smoking	0.77 (0.51-1.17)	.21
Disease activity		
Active	1.27 (1.04-1.55)	.02
Comorbidities		
Interstitial lung disease	1.81 (1.12-2.95)	.02
Obstructive lung disease	2.34 (1.69-3.24)	<.001
Cardiovascular disease	1.58 (1.13-2.21)	.007
Diabetes	1.54 (1.16-2.05)	.003
Hypertension	1.19 (0.95-1.50)	.12
Kidney disease	3.10 (1.70-5.66)	<.001
Cancer	1.16 (0.65-2.07)	.61

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Jak, Janus kinase; NA, not applicable; OR, odds ratio; TNF, tumor necrosis factor.

[a] All 6077 patients from the COVID-19 Global Rheumatology Alliance (GRA); the Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection (PsoProtect); and the Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) registries were included.

[b] Subcategories are mutually exclusive. Odds ratios were obtained using hierarchical multivariable mixed-effects logistic regression analysis with registry and calendar month random effects nested within country. Model was adjusted for all variables shown.

However, our results suggest worse outcomes associated with methotrexate monotherapy compared with TNF inhibitor monotherapy. This association could mean that TNF inhibitor therapy is exerting a protective benefit or that methotrexate therapy is exerting a harmful consequence. Notably, the direction of association was the same for methotrexate used in combination with TNF inhibitors, although the effect estimate crossed the line of no effect, which is possibly associated with the use of lower methotrexate doses in combination therapy compared with monotherapy.[27,28]

The timing of treatment initiation with Jak inhibitors may be an important factor associated with COVID-19 outcomes. The second iteration of the Adaptive COVID-19 Treatment Trial (ACTT-2) suggested a protective effect of treatment with baricitinib in combination with remdesivir therapy against unfavorable COVID-19 outcomes among some subgroups of patients with confirmed severe COVID-19.[29] However, population-based data from patients receiving Jak inhibitors before COVID-19 diagnosis suggest worse outcomes, which is consistent with the known association between this class of medications and reductions in the innate immune response, producing impaired viral clearance.[30] In our comparative analyses, we found that Jak inhibitor monotherapy was associated with higher odds of hospitalization or death than TNF inhibitor monotherapy.

Strengths and Limitations

This study has strengths. These strengths include the robust worldwide collaboration between 3 international registries, which enabled evaluation of a large geographically diverse sample of adults with IMIDs. To our knowledge, this study is the first to pool data across registries to evaluate COVID-19 outcomes among patients with IMIDs. Pooling data increased the power of the study, allowed for more granular analyses of medications, and improved generalizability across IMIDs. Notably, our analyses controlled for active disease, which is only possible through the use of registry data because this variable is not typically available in administrative databases or electronic health records. Furthermore, clinicians or trained staff reported directly to each registry, which likely increased the accuracy of the information.

This study also has limitations. These limitations include the risk of reporting bias because the registries used convenience sampling. However, the results of our sensitivity analysis suggest that reporting bias was not a substantial concern in the GRA registry. The threshold for hospitalization and the ways in which patients are treated for COVID-19 differs over time and across regions. Such

Table 4. Sensitivity Analysis of the Extent of Potential Reporting Bias Based on Data From the GRA Registry

	Estimates from GRA-specific analysis						
	Original		Reweighted[b]				
Exposure treatment regimen[a]	OR (95% CI)[c]	*P* value	OR (95% CI)[c]	*P* value	Standardized difference[d]	Regulatory agreement[e]	Estimate agreement[f]
TNF inhibitor monotherapy	1 [Reference]	NA	1 [Reference]	NA	NA	NA	NA
TNF inhibitor plus methotrexate	1.20 (0.80-1.79)	.38	0.96 (0.57-1.64)	.89	0.035	Yes	Yes
Methotrexate monotherapy	2.21 (1.59-3.08)	<.001	2.20 (1.82-2.65)	<.001	0.002	Yes	Yes
Jak inhibitor monotherapy	2.41 (1.46-3.99)	.001	1.88 (1.44-2.45)	<.001	0.072	Yes	Yes

Abbreviations: GRA, COVID-19 Global Rheumatology Alliance; Jak, Janus kinase; NA, not applicable; OR, odds ratio; TNF, tumor necrosis factor.

[a] The number of patients receiving azathioprine/6-mecaptopurine monotherapy or TNF inhibitors in combination with azathioprine/6-mecaptopurine therapy was too small in the rheumatology clinics to derive estimates for these exposure treatment regimens.

[b] Estimates were obtained after reweighting the covariate distribution of patients in the GRA registry to match those of rheumatology clinics from health care systems that systematically reported all confirmed and suspected COVID-19 patients, using the inverse odds of sampling weights technique.

[c] All ORs were derived using hierarchical multivariable mixed-effects logistic regression analysis with calendar month random effects nested within country and adjusted for the following: age, sex, current smoking, immune-mediated disease diagnosis, immune-mediated disease activity (remission vs active), important comorbidities (cardiovascular disease, diabetes, hypertension, obstructive lung disease, interstitial or other chronic lung disease, kidney disease, obesity [body mass index ≥30; calculated as weight in kilograms divided by height in meters squared], and cancer), and receipt of sulfasalazine, hydroxychloroquine or chloroquine, leflunomide, and prednisone-equivalent glucocorticoid dose.

[d] Standardized difference measured the extent of the difference between the original (potentially biased) and reweighted estimates. Standardized differences were derived from log ORs according to the methods in Franklin et al.[13] Values <0.1 were considered acceptable standardized differences.[14]

[e] Regulatory agreement indicates whether original estimates replicated the statistical significance and direction (when estimates were statistically significant) of reweighted estimates.

[f] Estimate agreement indicates whether the original estimate was within the 95% CI of the reweighted estimates.

differences have the potential to introduce bias if insufficiently accounted for in the analyses. Although we attempted to account for associations in hospitalization or death owing to unmeasured temporal and geographical factors, residual confounding may remain. Additional factors that we were unable to account for included duration and previous lines of IMID therapy. Furthermore, the lack of a global COVID-19 registration system limited the feasibility of including a control group. Although the case report forms were similar, the data domains across registries were not entirely uniform. For example, time and type of COVID-19 diagnosis, rheumatic disease activity, and certain comorbidities were recorded slightly differently across registries. These inconsistencies were addressed, to the extent possible, through the incorporation of registry-level random effects in multilevel modeling and through sensitivity analyses.

Conclusions

The results of this cohort study suggest that, among patients with IMIDs, receipt of TNF inhibitor monotherapy may be associated with a lower risk of COVID-19–associated hospitalization or death compared with other immunomodulatory treatment regimens. These findings support the continued use of TNF inhibitor monotherapy during the pandemic and warrant further research investigating the association of other biologic therapies with COVID-19 outcomes. Treatment with TNF inhibitor combination therapy was associated with a more favorable safety profile when methotrexate rather than azathioprine/6-mercaptopurine was used, suggesting that clinicians would benefit from weighing the risks vs benefits of deescalating treatment or changing medications when a patient is receiving concomitant TNF inhibitors and azathioprine/6-mercaptopurine.

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SUPPLEMENT 1.

eTable. Adjusted Registry-Specific Odds of COVID-19–Associated Hospitalization or Death

SUPPLEMENT 2.

Nonauthor Collaborators. Members of the Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection (PsoProtect); the Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD); and the COVID-19 Global Rheumatology Alliance (GRA)

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

TNFi is associated with positive outcome, but JAKi and rituximab are associated with negative outcome of SARS-CoV-2 infection in patients with RMD

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ABSTRACT

Introduction Several risk factors for severe COVID-19 specific for patients with inflammatory rheumatic and musculoskeletal diseases (RMDs) have been identified so far. Evidence regarding the influence of different RMD treatments on outcomes of SARS-CoV-2 infection is still poor.

Methods Data from the German COVID-19-RMD registry collected between 30 March 2020 and 9 April 2021 were analysed. Ordinal outcome of COVID-19 severity was defined: (1) not hospitalised, (2) hospitalised/not invasively ventilated and (3) invasively ventilated/deceased. Independent associations between demographic and disease features and outcome of COVID-19 were estimated by multivariable ordinal logistic regression using proportional odds model.

Results 2274 patients were included. 83 (3.6%) patients died. Age, male sex, cardiovascular disease, hypertension, chronic lung diseases and chronic kidney disease were independently associated with worse outcome of SARS-CoV-2 infection. Compared with rheumatoid arthritis, patients with psoriatic arthritis showed a better outcome. Disease activity and glucocorticoids were associated with worse outcome. Compared with methotrexate (MTX), TNF inhibitors (TNFi) showed a significant association with better outcome of SARS-CoV-2 infection (OR 0.6, 95% CI0.4 to 0.9). Immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide and ciclosporin) (OR 2.2, 95% CI 1.3 to 3.9), Janus kinase inhibitor (JAKi) (OR 1.8, 95% CI 1.1 to 2.7) and rituximab (OR 5.4, 95% CI 3.3 to 8.8) were independently associated with worse outcome.

Conclusion General risk factors for severity of COVID-19 play a similar role in patients with RMDs as in the normal population. Influence of disease activity on COVID-19 outcome is of great importance as patients with high disease activity—even without glucocorticoids—have a worse outcome. Patients on TNFi show a better outcome of SARS-CoV-2 infection than patients on MTX. Immunosuppressants, rituximab and JAKi are associated with more severe course.

Key messages

What is already known about this subject?

- Also in rheumatic and musculoskeletal diseases (RMDs) age, male sex and specific comorbidities are general risk factors for severity of SARS-CoV-2 infection.
- RMD disease activity and glucocorticoids are specific risk factors.

What does this study add?

- RMD treatment is associated with SARS-CoV-2 infection severity.
- While patients under TNFi treatment show better outcome, those under immunosuppressants, Janus kinase inhibitor (JAKi) and rituximab show worse outcome.

How might this impact on clinical practice or further developments?

- Patients with RMD under treatment with immunosuppressants, JAKi and rituximab need special guidance during the pandemic.

INTRODUCTION

Since the beginning of the SARS-CoV-2 pandemic, increasing evidence about COVID-19 in inflammatory rheumatic and musculoskeletal diseases (RMDs) has been gained. In the general population, age, male sex and certain chronic diseases such as cardiovascular disease (CVD) have been identified as risk factors for severity of COVID-19.[1 2] In patients with RMD, similar risk factors have been described. In addition, for those patients also RMD-specific risk factors play a role.[3–6] Disease activity of the underlying RMD, for example, is of utmost importance for the outcome of COVID-19.[4 6]

Since immunomodulatory treatment can influence the outcome of infectious diseases significantly, the impact of the RMD treatment is also of great interest for patients with RMD

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suffering from SARS-CoV-2 infection. On the one hand, certain immunomodulatory drugs have been proven beneficial in the course of a SARS-CoV-2 infection[7]; on the other hand, immunomodulatory drugs can be detrimental.[8] Moreover, timing and dosing of the treatment appears to be crucial. For example, dexamethasone is a standard treatment for severe COVID-19[7] at present, but a long-term glucocorticoid treatment due to RMD is associated with a worse outcome of SARS-CoV-2 infection.[4 6] The same might be true for Janus kinase inhibitor (JAKi) treatment.[9]

The impact of TNFi on SARS-CoV-2 infection is not completely understood. Use of TNFi in comparison to 'no disease-modifying anti-rheumatic drug (DMARD)' was associated with a lower risk of hospitalisation in the first analysis of the data from the Global Rheumatology Alliance (GRA).[3] However, it was not significantly associated with lower risk of mortality in a more recent analysis of the GRA in which MTX was used as reference category.[4] Potential beneficial effects of TNFi have also been described in patients with COVID-19 with inflammatory bowel disease.[10]

Due to the lack of interventional studies in patients with RMDs and SARS-CoV-2 infection, the effects of RMD treatment have been evaluated in observational studies only. In this analysis from the German COVID19-RMD registry, we analysed the risk factors for the severity of SARS-CoV-2 infection in patients with RMD, specifically focusing on the impact of RMD treatment.

METHODS

Data source

The German COVID-19 registry for patients with RMDs was founded in March 2020 by the German Society for Rheumatology, together with the Justus-Liebig-University Giessen. Rheumatologists voluntarily entered the data into a web-based registry with implemented plausibility checks (https://www.covid19-rheuma.de; for more details, see Hasseli *et al*[11]).

SARS-CoV-2 infection outcome parameters

The primary outcome of interest was the mutually exclusive ordinal COVID-19 severity outcome:

(1) neither hospitalised, ventilated nor deceased; (2) hospitalised with or without non-invasive ventilation, but neither invasively ventilated nor deceased; and (3) invasively ventilated or deceased. At the time of analysis, all patients were required to have a resolved clinical course.

Statistical analyses

Patient characteristics are shown descriptively, stratified by the three categories of the ordinal outcome. Independent associations between demographic and disease features and the ordinal COVID-19 outcome were estimated by multivariable ordinal logistic regression using the proportional odds model and were reported as OR and 95% CI. In the proportional odds model, an increase in severity is assumed to be equal across categories: the increase from 'neither hospitalised, ventilated nor deceased' to 'hospitalised with or without non-invasive ventilation, but neither invasively ventilated nor deceased' is treated in the same way as the increase from the latter category to 'invasively ventilated or deceased'. Potential deviations from this assumption were assessed graphically and did not show relevant deviation (data not shown). Covariates included in the model were age, sex, key comorbidities (hypertension alone or CVD alone, hypertension combined with CVD, chronic lung disease, chronic kidney disease (CKD) and diabetes), RMD or diagnostic group, rheumatic disease treatment prior to COVID-19 diagnosis (without glucocorticoids), as well as the combined status of disease activity as per the physician's global assessment (severe/high or moderate disease activity vs minimal/low disease activity or remission), and the prednisolone-equivalent glucocorticoid use (1–10 mg/day and >10 mg/day). The combined status of disease activity and glucocorticoid use represents both their main effects and interaction (in an additive sense) and is analysed to disentangle the effects of both factors.

All patients with confirmed SARS-CoV-2 infection were included in the main analyses. Patients with missing primary outcome (n=2) or missing values for age, sex and DMARDs (n=2) were excluded from analysis. Smoking status was missing in many cases. Therefore, we have not included smoking in the analysis. Missing values for glucocorticoid therapy and disease activity were derived by multiple imputation using full conditional specification.[12] Results of the ordinal logistic regression analyses for 10 imputed data sets were pooled by Rubin's rules.

For patients listed as having more than one RMD or being treated with more than one of the medications of interest, we created a hierarchy based on clinical expertise to categorise patients. We used the same hierarchy as in Strangfeld *et al*.[4] This process produces disjoint categories, allowing a clear reference group for interpretation of the regression models and avoiding collinearities. Patients with more than one of the following diseases were grouped according to the following hierarchy: systemic lupus erythematosus >vasculitis>other CTD >rheumatoid arthritis (RA) >psoriatic arthritis (PsA)>(other) spondyloarthritis (SpA) >other non-inflammatory joint diseases (IJDs)/non-CTD rheumatic disease; where 'X>Y' means that disease X has priority over disease Y and an individual who has both disease X and disease Y is counted as patient with disease X. Similarly, patients receiving multiple csDMARDs or immunosuppressants (except glucocorticoids) were grouped according to the following hierarchy: immunosuppressants>sulfasalazine>antimalarials>leflunomide>methotrexate. Patients receiving a bDMARD/tsDMARD alone or in combination were considered solely in the bDMARD/tsDMARD group. Patients with an IJD other than RA, PsA or SpA (n=6); patients treated with more than one bDMARD/tsDMARD (n=1); and patients receiving interleukin-1 inhibitors (n=27) or belimumab (n=11) were excluded from analysis due to low numbers.

Table 1 Patient characteristics

Parameter	Not hospitalised, no death	Hospitalised, no invasive ventilation or death	Invasive ventilation or death	Total
N	1771 (77.9)	374 (16.4)	129 (5.7)	2274
General				
Age (years)	55 (18)	67 (19)	71 (19)	57 (19)
66–75	226 (12.8)	90 (24.1)	38 (29.5)	354 (15.6)
>75	137 (7.7)	112 (29.9)	47 (36.4)	296 (13)
Male sex	546 (30.8)	130 (34.8)	67 (51.9)	743 (32.7)
Ever smoker	115 (96.6) n=119 Missing=1652	21 (100) n=21 Missing=353	9 (100) n=9 Missing=120	145 (97.3) n=149 Missing=2125
IJDs				
Rheumatoid arthritis	781 (44.1)	193 (51.6)	76 (58.9)	1050 (46.2)
Spondyloarthritis	251 (14.2)	28 (7.5)	6 (4.7)	285 (12.5)
Psoriatic arthritis	287 (16.2)	19 (5.1)	9 (7)	315 (13.9)
JIA (poly, oligo, not systemic)	6 (0.3)	0	0	6 (0.3)
All IJDs	1313 (74.1)	238 (63.6)	90 (69.8)	1641 (72.2)
CTDs/vasculitis				
SLE	91 (5.1)	12 (3.2)	2 (1.6)	105 (4.6)
CTDs (other than SLE)	134 (7.6)	29 (7.8)	13 (10.1)	176 (7.7)
Vasculitides	145 (8.2)	81 (21.7)	29 (22.5)	255 (11.2)
All CTD/vasculitides	364 (20.6)	121 (32.4)	43 (33.3)	528 (23.2)
Other RMDs				
Total	151 (8.5)	32 (8.6)	11 (8.5)	194 (8.5)
Disease activity	n=1751 Missing=20	n=355 Missing=19	n=109 Missing=20	n=2215 Missing=59
Remission	939 (53.6)	165 (46.5)	37 (33.9)	1141 (51.5)
Minimal/low disease activity	603 (34.4)	112 (31.5)	44 (40.4)	759 (34.3)
Moderate disease activity	169 (9.7)	57 (16.1)	12 (11)	238 (10.7)
Severe/high disease activity	40 (2.3)	21 (5.9)	16 (14.7)	77 (3.5)
Comorbidities				
Hypertension	524 (29.6)	186 (49.7)	83 (64.3)	793 (34.9)
Cardiovascular disease	121 (6.8)	97 (25.9)	51 (39.5)	269 (11.8)
Chronic lung disease	168 (9.5)	72 (19.3)	43 (33.3)	283 (12.4)
Chronic kidney disease	64 (3.6)	71 (19)	35 (27.1)	170 (7.5)
Obesity (BMI ≥30)	355 (20)	87 (23.3)	31 (24)	473 (20.8)
Diabetes	137 (7.7)	67 (17.9)	31 (24)	235 (10.3)
Cancer	50 (2.8)	25 (6.7)	10 (7.8)	85 (3.7)
Number of comorbidities	0 (1)	1.5 (2)	2 (3)	1 (2)
No comorbidity	896 (50.6)	74 (19.8)	15 (11.6)	985 (43.3)
≥3 comorbidities	135 (7.6)	94 (25.1)	53 (41.1)	282 (12.4)
DMARD therapies				
csDMARDs	639 (36.1)	125 (33.4)	37 (28.7)	801 (35.2)
Methotrexate (monotherapy)	381 (21.5)	84 (22.5)	22 (17.1)	487 (21.4)
Leflunomide	76 (4.3)	15 (4)	9 (7)	100 (4.4)
Sulfasalazine	51 (2.9)	12 (3.2)	4 (3.1)	67 (2.9)
Antimalarial	131 (7.4)	14 (3.7)	2 (1.6)	147 (6.5)

Continued

Table 1 Continued

Parameter	Not hospitalised, no death	Hospitalised, no invasive ventilation or death	Invasive ventilation or death	Total
Immunosuppressants	60 (3.4)	36 (9.6)	8 (6.2)	104 (4.6)
bDMARDs	653 (36.9)	102 (27.3)	41 (31.8)	796 (35)
TNF inhibitors	439 (24.8)	43 (11.5)	6 (4.7)	488 (21.5)
Abatacept	21 (1.2)	8 (2.1)	1 (0.8)	30 (1.3)
B cell-targeted bDMARDs	46 (2.6)	29 (7.8)	27 (20.9)	102 (4.5)
Rituximab	37 (2.1)	28 (7.5)	26 (20.2)	91 (4)
Belimumab	9 (0.5)	1 (0.3)	1 (0.8)	11 (0.5)
IL-6 inhibitors	47 (2.7)	9 (2.4)	3 (2.3)	59 (2.6)
IL-1 inhibitors	21 (1.2)	3 (0.8)	3 (2.3)	27 (1.2)
IL-17, IL-23, IL-12/23 inhibitors	79 (4.5)	10 (2.7)	1 (0.8)	90 (4)
tsDMARDs	108 (6.1)	33 (8.8)	14 (10.9)	155 (6.8)
JAK inhibitors	101 (5.7)	32 (8.6)	14 (10.9)	147 (6.5)
Apremilast	7 (0.4)	1 (0.3)	0	8 (0.4)
No DMARD therapies	311 (17.6)	79 (21.1)	29 (22.5)	419 (18.4)
Further therapies				
Glucocorticoids (#)	485 (27.5) n=1759 Missing=12	198 (52.9) n=373 Missing=1	78 (60.5) n=129 Missing=0	761 (33.6) n=2261 Missing=13
0 mg/day<glucocorticoids ≤10 mg/day	453 (25.8)	179 (48)	60 (46.5)	692 (30.6)
Glucocorticoids>10 mg/day	24 (1.4)	18 (4.8)	18 (14)	60 (2.7)
NSAIDs	395 (22.9) (n=1736 Missing=47	59 (16.3) (n=120 Missing=2	12 (9.9) n=83 Missing=0	466 (21.1) n=2208 Missing=66

Data are N (column %) for categorical variables or mean (SD) for continuous variables. Table includes all patients with a non-missing outcome and non-missing values for age, sex and DMARDs (four patients excluded). Data refer to patients with non-missing values for the respective variable; total N for patients with non-missing values is given in parentheses for variables with missing values; the total number of missing values is also given in parentheses, for the applicable variables. # denotes patients with a missing glucocorticoid dosage. For csDMARD therapies and immunosuppressants, only patients not simultaneously receiving a bDMARD/tsDMARD are included. For csDMARDs, patients are included who correspond to the specific therapy when applying the hierarchy described in the Methods section. bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTD, connective tissue disease; DMARD, disease-modifying anti-rheumatic drug; IJD, inflammatory joint disease; IL, interleukin; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; N, number; NSAID, non-steroidal anti-inflammatory drug; RMDs, rheumatic and musculoskeletal diseases; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

Regression coefficients were considered statistically significant for p values <0.05. All analyses were conducted in SAS V.9.4 or R V.4.0.4.

RESULTS

Patient characteristics

Baseline characteristics of the patients are shown in table 1. Of the 2274 patients included, 1771 (78%) did not require hospitalisation. Eighty-three patients died, resulting in a case fatality rate of 3.6%.

The mean age of all patients was 57 years; 67% were female. The most common RMD was RA with 46%, followed by PsA (14%), SpA (13%) and vasculitides (11%).

Eighty-six per cent of patients had a PCR-confirmed diagnosis of SARS-CoV-2 infection; 8% had only an antibody-confirmed diagnosis; the remaining patients had an unknown/other type of diagnosis (two patients were diagnosed based on symptoms only). For all patients, the outcome of SARS-CoV-2 infection was known.

RMD treatments

At the time of SARS-CoV-2 infection, 18% did not receive any DMARD treatment (see table 1). Immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide and ciclosporin) were used in 5%, csDMARDs in 35%, bDMARDs in 35% and tsDMARDs in 7%. Methotrexate was the most common csDMARD, and TNFi was

Table 2 Results of the multivariable ordinal logistic regression using the proportional odds model

Ordinal regression (proportional odds model)	OR	95% CI
General		
Age ≤65 years	1.0	Reference
65 years<age≤75	**2.6**	**2.0 to 3.6**
Age >75	**3.6**	**3.0 to 5.0**
Male sex (vs female)	**1.7**	**1.3 to 2.1**
Comorbidities		
Hypertension alone or CVD alone	**1.5**	**1.2 to 2.0**
Hypertension and CVD	**2.4**	**1.7 to 3.6**
Chronic lung disease	**2.0**	**1.5 to 2.6**
Chronic kidney disease	**1.8**	**1.2 to 2.5**
Diabetes mellitus	1.3	0.9 to 1.8
Rheumatic disease		
Rheumatoid arthritis	1.0	Reference
Systemic lupus erythematosus	0.5	0.2 to 1.1
Vasculitides	1.1	0.7 to 1.5
Other connective tissue diseases	0.9	0.6 to 1.5
Psoriatic arthritis	**0.5**	**0.3 to 0.7**
Spondyloarthritides	0.8	0.5 to 1.3
Other rheumatic diseases (not IJDs/CTDs/vasculitis)	1.0	0.6 to 1.8
Medication*		
Methotrexate (monotherapy)	1.0	Reference
No DMARD therapy	0.9	0.7 to 1.4
Leflunomide	0.8	0.5 to 1.4
Antimalarials	0.7	0.4 to 1.3
Sulfasalazine	1.1	0.6 to 2.1
Immunosuppressants	**2.2**	**1.3 to 3.9**
TNF inhibitors	**0.6**	**0.4 to 0.9**
Abatacept	1.3	0.5 to 3.0
Rituximab	**5.4**	**3.3 to 8.8**
IL-6 inhibitors	0.7	0.3 to 1.5
IL-17/IL-23/IL-12+23 inhibitors	0.9	0.4 to 1.9
JAK inhibitors	**1.8**	**1.1 to 2.7**
Disease activity and glucocorticoids		
Remission/low DA, no GCs	1.0	(Reference)
Remission/low DA, GCs 1–10 mg/day	**1.6**	**1.2 to 2.0**
Remission/low DA, GCs>10 mg/day	**4.6**	**1.9 to 11.4**
Moderate/high DA, no GCs	**2.0**	**1.3 to 3.1**
Moderate/high DA, GCs 1–10 mg/day	**2.4**	**1.5 to 3.7**
Moderate/high DA, GCs >10 mg/day	**5.3**	**2.5 to 10.9**

Ordinal outcome of COVID-19 severity was defined as (1) not-hospitalised, (2) hospitalised but not invasively ventilated and (3) invasively ventilated/deceased. Missing values imputed via multiple imputation. Effects significant at level α=0.05 are marked in bold. N=2222. Compared with table 1, the following numbers of patients were excluded: 27 patients receiving IL-1 inhibitors, 11 patients receiving belimumab, 8 patients receiving apremilast, 6 patients with non-systemic JIA, 1 patient receiving multiple bDMARDs/tsDMARDs.
*Patients receiving multiple csDMARDs or immunosuppressants (except glucocorticoids) were grouped according to the following hierarchy: immunosuppressants>sulfasalazine>antimalarials>leflunomide>methotrexate. Patients receiving a bDMARD/tsDMARD alone or in combination were considered solely in the bDMARD/tsDMARD group.
bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTD, connective tissue disease; CVD, cardiovascular disease; DA, disease activity; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; IJD, inflammatory joint disease; IL, interleukin; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

the most common bDMARD. Rituximab was used in 91 patients (4%), and JAKi was used in 147 patients (6.5%).

SARS-CoV-2 infection outcome analysis

Age above 65 years was associated with higher COVID-19 severity with an OR of 2.6 (95% CI 2.0 to 3.6) and above 75 years with an OR of 3.6 (95% CI 3.0 to 5.0) (table 2 and figure 1A). Male sex was also associated with greater severity (OR 1.7, 95% CI 1.3 to 2.1).

Arterial hypertension, CVD, chronic lung disease (including chronic obstructive pulmonary disease, asthma and interstitial lung diseases), and CKD showed significant associations with COVID-19 severity (table 2 and figure 1B). The strongest association was found for patients having both comorbidities, arterial hypertension and CVD (OR 2.4, 95% CI 1.7 to 3.6).

With respect to the underlying RMD entity, PsA was associated with less severe COVID-19 course in comparison to RA (OR 0.5, 95% CI 0.27 to 0.74) (table 2 and figure 1C).

Since disease activity and the use of glucocorticoids are usually linked, both factors were analysed jointly. The results are shown in table 2 and figure 1D. Remission/low disease activity *with* low dose GCs (1–10 mg/d) showed a significant association with worse outcome (OR 1.6, 95% CI: 1.2 to 2.0) compared with remission/low disease activity *without* GCs. This effect increased with higher GC doses (OR 4.6, 95% CI 1.9 to 11.4). Moderate/high disease activity but no GCs were also associated with a worse outcome compared with remission/low disease activity with no GCs (OR 1.99, 95% CI 1.28 to 3.11). Moderate/high disease activity with low-dose GC were associated with a worse COVID-19 outcome with an OR of 2.4 (95% CI 1.5 to 3.7), and in case of moderate/high disease activity with high-dose GC, this was even more prominent with an OR of 5.3 (95% CI 2.53 to 10.9).

For the analysis of the impact of RMD treatment on the outcome of SARS-CoV-2 infection, MTX monotherapy was used as reference (table 2 and figure 1E). Treatment with immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide and ciclosporin) was associated with a higher COVID-19 severity (OR 2.2, 95% CI 1.3 to 3.9). JAKis were also associated with a significantly worse severity (OR 1.8, 95% CI 1.1 to 2.7). The strongest association with worse outcome of COVID-19 was found for rituximab with an OR of 5.4 (95% CI 3.3 to 8.8). In contrast, TNFi showed a significant association with a better outcome of SARS-CoV-2 infection with an OR of 0.6 (95% CI 0.4 to 0.9).

DISCUSSION

This analysis adds evidence that medication for RMD has a considerable impact on the course of SARS-CoV-2 infection. Two main results could be retrieved from this analysis: (1) TNFi is not associated with a more severe course of SARS-CoV-2 infection in patients with RMD and, (2) in contrast, immunosuppressants, JAKis and rituximab

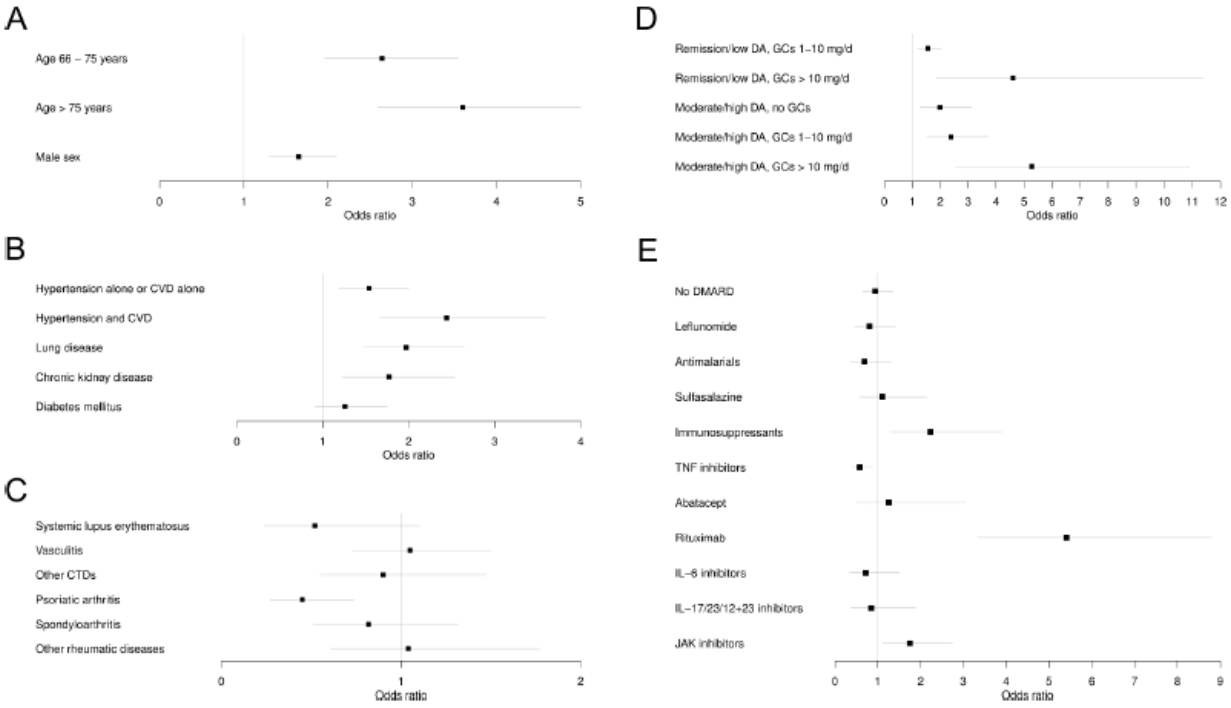

Figure 1 (A–E) Results of the multivariable ordinal logistic regression using the proportional odds model and reported as OR and 95% CI for each regressor variable. Associations with SARS-CoV-2 infection severity are shown with (A) general factors, (B) comorbidities, (C) RMD diagnosis, (D) RMD disease activity and glucocorticoids, (E) RMD treatment (immunosuppressants: mycophenolate mofetil, azathioprine, cyclophosphamide and ciclosporin). The reference categories are as follows: (A) ≤65 years, ≤65 years, female sex; (B) the non-presence of the specific comorbidity; (C) rheumatoid arthritis; (D) remission/low disease activity, no glucocorticoids; and (E) methotrexate monotherapy. Missing values were imputed via multiple imputation. N=2222. Compared with table 1, the following numbers of patients were excluded: 27 patients receiving IL-1 inhibitors, 11 patients receiving belimumab, 8 patients receiving apremilast, 6 patients with non-systemic JIA, one patient receiving multiple bMARDs/tsDMARDs. bDMARD, biological disease-modifying antirheumatic drug; CVD, cardiovascular disease; CTD, connective tissue diseases; DMARD, disease-modifying anti-rheumatic drugs; DA, disease activity; GC, Glucocorticoids; IL, interleukin; JAK, Janus kinase; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drugs.

are associated with a more severe course. Moreover, it could be confirmed that general risk factors like age, male sex and certain chronic conditions are also associated with greater severity of SARS-CoV-2 infection in patients with underlying RMD.[1 2]

RMD-specific risk factors have been described. The impact of disease activity and GC use are of utmost importance. Disease activity and the use of GC are usually linked. Analysing these effects separately from each other is very difficult because of the known confounding by indication in the setting of observational data. In a correspondence to the COVID-19 mortality analysis of the GRA data set,[4] this interaction was shown.[13] Here, we present similar results. However, in this analysis, GC use was associated with worse outcome even in patients in remission or low disease activity.

In this analysis, PsA was associated with a better COVID-19 course compared with RA. In the COVID-19 mortality analysis, PsA was not significantly associated but also showed an OR of less than 1.0 (0.75, 95% CI 0.53 to 1.07). Whether the positive association seen in our analysis is due to true differences between the diseases or unmeasured confounders is not clear. However, the risk of severe infection in bDMARD-treated patients with psoriasis compared with patients with RA is much lower, which might be a signal of different susceptibility for severe infections.[14]

A very important finding of our analysis is the potential beneficial effect of TNFi. This association was not seen in an earlier mortality analysis, although TNFi showed also an OR of less than 1.0 (0.9; 95% CI: 0.5 to 1.4).[4] This discrepancy might be due to the large heterogeneity in the GRA data set with large differences between the countries regarding the outcomes. In the analysis by Sparks *et al.* TNFi were used as reference medication and therefore, due to methodological reasons, the impact of TNFi could not be estimated in this study.[5] There are also clinical trials using TNFi in different settings of COVID-19.[15]

In the GRA analysis concerning the risk of mortality, sulfasalazine was significantly associated with mortality.[4] In our analysis, sulfasalazine was not associated with COVID-19 severity, which may be due to more homogenous data with regard to healthcare system-related factors.

Regarding the influence of rituximab, there is growing evidence for an association with a worse outcome. This has been shown in various settings in RMDs.[4 5 16–18] In our analysis, we confirmed these results. The influence of B-cell depletion/anti-CD20 antibodies like rituximab on COVID-19 outcome has also been studied in other diseases in which these treatments are used.[19 20] For example, observational studies from multiple sclerosis showed a similar association of rituximab with severe COVID-19 outcome as in RMD.[21]

Data addressing an influence of JAKis on COVID-19 outcome are still limited. Thus, our analysis adds important knowledge showing an association of JAKi as RMD treatment with a more severe course of COVID-19. A negative association with COVID-19 outcome was also seen in the RA analysis of the GRA data set.[5] In an analysis from Sweden, an increased risk of COVID-19-related hospitalisation as well as COVID-19-related death has been described for patients under therapy with JAKis.[16] In contrast, owing to their anti-inflammatory potential, JAKis have been approved for the short-term treatment of severe COVID-19.[9 22] Here, the timing and duration of the treatment seems to play a role, with negative impact in patients with RMD pretreated with JAKis and potential benefits when initiated to treat severe SARS-CoV-2 infection. A pathophysiological explanation could be that type I interferon response is crucial in the initial phase of infection for a good outcome of SARS-CoV2 infection.[23] Therefore, inhibition of the type I interferon pathway by JAKi in the early phase of infection might contribute to more severe COVID-19.

The strengths of this analysis in comparison to the GRA data lie in the fact that our data are more homogenous as they were collected in a single country within one healthcare system and similar treatments and chances of care for all included patients.

However, there also are study limitations. Missing data on known confounders like RMD disease duration and number of RMD pretreatments limit the interpretation. Especially for rituximab and JAKi, it is known that they are often used in non-responder to MTX/TNFi.[24 25] Therefore, the negative impact of those therapies on COVID-19 severity needs to be interpreted carefully. Similarly, we do not have detailed data on RTX dosage and—even more important—time of last infusion to be able to calculate the number of days between RTX treatment and date of SARS-CoV-2 infection. Furthermore, we do not know if the RMD treatment was paused due to acute SARS-CoV-2 infection. Although most patients continue their RMD treatment in the pandemic as stated in the treatment recommendations, in the case of an acute symptomatic infection especially in hospitalised patients, it is recommended to pause the immunomodulating treatment.[26–28] Differential effects of the RMD treatment might therefore also be explained by different half-lives of these drugs.

In conclusion, risk factors for higher severity of SARS-CoV-2 infection known for the general population, such as age, male sex and certain chronic conditions, play a similar role in patients with RMDs. In addition, further risk factors need to be taken into account, for example, the influence of higher disease activity with an increased risk of worse outcome even without using GCs on the one hand and association of chronically administered GCs with a similar worse outcome on the other. Regarding RMD medication, our data show that treatment with TNFi was associated with better outcome of SARS-CoV-2 infection than MTX. Moreover, treatment with immunosuppressants, JAKi and rituximab was associated with worse outcome of SARS-CoV-2 infection. These associations may be attributed to residual and unmeasured confounding due to higher burden of comorbidity or cumulative effect of therapies. Taken together, while it is crucial to control RMD disease activity, the medication used to achieve this control needs to be carefully chosen.

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3.7 COVID-19 bei systemischem Lupus erythematodes und bei Vaskulitiden

Originalarbeit 13:

Ugarte-Gil MF, Alarcón GS, Izadi Z, Duarte-García A, Reátegui-Sokolova C, Clarke AE, Wise L, Pons-Estel GJ, Santos MJ, Bernatsky S, Ribeiro SLE, Al Emadi S, Sparks JA, Hsu TY, Patel NJ, Gilbert EL, Valenzuela-Almada MO, Jönsen A, Landolfi G, Fredi M, Goulenok T, Devaux M, Mariette X, Queyrel V, Romão VC, Sequeira G, **Hasseli R**, Hoyer B, Voll RE, Specker C, Baez R, Castro-Coello V, Maldonado Ficco H, Reis Neto ET, Ferreira GAA, Monticielo OAA, Sirotich E, Liew J, Hausmann J, Sufka P, Grainger R, Bhana S, Costello W, Wallace ZS, Jacobsohn L, Taylor T, Ja C, Strangfeld A, Mateus EF, Hyrich KL, Carmona L, Lawson-Tovey S, Kearsley-Fleet L, Schäfer M, Machado PM, Robinson PC, Gianfrancesco M, Yazdany J.

Characteristics associated with poor COVID-19 outcomes in individuals with systemic lupus erythematosus: data from the COVID-19 Global Rheumatology Alliance.

Ann Rheum Dis. 2022 Feb 16:annrheumdis-2021-221636. doi: 10.1136/annrheumdis-2021-221636

Originalarbeit 14:

Sattui SE, Conway R, Putman MS, Seet AM, Gianfrancesco MA, Beins K, Hill C, Liew D, Mackie SL, Mehta P, Neill L, Gomez G, Salinas MIH, Maldonado FN, Mariz HA, de Sousa Studart SA, Araujo NC, Knight A, Rozza D, Quartuccio L, Samson M, Bally S, Maria AT, Chazerain P, **Hasseli R**, Müller-Ladner U, Hoyer BF, Voll R, Torres RP, Luis M, Ribeirio SLE, Al-Emadi S, Sparks JA, Hsu TY, D'Silva KM, Patel NJ, Wise L, Gilbert E, Almada MV, Duarte-García A, Ugarte-Gil M, Jacobsohn L, Izadi Z, Strangfeld A, Mateus EF, Hyrich KL, Gossec L, Carmona L, Lawson-Tovey S, Kearsley-Fleet L, Schaefer M, Sirotich E, Hausmann JS, Sufka P, Bhana S, Liew JW, Grainger R, Machado PM, Wallace ZS, Yazdany J, Robinson PC; Global Rheumatology Alliance. *Outcomes of COVID-19 in patients with primary systemic vasculitis or polymyalgia rheumatica from the COVID-19 Global Rheumatology Alliance physician registry: a retrospective cohort study.*

Lancet Rheumatol. 2021 Dec;3(12):e855-e864. doi: 10.1016/S2665-9913(21)00316-7

Zusammenfassung:

Bei den ersten Arbeiten lag der Fokus der Auswertungen innerhalb der Gruppe der ERE bei inflammatorischen Arthritiden, da sie die größte Krankheitsgruppe darstellen und basierend auf den hohen Fallzahlen auch aussagekräftige Resultate generiert werden konnten. Im Verlauf der Pandemie nahmen jedoch auch die SARS-CoV-2-Fälle bei Kollagenosen und Vaskulitiden zu. Dennoch waren die länderspezifischen Daten nicht ausreichend, um wertvolle Erkenntnisse zu gewinnen. Somit erfolgte auch hier eine internationale Kooperation, um mit einer höheren Fallzahl aussagekräftige Resultate zu genieren und dadurch weitere Informationen für die Betreuung dieser PatientInnen zu gewinnen.

PatientInnen mit systemischem Lupus erythematodes (SLE) benötigen in der Regel eine immunsupprimierende Therapie und weisen eine höhere Prävalenz von Komorbiditäten auf, so dass diese bereits per se ein erhöhtes Risiko für einen schweren Verlauf einer SARS-CoV-2-Infektion haben könnten. Bislang gab es aber keine ausreichenden Analysen zum Verlauf einer SARS-CoV-2-Infektion bei SLE-PatientInnen. Zwar konnte in der Analyse „OpenSAFELY“ bei über 17 Millionen SARS-CoV-2-Infizierten ein höheres Mortalitätsrisiko für PatientInnen mit SLE oder rheumatoider Arthritis nachgewiesen werden, jedoch erfolgte keine Bewertung der Therapie der ERE oder der Einfluss der Krankheitsaktivität [207].

Aus diesem Grund erfolgte eine gepoolte Analyse der Daten aus dem globalen Register (Originalarbeit *13*). Diese schloss alle Fälle während des Zeitraums März 2020 bis Juni 2021 ein. Für die weitere Untersuchung der SARS-CoV-2-Verläufe wurde eine Ordinalskala definiert:

1) keine Hospitalisierung
2) Hospitalisierung ohne jegliche Sauerstofftherapie
3) Hospitalisierung mit jeglicher Sauerstofftherapie
4) Tod

In dem genannten Zeitraum wurden 1606 SLE-PatientInnen in den Registern erfasst. Die Mehrheit der SLE-PatientInnen wies einen milden Verlauf auf (70% nicht hospitalisiert), 11% wurden stationär ohne jegliche Sauerstofftherapie behandelt, 13% erhielten eine Sauerstofftherapie und die Letalität betrug 6,5%. Das Alter lag im Durchschnitt bei 44 Jahren. Die PatientInnen waren in 90% der Fälle weiblich. Neben den allgemeingültigen Risikofaktoren, wie z.B. Alter, männliches Geschlecht und Begleiterkrankungen, wiesen auch hier SLE-PatientInnen mit moderater (OR 1,6; 95%CI 1,0 – 2,5) oder hoher Krankheitsaktivität (OR 3,9; 95%CI 2,1 – 7,3) im Vergleich zu PatientInnen in Remission eine Assoziation mit schwereren Infektionsverläufen auf.

Bei milden Verläufen eines SLE wird in der Regel Hydroxychloroquin eingesetzt [108]. Somit diente die Monotherapie mit Hydroxychloroquin für die weitere Analyse als Referenzgruppe. Nach Geschlechter- und Altersadjustierung waren der Einsatz von Mycophenolat (OR 1,4; 95%CI 1,1 – 1,8), Cyclophosphamid (OR 2,6; 95%CI 1,2 – 5,3) und Rituximab (OR 1,7; 95%CI 1,0 – 2,8) mit schwereren Verläufen der Infektion assoziiert. Dagegen zeigte sich unter Therapie mit Methotrexat (OR 0,7; 95%CI 0,5 – 1,0) und Belimumab (OR 0,5; 95%CI 0,3 – 0,9) eine Assoziation mit milderen Infektionsverläufen. Der Einsatz von Azathioprin unterschied sich nicht von Hydroxychloroquin hinsichtlich des Infektionsverlaufes. SLE-

PatientInnen unter Prednisolontherapie wiesen eine dosisabhängige, höhere Assoziation mit schweren COVID-19-Verläufen auf, im Gegensatz zu PatientInnen ohne Glukokortikosteroidtherapie (1-5 mg Prednisolon/Tag: OR 1,9; 95%CI 1,3 – 2,7; 6-9 mg Prednisolon/Tag: OR 2,5; 95%CI 1,3 – 4,9; über 10 mg Prednisolon/Tag: OR 2,0; 95%CI 1,3 – 3,0). Eine hohe Krankheitsaktivität war ebenfalls mit schweren Verläufen assoziiert (OR 3,94; 95%CI 2,1 – 7,3).

Somit decken sich die Beobachtungen bei den inflammatorischen Arthritiden als auch bei SLE-PatientInnen: hohe Krankheitsaktivität, der Einsatz von Glukokortikosteroiden und Immunsuppressiva sind mit schweren COVID-19-Verläufen assoziiert.

Wie gestaltet sich jedoch das Risiko für einen schweren COVID-19-Verlauf bei ERE, die primär mit Glukokortikosteroiden therapiert werden, wie z.B. bei der Polymyalgia rheumatica, der Großgefäßvaskulitis oder den ANCA-assoziierten Vaskulitiden [208]? Aufgrund der Vaskulitis kann es ohne Therapie zu ischämischen Ereignissen oder sogar Organschäden kommen. Zudem treten Vaskulitiden in der Regel im höheren Lebensalter auf, so dass unabhängig von der Vaskulitis PatientInnen ein höheres Risiko für schwere Verläufe einer SARS-CoV-2-Infektion aufweisen. Die Vaskulitis könnte zudem die Grundlage für die endotheliale Dysfunktion im Rahmen von COVID-19 bieten. Bislang konnte der Verlauf einer Infektion bei diesen Erkrankungen aufgrund der limitierten Patientenzahl nicht ausreichend geklärt werden. Deshalb erfolgte eine gepoolte Analyse der internationalen Register im Rahmen einer globalen Auswertung (Originalarbeit *14*). Im Zeitraum von März 2020 bis April 2021 wurden 1202 PatientInnen mit einer Vaskulitis erfasst, 61% davon weiblich.

Das Alter lag im Median bei 64 Jahren. Darunter befanden sich 31% PatientInnen mit einer Polymyalgie, 29% mit einer ANCA-assoziierten Vaskulitis, 15% mit einer Riesenzellarteriitis, 9% mit einem Morbus Behçet und 15% mit anderen Formen einer Vaskulitis. Der Ausgang der Infektion war bei 85% der Fälle zum Zeitpunkt der Auswertung bekannt. Davon waren 50% im Rahmen der SARS-CoV-2-Infektion nicht hospitalisiert, 11% wurden stationär ohne jegliche Sauerstofftherapie behandelt, 23% mit jeglicher Sauerstofftherapie und 15% wiesen einen letalen Verlauf auf. Innerhalb der einzelnen Krankheitsgruppen unterschieden sich die Ergebnisse jedoch. Beispielsweise betrug die Letalitätsrate beim Morbus Behçet 2%, wohingegen die Letalität bei ANCA-assoziierten Vaskulitiden bei 22% lag. Für die weitere Analyse wurde auch hier die definierte Ordinalskala aus der Originalarbeit *13* verwendet. Der Fokus lag, aufgrund der Fallzahlen, in der Auswertung der Fälle mit Riesenzellarteriitis, Polymyalgie und ANCA-assoziierten Vaskulitiden. Neben den bereits bekannten allgemeingültigen Risikofaktoren, wie Alter, Komorbiditäten und männliches Geschlecht,

waren schwere Verläufe mit dem Einsatz von mindestens 10 mg/Tag Prednisolon und höherer Krankheitsaktivität assoziiert. Das Risiko war bei allen Krankheitsgruppen nachweisbar, jedoch in unterschiedlicher Ausprägung. Deskriptiv wiesen PatientInnen mit einer Vaskulitis im Vergleich zu PatientInnen mit anderen ERE höhere Hospitalisierungs- und Mortalitätsraten auf..

EPIDEMIOLOGICAL SCIENCE

Characteristics associated with poor COVID-19 outcomes in individuals with systemic lupus erythematosus: data from the COVID-19 Global Rheumatology Alliance

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ABSTRACT

Aim To determine characteristics associated with more severe outcomes in a global registry of people with systemic lupus erythematosus (SLE) and COVID-19.

Methods People with SLE and COVID-19 reported in the COVID-19 Global Rheumatology Alliance registry from March 2020 to June 2021 were included. The ordinal outcome was defined as: (1) not hospitalised, (2) hospitalised with no oxygenation, (3) hospitalised with any ventilation or oxygenation and (4) death. A multivariable ordinal logistic regression model was constructed to assess the relationship between COVID-19 severity and demographic characteristics, comorbidities, medications and disease activity.

Results A total of 1606 people with SLE were included. In the multivariable model, older age (OR 1.03, 95% CI 1.02 to 1.04), male sex (1.50, 1.01 to 2.23), prednisone dose (1–5 mg/day 1.86, 1.20 to 2.66, 6–9 mg/day 2.47, 1.24 to 4.86 and ≥10 mg/day 1.95, 1.27 to 2.99), no current treatment (1.80, 1.17 to 2.75), comorbidities (eg, kidney disease 3.51, 2.42 to 5.09, cardiovascular disease/hypertension 1.69, 1.25 to 2.29) and moderate or high SLE disease activity (vs remission; 1.61, 1.02 to 2.54 and 3.94, 2.11 to 7.34, respectively) were associated with more severe outcomes. In age-adjusted and sex-adjusted models, mycophenolate, rituximab and cydophosphamide were associated with worse outcomes compared with hydroxychloroquine; outcomes were more favourable with methotrexate and belimumab.

Conclusions More severe COVID-19 outcomes in individuals with SLE are largely driven by demographic factors, comorbidities and untreated or active SLE. Patients using glucocorticoids also experienced more severe outcomes.

INTRODUCTION

During the COVID-19 pandemic, individuals with systemic lupus erythematosus (SLE) have been of particular concern. SLE disproportionately impacts populations most severely affected by COVID-19, including those from non-white racial and ethnic groups, and those with low socioeconomic status.[1] Moreover, individuals with SLE are often heavily immunosuppressed and have a high comorbidity burden with multiple risk factors for more severe COVID-19. Although previous analyses have evaluated outcomes of infection with SARS-Cov-2 in rheumatic diseases as a group, data on individuals with SLE are limited, and it remains unclear which risk factors are associated with worse COVID-19 outcomes in this population.

Key messages

What is already known about this subject?

- Demographic factors as well as comorbidities have been associated with poorer COVID-19 outcomes in the general population.
- The COVID-19 Global Rheumatology Alliance has reported glucocorticoid dose (≥10 mg/day), some immunosuppressive drugs and disease activity as predictors of poorer COVID-19 outcomes in individuals with different rheumatic diseases.

What does this study add?

- More severe COVID-19 outcomes in individuals with systemic lupus erythematosus (SLE) are mainly driven by demographic factors, comorbidities and untreated or active SLE.
- Individuals using glucocorticoids (even low dose) experienced more severe outcomes.

How might this impact on clinical practice or future developments?

- Individuals with lupus and these characteristics should be prioritised for close monitoring, counselled to receive vaccination, and receive preventive therapies if infected with SARS-CoV2.

Data from the COVID-19 Global Rheumatology Alliance (C19-GRA) registry, a large physician reported registry of individuals with rheumatic diseases and COVID-19, suggest that those with moderate or high disease activity, as well as those receiving specific medications, including moderate or high doses of prednisone, rituximab, immunosuppressive drugs (ie, mycophenolate mofetil/mycophenolic acid (MMF), tacrolimus, azathioprine and cyclophosphamide) compared with a reference group of individuals receiving methotrexate have poorer outcomes.[2] Furthermore, in an analysis of patients in the C19-GRA registry with rheumatoid arthritis (RA), treatment with rituximab or Janus Kinase (JAK) inhibitors was associated with poorer outcomes compared with treatment with tumour necrosis factor inhibitors.[3] However, medications associated with more severe COVID-19 outcomes in SLE have not been extensively examined.

OpenSAFELY, a large analysis of primary care records of >17 million adults linked to 10 926 COVID-19-related deaths reported that after adjustment for a wide variety of factors such as demographic characteristics and comorbidities, those with autoimmune disease (SLE, RA or psoriasis as a group) had a higher risk of mortality, but this study did not adjust for medication use, nor did it evaluate SLE as a discrete or separate disease.[4] Several case series or single-centre/country studies suggest that some individuals with SLE can have a severe disease course, but the small size of these studies has precluded a comprehensive analysis of risk factors for poor COVID-19 outcomes.[5–10]

We used the C19-GRA registry to identify sociodemographic and clinical factors associated with more severe COVID-19 outcomes in individuals with SLE.

METHODS

Data source

Subjetcs with rheumatic disease and COVID-19 from the C19-GRA registry and European Alliance of Associations for Rheumatology (EULAR) COVID-19 registry were included in the analyses, which covered the period from 12 March 2020 to 1 June 2021. Data entry portals include one limited to European countries (eular.org/eular_covid19_database.cfm; hosted by The University of Manchester, UK) and a second for all other countries (rheum-covid.org/provider-global/; hosted by the University of California, San Francisco (UCSF), California, USA).[11 12] Cases are entered into these registries by their treating clinicians. This study includes all individuals from these registries with SLE diagnosed with COVID-19 by 1 June 2021. Prior studies using C19-GRA and EULAR databases have included some individuals also reported in this study,[2 13 14] but the number of individuals in this analysis is significantly higher than reported in previous publications.

Data quality was assessed by the data coordinating centres at UCSF and the University of Manchester and included procedures to identify and remove any duplicate cases.

COVID-19 outcomes

We used an ordinal severity outcome in the analyses, with mutually exclusive categories including: (1) not hospitalised, (2) hospitalised with no oxygenation, (3) hospitalised with any ventilation or oxygenation or (4) death. These outcomes were chosen so that the analyses could reflect the full spectrum of disease associated with COVID-19 and are analogous to outcome measures used in many trials evaluating COVID-19 therapeutics. Only the highest severity level of the outcome occurring during the patient's disease course was included, and all individuals were required to have a resolved clinical course.

Covariates, including medication exposure

Covariates included demographic characteristics, including age, sex and region (Europe, the USA and Canada, Latin America and other), as well as clinical characteristics, including number of comorbidities (including lung, liver or neurological diseases, cancer, diabetes, obesity, among others), specific comorbidities (chronic renal insufficiency or end-stage renal disease and hypertension or cardiovascular disease), disease activity (assessed by a physician global assessment categorised as remission, low, moderate or high), dose of glucocorticoids (GCs; entered as daily oral prednisone equivalents) and use of immunosuppressive or immunomodulating medications. Additionally, the date of the case report was analysed in three time periods: 24 March 2020 to 15 June 2020, 16 June 2020 to 30 September 2020 and 1 October 2020 to 1 June 2021. The first period ended at the release of the RECOVERY study, which changed COVID-19 treatment protocols to incorporate GCs.[15] The second cut-off was based on the beginning of the second wave in many countries around the world.

Medications taken by patients prior to COVID-19 were categorised as: conventional synthetic drugs (antimalarials (hydroxychloroquine, chloroquine), conventional disease-modifying monotherapies generally considered to represent less intensive immunosuppression (sulfasalazine, methotrexate and leflunomide), conventional disease-modifying monotherapies with more intense immunosuppressive drugs (MMF, tacrolimus, cyclophosphamide, ciclosporin, azathioprine)); biologics (abatacept, belimumab, rituximab, interleukin (IL)-6 inhibitors, IL-12/IL-23 inhibitors, IL-17 inhibitors, tumour necrosis factor inhibitors (anti-TNF)) and targeted synthetic drugs, specifically JAK inhibitors and GCs. In analyses, we divided medications into five groups: no SLE medications, antimalarial only, conventional disease-modifying monotherapies generally considered to represent less intensive immunosuppression (sulfasalazine, methotrexate and leflunomide), conventional disease-modifying

monotherapies with more intense immunosuppressive drugs (MMF, tacrolimus, cyclophosphamide, ciclosporin, azathioprine), biologic/targeted synthetic drug monotherapy and finally combination therapy with conventional and biologic disease-modifying immunosuppressive drugs. GCs were categorised into four groups by dose: prednisone dose=0 mg/day, between 1 and 5 mg/day, between 6 and 9 mg/day and ≥10 mg/day.

Statistical analyses

We used proportional odds logistic regression with severity as dependent variable, and covariates as described in the next paragraphs. This is similar to using binary logistic regression for each of the three possible dichotomisations of the four-category dependent variable, with the assumption that the OR is the same for each cut-off. The parallel lines test for proportional odds ordinal logistic regression confirmed that this assumption was not violated.

Models included demographic variables and clinical characteristics as well as the time period in the pandemic during which the case was reported. Random effects were included for country and time. These variables were applied to capture the significant variability in regulations enforcing personal protective equipment, hospital resource allocation and quarantine procedures between countries and over the course of the pandemic.

We assumed that missing data were 'missing at random' and missing data were handled using multiple imputation, with 50 imputed data sets.

In all models, we included sex, age, region, GCs as a categorical variable (0, 1–5, 6–9, ≥10 mg/day), immunosuppressive medication category, time period and random effects of country and time. To assess the additional impact of comorbidities, we constructed an additional model that included the number of comorbidities and, separately, that included key comorbidities in SLE, including renal disease and hypertension/cardiovascular disease. Finally, we constructed a model that included the above variables but additionally included SLE disease activity.

We conducted several additional analyses to examine associations of six medications of interest in SLE with COVID-19 outcomes: methotrexate (n=173), azathioprine (n=235), MMF (n=332), cyclophosphamide (n=29), rituximab (n=68) and belimumab (n=104). In these analyses, the drug of interest was excluded from the medication category of monotherapies with immunosuppressive drugs or from the biologics/targeted synthetic only category, and their effects were estimated separately. Four models were constructed for each medication: (1) unadjusted, (2) age-adjusted and sex-adjusted, (3) adjusted for age, sex, renal disease, hypertension/cardiovascular disease, comorbidity count, disease activity, region, time period and (4) confirmed cases (diagnosis made by PCR, antibody or antigen) adjusted for age, sex, renal disease, hypertension/cardiovascular disease, comorbidity count, disease activity, region and time period. Additionally, to evaluate the interaction between GC therapy and disease activity, an additional analysis was done adding this multiplicative interaction term.

A sensitivity analysis combining mechanical ventilation or death in the highest category was also performed.

Results were considered statistically significant using a two-sided p<0.05. Analyses were conducted in R V.4.0.2 (R Core Team, 2020).

RESULTS

As of 1 June 2021, 1922 subjects with SLE and COVID-19 were reported in the C19-GRA and EULAR registries. Baseline demographic and clinical characteristics are shown in table 1. Individuals were predominantly female (90.4%) and the mean age was 44.4 years (SD=14.1). Of the 1922 cases, 555 (28.9%) were reported from the USA and Canada, 543 (28.3%) from Europe, 643 (33.5%) from Latin America and 181 (9.4%) from other regions. The majority were non-white (57.3%).

Antimalarials were used as monotherapy by 665 individuals (34.6%), more intense immunosuppressive monotherapies (MMF, tacrolimus, cyclophosphamide, ciclosporin, azathioprine, with or without antimalarials) were used by 630 individuals

Table 1 Characteristics of patients with SLE at the time of COVID-19 diagnosis (n=1922)

Characteristics	Mean (SD) or number (percentage)
Age, years, mean (SD)	44.4 (14.1)
Female, n (%)	1734 (90.4%)
Race/Ethnicity, n (%)	
White	639 (33.3%)
Non-white	1102 (57.3%)
Missing	181 (9.4%)
Region, n (%)	
Europe	543 (28.3%)
USA and Canada	555 (28.9%)
Latin America	643 (33.5%)
Other	181 (9.4%)
Time period, n (%)	
<15 June 2020	733 (38.1%)
16 June–30 September 2020	444 (23.1%)
1 October 2020–12 April 2021	745 (38.8%)
Comorbidities, n (%)	
0	1098 (57.1%)
1	511 (26.6%)
≥2	313 (16.3%)
Specific comorbidities, n (%)	
Chronic renal insufficiency or ESRD	223 (11.8%)
Hypertension or cardiovascular disease	597 (31.1%)
Disease activity, n (%)	
Remission	587 (30.5%)
Minimal or low	700 (36.4%)
Moderate	229 (11.9%)
Severe or high	77 (4.0%)
Missing	329 (17.1%)
Prednisone dose*, n (%)	
0 mg/day	846 (44.0%)
1–5 mg/day	467 (24.3%)
6–9 mg/day	78 (4.1%)
≥10 mg/day	280 (14.6%)
Missing	251 (13.1%)
Medication category, n (%)	
Antimalarials only	665 (34.6%)
No SLE therapy	230 (12.0%)
Oral synthetic drug monotherapy with methotrexate, leflunomide or sulfasalazine only†	175 (9.1%)
Oral synthetic drug monotherapy with (mycophenolate/mycophenolic acid, tacrolimus, cyclophosphamide, ciclosporin or azathioprine)†	630 (32.8%)
Biologic/Targeted synthetic monotherapy	45 (2.3%)
Biologic/Targeted and immunosuppressive drug combination therapy†	177 (9.2%)

*All glucocorticoids were converted to prednisone-equivalent doses.
†These patients could be also on antimalarials.
ESRD, end-stage renal disease; SLE, systemic lupus erythematosus.

Table 2 Ordinal COVID-19 severity outcome as a function of medication class in individuals with SLE (n=1606)

	Total (n=1606)	Antimalarial only (n=532)	No DMARD (n=182)	Monotherapy with methotrexate, leflunomide or sulfasalazine only* (n=152)	Monotherapy with mycophenolate/ mycophenolic acid, tacrolimus, cyclophosphamide, ciclosporin or azathioprine* (n=539)	Biologic/Targeted monotherapy* (n=40)	Biologic/Targeted+ immunosuppressive drug combination therapy* (n=161)
Not hospitalised	1118 (69.6%)	401 (75.4%)	102 (56.0%)	117 (77.0%)	358 (66.4%)	27 (67.5%)	113 (70.2%)
Hospitalised with no oxygenation	169 (10.5%)	50 (9.4%)	26 (14.3%)	14 (9.2%)	62 (11.5%)	4 (10.0%)	13 (8.1%)
Hospitalised with any ventilation/oxygenation	214 (13.3%)	53 (10.0%)	34 (18.7%)	14 (9.2%)	84 (15.6%)	6 (15.0%)	23 (14.3%)
Death	105 (6.5%)	28 (5.3%)	20 (11.0%)	7 (4.6%)	35 (6.5%)	3 (7.5%)	12 (7.5%)

*These patients could be also on antimalarials.
DMARD, disease-modifying antirheumatic drug; SLE, systemic lupus erythematosus.

(32.8%) at the time of COVID-19 onset. Two hundred and thirty (12.0%) individuals did not take immunosuppressive drugs or antimalarials. Eight hundred and forty-six (44.0%) individuals did not take prednisone, 467 (24.3%) individuals took between 1 and 5 mg/day, 78 (4.1%) individuals took between 6 and 9 mg/day and 280 (14.6%) individuals took a dose ≥10 mg/day.

Clinical outcomes, as well as outcomes as a function of treatment, for 1606 individuals were captured and are shown in table 2. The majority of individuals (69.6%) were not hospitalised. In the model including demographics, clinical characteristics, medications and disease activity, there were significant associations between demographic factors (older age, male sex, geographic location (being from outside of Europe, USA and Canada and Latin America), time period of the pandemic) and the ordinal severity outcome. Among comorbidities, chronic renal insufficiency or end-stage renal disease, hypertension/cardiovascular disease and the number of other comorbidities were associated with more severe outcomes. GC use was also associated with more severe outcomes compared with those without GCs. Those who were not being treated for their SLE, or had moderate or high SLE disease activity also experienced more severe outcomes compared with those on remission (table 3). These findings were consistent across various sensitivity analysis models (online supplemental table 1).

Finally, additional analyses were performed to assess the associations of methotrexate, azathioprine, MMF, cyclophosphamide, rituximab and belimumab separately with the ordinal severity outcome, demonstrating that there was no independent association of these drugs with the ordinal severity outcome in the fully adjusted model; however, rituximab was associated with poorer outcomes and belimumab with better outcomes in the unadjusted as well as the age-adjusted and sex-adjusted model, and MMF and cyclophosphamide were associated with poorer outcomes and methotrexate was associated with better outcomes only in the age-adjusted and sex-adjusted model (table 4). There was no statistically significant interaction between GC dose and disease activity or between DMARD use and disease activity (data not shown).

The results were nearly identical (online supplemental tables 2 and 3) in the alternative model in which mechanical ventilation and death were combined to constitute the highest category.

DISCUSSION

During the COVID-19 pandemic, rheumatologists have been particularly concerned about individuals with SLE. These individuals are often significantly immunosuppressed, commonly use moderate or high doses of GCs and have a high comorbidity burden. Moreover, many types of immune dysregulation occur in SLE, including in the interferon pathway, which is critical to the innate immune response during SARS-CoV-2 infection.[16] However, SLE is a relatively uncommon disease and it has been difficult to accumulate a sufficient number of cases to examine risk factors for poor COVID-19 outcomes in this

Table 3 Multivariable ordinal regression model examining characteristics associated with more severe COVID-19 outcomes in individuals with SLE

Covariate	OR (95% CI)	P value
Age (years)	1.03 (1.02 to 1.04)	<0.001**
Sex		
Male	1.50 (1.01 to 2.23)	0.042*
Region		
Europe	Reference	
USA and Canada	0.82 (0.22 to 3.02)	0.76
Latin America	1.97 (0.87 to 4.48)	0.11
Other	4.79 (2.21 to 10.37)	<0.001**
Time period		
≤15 June 2020	Reference	
16 June–30 September 2020	0.50 (0.35 to 0.72)	<0.001**
1 October 2020–12 April 2021	0.40 (0.29 to 0.57)	<0.001**
GC dose		
0 mg/day	Reference	
1–5 mg/day	1.86 (1.30 to 2.66)	<0.001**
6–9 mg/day	2.47 (1.25 to 4.86)	0.009**
≥10 mg/day	1.95 (1.27 to 2.99)	0.002**
Medication category		
Antimalarial only	Reference	
No SLE therapy	1.80 (1.17 to 2.75)	0.007**
Monotherapy with methotrexate, leflunomide or sulfasalazine only†	0.74 (0.44 to 1.24)	0.25
Monotherapy with mycophenolate/mycophenolic acid, tacrolimus, cyclophosphamide, ciclosporin or azathioprine†	1.01 (0.71 to 1.43)	0.95
Biologic/Targeted synthetic drug monotherapy	1.38 (0.58 to 3.26)	0.47
Biologic/Targeted synthetic drug and immunosuppressive drug combination therapy†	1.17 (0.72 to 1.91)	0.52
Number of comorbidities (excluding renal and cardiovascular disease/hypertension)	1.60 (1.24 to 2.07)	<0.001**
Chronic renal insufficiency or end-stage renal disease	3.51 (2.42 to 5.09)	<0.001**
Cardiovascular/Hypertension	1.69 (1.25 to 2.29)	<0.001**
Disease activity		
Remission	Reference	
Minimal or low	0.86 (0.61 to 1.21)	0.38
Moderate	1.61 (1.02 to 2.54)	0.041*
Severe or high	3.94 (2.11 to 7.34)	<0.001**

Each model adjusted for all variables listed, and random effects for country and time.
*P<0.05; **p<0.01.
†These patients could be also on antimalarials.
GC, glucocorticoids; SLE, systemic lupus erythematosus.

Table 4 Ordinal regression models examining the association between individual medications and more severe COVID-19 outcomes in individuals with SLE

	Number of individuals taking medication prior to COVID-19 diagnosis with observed outcome	Unadjusted n=1606		Age-adjusted and sex- adjusted n=1606		Fully adjusted model † n=1606		Fully adjusted model +confirmed COVID-19‡ n=1283	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Methotrexate	173	0.71 (0.50 to 1.01)	0.06	0.67 (0.47 to 0.97)	0.032*	0.71 (0.43 to 1.16)	0.17	0.71 (0.40 to 1.25)	0.23
Azathioprine	235	0.88 (0.66 to 1.19)	0.42	0.95 (0.70 to 1.29)	0.75	0.87 (0.57 to 1.34)	0.53	0.89 (0.54 to 1.47)	0.65
Mycophenolate/Mycophenolic acid	332	1.20 (0.93 to 1.55)	0.15	1.36 (1.05 to 1.76)	0.021*	1.08 (0.73 to 1.59)	0.72	1.27 (0.82 to 1.98)	0.29
Cyclophosphamide	29	1.92 (0.95 to 3.91)	0.07	2.55 (1.23 to 5.28)	0.012*	–	–	–	–
Rituximab	68	1.62 (1.00 to 2.63)	0.049*	1.69 (1.04 to 2.75)	0.036*	1.56 (0.84 to 2.90)	0.16	1.91 (0.97 to 3.79)	0.063
Belimumab	104	0.52 (0.32 to 0.86)	0.011*	0.51 (0.31 to 0.85)	<0.001**	0.66 (0.34 to 1.28)	0.22	0.65 (0.31 to 1.34)	0.24

*P<0.05; **p<0.01.
†Model adjusted for age, sex, renal disease, hypertension/cardiovascular disease, comorbidity count, disease activity, region, time period, glucocorticoid and and other DMARD medication categories; random effects applied for country and time. Reference group=antimalarial only.
‡Confirmed cases were defined as having a diagnosis made by PCR, antibody or antigen test or a CT scan.
DMARD, disease-modifying antirheumatic drug; SLE, systemic lupus erythematosus.

vulnerable population. Here, we report the largest study of SLE and COVID-19 to date. In our analyses of over 1600 cases, we found that the use of GCs, having untreated or active SLE, or using rituximab was associated with more severe COVID-19 outcomes. In addition to these factors specific to SLE, our findings also highlight that many factors associated with more severe COVID-19 outcomes in the general population are important in SLE, including male gender,[15 17 18] age[17–20] and comorbidity burden.[17–19]

Prednisone use, even at relatively low doses of <5 mg/day, was associated with poorer outcomes in our analysis. In the C19-GRA registry, which included a wide array of rheumatic diseases, only prednisone at doses ≥10 mg/day was associated with hospitalisation or mortality.[4 13] Interestingly, in additional analyses of the registry we found that in the absence of disease activity, the relationship between GC and mortality diminished.[21] However, in SLE, even low doses of GCs were associated with more severe COVID-19 outcomes, including in those with low disease activity. Like our results, in a small study from Belgium, glucocorticoid dose was positively associated with a higher risk of hospitalisation in patients with SLE.[22] These findings suggest that GCs are of special concern during the pandemic for people with SLE.

Our analyses also demonstrated that individuals not receiving treatment for their SLE at the time of COVID-19 diagnosis had poorer outcomes. The poor outcomes seen in this group may be multifactorial, and it is plausible that social risk factors play a role, such as lack of access to SLE care or treatment, or poor adherence with medications. Consistent with these results, individuals outside Europe, the USA and Canada had a poorer outcome, possibly related to healthcare access, but it was not statistically significant for Latin American individuals. Poverty and inequality have been associated with a higher risk and severity of COVID-19 globally,[14 23] and it is likely that health disparities in SLE may be exacerbated by the pandemic.

Rituximab has been associated with poorer outcomes in patients with RA.[2] We also found this association in SLE in our analysis, but it was present only in the unadjusted and age-adjusted and sex-adjusted models; this may be due to the smaller number of individuals on rituximab in our study and resultantly low power in statistical analyses (n=68). In fully adjusted models (including confirmed cases and those diagnosed based on symptoms and epidemiological criteria), there was a trend for an association between rituximab and poorer outcomes. It is important to point out that in the age-adjusted and sex-adjusted models MMF, cyclophosphamide was associated with poorer outcomes. Cyclophosphamide was not evaluated in a fully adjusted model due to a small sample size. These findings are similar to what has been reported in other studies. For example, in a recent meta-regression including several rheumatic diseases, GC use and immunosuppressive drugs use in monotherapy or combination were associated with hospitalisation and death from COVID-19.[24] Patients using belimumab generally had more favourable outcomes in our study; it is unclear if this may partly reflect confounding by healthcare access or socioeconomic status, as this drug is more commonly used in high-income nations. The association between methotrexate and better outcomes in the age-adjusted and sex-adjusted model could be related to a better disease activity control, as it did not remain significantly associated in the fully adjusted model. Because there were multiple comparisons, significance should be interpreted with caution. Given that there were six statistical comparisons made, one approach is to adjust the p value to a 0.01 level of significance. Using this more conservative approach, belimumab still remains statistically associated with less severe COVID-19 outcomes in the age-adjusted and sex-adjusted model.

Previous investigators have found an association between SLE disease activity and serious infections.[25] It is likely that both underlying immune dysfunction and the use of immunosuppressive therapies increase the risk of infection in SLE, which would explain the association between SLE disease activity and the severity of SARS-CoV-2 infection reported here.

The prognosis of patients with COVID-19 has improved over the course of the pandemic, which may be the result of many factors, including more widespread testing (leading to diagnosis of milder cases), improved pharmacological therapy and a better understanding of the timing, method of ventilatory support in critically ill patients and vaccination status for the most recent cases. Our findings suggest that patients with SLE diagnosed in later periods of the pandemic had better outcomes relative to the first part of the pandemic, which is consistent with the overall trends in the general population.[26]

It is important to note that chronic kidney disease, a common and serious complication of SLE, has one of the strongest associations with poor COVID-19 outcomes. Chronic kidney disease is also an important risk factor for severe COVID-19 in the general population and may even pose a greater risk than the presence of diabetes.[27] In addition to renal disease, our findings indicate that other comorbidities also increase the risk of severe outcomes, which is consistent with numerous previous studies.[4 19 21] In SLE, medications, particularly GCs, can impact important comorbidities such as hypertension,

diabetes or obesity,[28] which likely increases vulnerability to severe COVID-19 outcomes.

Several limitations of this study should be noted. First, the C19-GRA is a registry that is predicated on physician reporting of COVID-19 in patients with rheumatic disease, and as such, may be skewed to include more severe COVID-19 cases. Patients with more severe COVID-19 are more likely to come to the attention of their rheumatology provider. Second, even though we were able to examine the relationship of several factors with more severe outcomes, we cannot exclude other confounders like access to healthcare or socioeconomic status. Third, although the physician global assessment is a valid, responsive and feasible instrument, given its less than optimal reliability it is not ideal to just assess it to the exclusion of the patient's assessment or other measures of disease activity; this is a limitation of our study. Finally, we were underpowered to look at some important treatments for SLE, such as cyclophosphamide, in our fully adjusted models; data on voclosporin and anifrolumab, two newly approved therapies for SLE, were not available in the registry at the time of our analyses.

In conclusion, we found that in addition to age, male sex and comorbidities, the use of GCs and having untreated or active disease were associated with more severe COVID-19 outcomes in individuals with SLE. Individuals with these characteristics should be prioritised for close monitoring, counselled to receive vaccination and receive preventive therapies such as monoclonal antibodies (when available) if exposed to SARS-CoV-2.

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Outcomes of COVID-19 in patients with primary systemic vasculitis or polymyalgia rheumatica from the COVID-19 Global Rheumatology Alliance physician registry: a retrospective cohort study

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Summary

Background Patients with primary systemic vasculitis or polymyalgia rheumatica might be at a high risk for poor COVID-19 outcomes due to the treatments used, the potential organ damage cause by primary systemic vasculitis, and the demographic factors associated with these conditions. We therefore aimed to investigate factors associated with COVID-19 outcomes in patients with primary systemic vasculitis or polymyalgia rheumatica.

Methods In this retrospective cohort study, adult patients (aged ≥18 years) diagnosed with COVID-19 between March 12, 2020, and April 12, 2021, who had a history of primary systemic vasculitis (antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis, giant cell arteritis, Behçet's syndrome, or other vasculitis) or polymyalgia rheumatica, and were reported to the COVID-19 Global Rheumatology Alliance registry were included. To assess COVID-19 outcomes in patients, we used an ordinal COVID-19 severity scale, defined as: (1) no hospitalisation; (2) hospitalisation without supplemental oxygen; (3) hospitalisation with any supplemental oxygen or ventilation; or (4) death. Multivariable ordinal logistic regression analyses were used to estimate odds ratios (ORs), adjusting for age, sex, time period, number of comorbidities, smoking status, obesity, glucocorticoid use, disease activity, region, and medication category. Analyses were also stratified by type of rheumatic disease.

Findings Of 1202 eligible patients identified in the registry, 733 (61·0%) were women and 469 (39·0%) were men, and their mean age was 63·8 years (SD 17·1). A total of 374 (31·1%) patients had polymyalgia rheumatica, 353 (29·4%) had ANCA-associated vasculitis, 183 (15·2%) had giant cell arteritis, 112 (9·3%) had Behçet's syndrome, and 180 (15·0%) had other vasculitis. Of 1020 (84·9%) patients with outcome data, 512 (50·2%) were not hospitalised, 114 (11·2%) were hospitalised and did not receive supplemental oxygen, 239 (23·4%) were hospitalised and received ventilation or supplemental oxygen, and 155 (15·2%) died. A higher odds of poor COVID-19 outcomes were observed in patients who were older (per each additional decade of life OR 1·44 [95% CI 1·31–1·57]), were male compared with female (1·38 [1·05–1·80]), had more comorbidities (per each additional comorbidity 1·39 [1·23–1·58]), were taking 10 mg/day or more of prednisolone compared with none (2·14 [1·50–3·04]), or had moderate, or high or severe disease activity compared with those who had disease remission or low disease activity (2·12 [1·49–3·02]). Risk factors varied among different disease subtypes.

Interpretation Among patients with primary systemic vasculitis and polymyalgia rheumatica, severe COVID-19 outcomes were associated with variable and largely unmodifiable risk factors, such as age, sex, and number of comorbidities, as well as treatments, including high-dose glucocorticoids. Our results could be used to inform mitigation strategies for patients with these diseases.

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Introduction

Patients with autoimmune conditions could be at an increased risk of hospitalisation or death from COVID-19.[1] Previous studies, including analyses from the COVID-19 Global Rheumatology Alliance physician registry, have reported associations between worse COVID-19 outcomes

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Research in context

Evidence before this study

Data from large registries, including the COVID-19 Global Rheumatology Alliance physician registry, have reported associations between poor COVID-19 outcomes and older age, having comorbidities, receiving a prednisolone-equivalent dose of 10 mg/day or higher, and use of rituximab. However, only small studies or case reports have described outcomes of COVID-19 in patients with primary systemic vasculitis. We searched Pubmed on May 15, 2021, using the search tems "COVID-19", "vasculitis", "ANCA vasculitis", "Giant cell arteritis", "Polymyalgia Rheumatica". We searched for primary research including case-series published in any language between Jan 1, 2020, and May 1, 2021. Case reports were excluded. We found five studies describing COVID-19 outcomes in patients with primary systemic vasculitis.

Added value of this study

In this analysis of patients with primary systemic vasculitis or polymyalgia rheumatica, including 155 (15·2%) patients who were reported to have died, older age, male sex, a glucocorticoid dose of 10 mg/day or higher, moderate or severe disease activity, and a high number of comorbidities were associated with poor COVID-19 outcomes. Risk factors for poor outcomes were older age and obesity in patients with giant cell arteritis; older age, moderate, or high or severe disease activity, and rituximab or cyclophosphamide use in patients with ANCA-associated vasculitis; and older age in patients with polymyalgia rheumatica.

Implications of all the available evidence

Different risk factors, including particular treatments and increased disease activity, were associated with poor COVID-19 outcomes in patients with primary systemic vasculitis or polymyalgia rheumatica. The identified risk factors could help to guide physicians in recommending mitigation strategies for their patients.

in patients with rheumatic disease and the following risk factors: older age, a high burden of comorbidities, high doses of glucocorticoids, high disease activity, and the use of particular conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) and biological and targeted synthetic DMARDs.[2–4] However, patients with rheumatic diseases differ greatly in their demographic profiles and in their exposure to immunosuppressive therapies.

The primary systemic vasculitides are characterised by vascular inflammation, which can lead to ischaemic events and end-organ damage. Patients with primary systemic vasculitis could be at a high risk for poor outcomes following COVID-19 due to the use of immunosuppressive therapies, such as high doses of glucocorticoids, rituximab, and other DMARDs. Patients with primary systemic vasculitis might also have comorbidities, such as pulmonary or renal disease, which have been associated with poor COVID-19 outcomes in the general population. Finally, in addition to demographic factors, such as older age, there could be an increased susceptibility to the endothelial dysfunction described in COVID-19.[5] It is therefore important to understand the factors associated with poor COVID-19 outcomes in patients with primary systemic vasculitis. Similar to these patients, those with polymyalgia rheumatica might also be at high risk for poor COVID-19 outcomes, given that they have similar age demographics and also receive long-term treatment with glucocorticoids.[6] The outcomes of COVID-19 in this patient population have not yet been reported.

To our knowledge, no large, well characterised studies done to date have investigated COVID-19 outcomes in patients with specific vasculitis subtypes or polymyalgia rheumatica. The objective of this disease-specific analysis of data from the COVID-19 Global Rheumatology Alliance physician registry was to describe the presentation of COVID-19 among patients with primary systemic vasculitis and polymyalgia rheumatica, and to identify factors associated with poor COVID-19 outcomes.

Methods

Study design and participants

In this retrospective cohort study, we sourced data from the COVID-19 Global Rheumatology Alliance physician registry and the European Alliance of Associations for Rheumatology (EULAR) COVID-19 registry. These registries contain provider-reported cases of COVID-19 among patients with rheumatic diseases.[2,3,7–9] Cases are voluntarily entered by rheumatologists or other health-care providers. Data are entered directly into the global or European data entry systems, or transferred from national registries (France, Germany, Italy, Portugal, or Sweden). Patients aged 18 years and older diagnosed with COVID-19 (confirmed or presumptive) between March 12, 2020, and April 12, 2021, who had a history of primary systemic vasculitis or polymyalgia rheumatica were included. Primary systemic vasculitis included antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis, microscopic polyangiitis, or eosinophilic granulomatosis with polyangiitis), giant cell arteritis, Behçet's syndrome, and other vasculitides including Kawasaki disease. A text entry option was available when inputting data to the registry to provide a specific diagnosis or another diagnosis, if not listed. Data quality was assessed by the University of California (San Francisco, CA, USA) and the University of Manchester (Manchester, UK), both of

which confirmed that there were no duplicates in the data entries. Given the nature of the data collected, the UK Health Research Authority and the University of California San Francisco institutional review board considered this study exempt from the need to obtain patient consent. Both institutions provided ethics approval for this study.

Procedures

Data from the COVID-19 Global Rheumatology Alliance and EULAR COVID-19 registries were collected for analysis on April 15, 2020, by the GRA data analytic center at the University of California San Francisco. All patients with primary systemic vasculitis or polymyalgia rheumatica were included in the main analysis. Given disease-specific differences in treatments and risk factors for COVID-19 outcomes, subgroup analyses were done for the following specific diagnoses: giant cell arteritis, ANCA-associated vasculitis, polymyalgia rheumatica, Behçet's syndrome, and other vasculitis.

Immunosuppressive therapies for primary systemic vasculitis at the time of COVID-19 infection were included in the analyses and categorised into groups. DMARDs were categorised as conventional synthetic DMARDs (including antimalarials, apremilast, azathioprine or 6-mercaptopurine, colchicine, cyclosporine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil or mycophenolic acid, sulfasalazine, and tacrolimus) and biological and targeted synthetic DMARDs (including abatacept, rituximab, anakinra, canakinumab, tocilizumab, sarilumab, infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol). Rituximab, cyclophosphamide, and glucocorticoids were also analysed separately; glucocorticoids were categorised by the prednisolone-equivalent dose (0 mg/day, 1–5 mg/day, 6–9 mg/day, or ≥10 mg/day).

The primary outcome was COVID-19 outcome, assessed by use of an ordinal COVID-19 severity scale, which was defined as: (1) no hospitalisation (ie, admission to hospital); (2) hospitalisation with no supplemental oxygen; (3) hospitalisation with any supplemental oxygen or mechanical ventilation; and (4) death.

Relevant covariates included age (analysed as a continuous variable and by decade), sex (female or male), race or ethnicity (White, Black, Latin American, or other), time period (on or before June 15, 2020; June 16 to Sept 30, 2020; or Oct 1, 2020, to April 12, 2021),[10] comorbidities (hypertension, cardiovascular disease, diabetes, chronic kidney disease, lung disease, interstitial lung disease, or cancer), number of comorbidities (analysed as a continuous variable), body-mass index (BMI; obese [BMI ≥30 kg/m²] or non-obese [BMI <30 kg/mg²]), smoking status (ever or never smoker), disease activity, as per the physician's global assessment (remission, low, moderate, or high or severe), and region (Europe, North America, South America, or other). Other regions included Asia, Eastern Mediterranean, South-East Asia, and Western Pacific region.

Statistical analysis

Categorical variables are reported as numbers and percentages, and continuous variables are reported as means (SD) or medians (IQR). Data were analysed by ordinal logistic regression, and associations were estimated with odds ratios (ORs) and their associated 95% CIs. Only patients with complete outcome data were included in the models. Missing data for other variables were assumed to be missing at random. Multiple imputation was performed for all models to obtain pooled estimates for disease activity, smoking, and glucocorticoid use. An overall model included sex, age, glucocorticoid use as a categorical variable (ie, prednisolone-equivalent dose categories), medication category (no DMARDs, conventional synthetic DMARDs only, biological or targeted synthetic DMARDs only, combined biological or targeted synthetic plus conventional synthetic DMARDs, rituximab only, or cyclophosphamide only), time period, number of comorbidities, smoking status, obesity (ie, a BMI of ≥30 kg/m²), disease activity, and region. Individual ordinal regression models, which included the same covariates but with different medication categories (ie, no DMARDs, methotrexate, leflunomide, IL-6 inhibitor, azathioprine, rituximab, or cyclophosphamide), were also constructed for giant cell arteritis, ANCA-associated vasculitis, and polymyalgia rheumatica. In all models, age was treated as a continuous variable by decade, and a nominal test was used to confirm that the parallel regression assumption was met. An interaction term between prednisolone usage (binary) and disease activity was included as an exploratory analysis in the overall population.[3,4] We also did a sensitivity analysis including independent comorbidities (hypertension, cardiovascular disease, diabetes, chronic kidney diseases, lung disease, or interstitial lung disease) in patients with ANCA-associated vasculitis. Results were considered statistically significant at a two-sided p value of less than 0·05. Analyses were done in R, version 4.0.2.

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The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 12, 2020, and April 12, 2021, 1202 cases of COVID-19 in patients with primary systemic vasculitis or polymyalgia rheumatica were reported to the COVID-19 Global Rheumatology Alliance physician registry and were included in our analysis (figure). 733 (61·0%) of patients were women and 469 (39·0%) were men, and the mean age of patients was 63·8 (SD 17·1) years. Most patients were from Europe (704 [58·6%] patients) and North America (328 [27·3%]). Polymyalgia rheumatica

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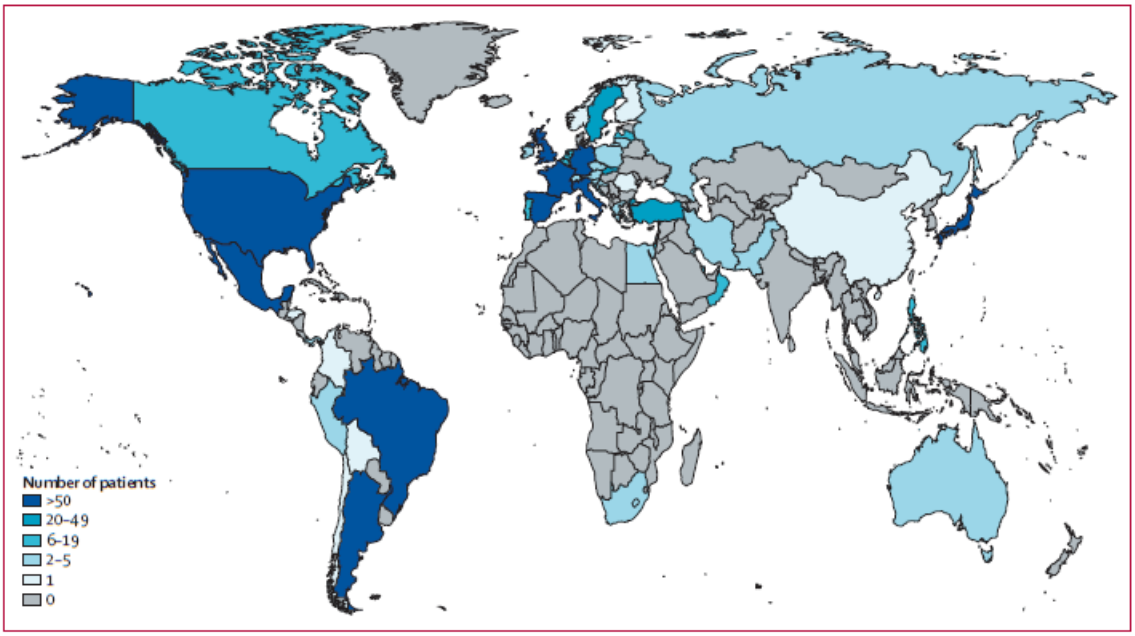

Figure: Global distribution of patients with primary systemic vasculitis and polymyalgia rheumatica who had COVID-19 in the COVID-19 Global Rheumatology Alliance physician registry

was the most common diagnosis (374 [31·1%] patients), followed by ANCA-associated vasculitis (353 [29·4%]), giant cell arteritis (183 [15·2%]), other vasculitis (180 [15·0%]), and Behçet's syndrome (112 [9·3%]; table 1). The most common comorbidities were hypertension (564 [46·9%]), cardiovascular disease (222 [18·5%]), diabetes (216 [18·0%]), lung disease (212 [17·6%]), and chronic kidney disease (160 [13·3%]). Most patients were in remission (442 [36·8%]) or had low disease activity (370 [30·8%]) at the time of COVID-19 diagnosis. A total of 752 (62·6%) patients were taking glucocorticoids and 631 (52·5%) were taking DMARDs.

Among the 1020 patients for whom outcomes were reported, 512 (50·2%) were not hospitalised (table 2). The baseline characteristics of these 1020 patients, stratified according to primary systemic vasculitis subtype and polymyalgia rheumatica, are presented in the appendix (pp 1–3). Based on the ordinal COVID-19 severity scale, 114 (11·2%) patients were hospitalised and required no supplemental oxygen, 239 (23·4%) were hospitalised and required ventilation or supplemental oxygen, and 155 (15·2%) died (table 2). In an ordinal regression model that included all disease types, patients had higher odds of worse COVID-19 outcomes if they were older (per each additional decade of life OR 1·44 [95% CI 1·31–1·57]), male compared with female (1·38 [1·05–1·80]), had a greater number of comorbidities (per each additional comorbidity 1·39 [1·23–1·58]), were taking 10 mg/day or more of prednisolone compared with none (2·14 [1·50–3·04]), or had moderate, or high or severe disease activity compared with disease remission or low disease activity (2·12 [1·49–3·02]; table 3). Patients were less likely to have worse outcomes if they developed COVID-19 between Oct 1, 2020, and April 12, 2021, compared with on or before June 15, 2020 (0·39 [0·30–0·51]). An exploratory analysis that included an interaction term between prednisone use and disease activity was not significant (p=0·27).

Among 158 patients with giant cell arteritis, 69 (43·7%) were not hospitalised, 19 (12·0%) were hospitalised and required no supplemental oxygen, 38 (24·1%) were hospitalised and required ventilation or supplemental oxygen, and 32 (20·3%) died. In a multivariable ordinal regression model, factors associated with a higher odds of worse COVID-19 outcomes included older age (per each additional decade of life OR 1·89 [95% CI 1·27–2·83]) and obesity compared with non-obesity (2·98 [1·18–7·55]; table 4). Patients diagnosed with COVID-19 between Oct 1, 2020, and April 12, 2021, were less likely to have severe outcomes than those diagnosed on or before June 15, 2020 (0·28 [0·13–0·62]).

Among 294 patients with ANCA-associated vasculitis, 110 (37·4%) were not hospitalised, 30 (10·2%) were hospitalised and required no supplemental oxygen, 89 (30·3%) were hospitalised and required ventilation or supplemental oxygen, and 65 (22·1%) died. In a multivariable ordinal regression model, factors associated with higher odds of worse COVID-19 outcomes included older age (per each additional decade of age OR 1·60 [95% CI 1·33–1·91]), rituximab use compared with no DMARD use (2·15 [1·15–4·01]), cyclophosphamide use compared with no DMARD use

	All patients (n=1202)
Mean age, years	63·8 (17·1)
Sex	
Female	733 (61·0%)
Male	469 (39·0%)
Race or ethnicity	
White	724 (60·2%)
Black	19 (1·6%)
Latin American	145 (12·1%)
Other	110 (9·2%)
Missing	204 (17·0%)
Region	
Europe	704 (58·6%)
North America	328 (27·3%)
South America	90 (7·5%)
Other	80 (6·7%)
Time period	
June 15, 2020, or before	502 (41·8%)
June 16, 2020, to Sept 30, 2020	164 (13·6%)
Oct 1, 2020, to April 12, 2021	536 (44·6%)
Diagnosis	
ANCA-associated vasculitis	353 (29·4%)
Giant cell arteritis	183 (15·2%)
Polymyalgia rheumatica	374 (31·1%)
Behçet's syndrome	112 (9·3%)
Other vasculitis	180 (15·0%)
Number of comorbidities	
0	428 (35·6%)
1	388 (32·3%)
≥2	386 (32·1%)
Comorbidities	
Hypertension	564 (46·9%)
Cardiovascular disease	222 (18·5%)
Diabetes	216 (18·0%)
Chronic kidney disease	160 (13·3%)
Lung disease*	212 (17·6%)
Interstitial lung disease	44 (3·7%)
Cancer	77 (6·4%)
Body-mass index ≥30 mg/kg²	240 (20·0%)
(Table 1 continues in next column)	

	All patients (n=1202)
(Continued from previous column)	
Smoking status	
Ever smoker	265 (22·0%)
Never smoker	448 (37·3%)
Missing	489 (40·7%)
Median glucocorticoid dose, mg/day†	6·0 (5·0–12·0)
Categorical glucocorticoid (prednisolone equivalent) dose, mg/day	
0	369 (30·7%)
1–5	367 (30·5%)
6–9	99 (8·2%)
≥10	286 (23·8%)
Missing	81 (6·7%)
Disease activity	
Remission	442 (36·8%)
Low	370 (30·8%)
Moderate	112 (9·3%)
High or severe	54 (4·5%)
Missing	224 (18·6%)
Medication	
No DMARDs	571 (47·5%)
Conventional synthetic DMARDs only	367 (30·5%)
Biological or targeted synthetic DMARDs only	193 (16·1%)
Combined biological or targeted synthetic plus conventional synthetic DMARDs	71 (5·9%)
Rituximab only‡	128/353 (36·3%)
Cyclophosphamide only	20 (1·7%)

Data are mean (SD), n (%), median (IQR), or n/N (%). ANCA=antineutrophil cytoplasmic antibody. DMARD=disease-modifying antirheumatic drug. *Includes interstitial lung disease, chronic obstructive pulmonary disease, asthma, or other lung diseases. †Excludes non-users of glucocorticoids. ‡In patients with antineutrophil cytoplasmic antibody-associated vasculitis only.

Table 1: **Baseline characteristics of patients with primary systemic vasculitis or polymyalgia rheumatica at the time of COVID-19 onset**

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See Online for appendix

(4·30 [1·10–16·75]), and moderate, or high or severe disease activity compared with low disease activity (2·16 [1·01–4·31]; table 4). Patients diagnosed with COVID-19 between Oct 1, 2020, and April 12, 2021, had a lower odds of severe outcomes than those diagnosed on or before June 15, 2020 (0·47 [0·27–0·81]). In a sensitivity analysis that included individual comorbidities, only chronic kidney disease (2·12 [1·17–3·84]) was associated with a higher odds of worse COVID-19 outcomes compared with not having chronic kidney disease in patients with ANCA-associated vasculitis (appendix pp 4–5).

Among 323 patients with polymyalgia rheumatica, 187 (57·9%) were not hospitalised, 30 (9·3%) were hospitalised and required no supplemental oxygen, 71 (22·0%) were hospitalised and required ventilation or supplemental oxygen, and 35 (10·8%) died. In a multivariable ordinal regression model, factors associated with higher odds of worse COVID-19 severity included older age (per each additional decade of life OR 2·75 [95% CI 2·00–3·80]; table 4). Patients diagnosed with COVID-19 between Oct 1, 2020, and April 12, 2021, had a lower odds of severe outcomes than those diagnosed on or before June 15, 2020 (0·28 [0·16–0·47]).

Among 97 patients with Behçet's syndrome, 69 (71·1%) were not hospitalised, 15 (15·5%) required hospitalisation with no supplemental oxygen, 11 (11·3%) required hospitalisation and ventilation or supplemental oxygen, and two (2·1%) died (table 2). Due to the low number of events among Behçet's syndrome patients, ordinal

	All patients (n=1020)	Giant cell arteritis (n=158)	ANCA-associated vasculitis (n=294)	Polymyalgia rheumatica (n=323)	Behçet's syndrome (n=97)	Other vasculitis (n=148)
Not hospitalised	512 (50·2%)	69 (43·7%)	110 (37·4%)	187 (57·9%)	69 (71·1%)	77 (52·0%)
Hospitalisation with no supplemental oxygen	114 (11·2%)	19 (12·0%)	30 (10·2%)	30 (9·3%)	15 (15·5%)	20 (13·5%)
Hospitalisation with ventilation or supplemental oxygen	239 (23·4%)	38 (24·1%)	89 (30·3%)	71 (22·0%)	11 (11·3%)	30 (20·3%)
Death	155 (15·2%)	32 (20·3%)	65 (22·1%)	35 (10·8%)	2 (2·1%)	21 (14·2%)

Data are n (%). This analysis excludes 182 patients with missing outcome data. ANCA=antineutrophil cytoplasmic antibody.

Table 2: **Outcomes according to the ordinal COVID-19 severity scale by type of disease**

regression models were not constructed due to insufficient power.

Finally, among 148 patients with other types of vasculitis, 77 (52·0%) did not require hospitalisation, 20 (13·5%) required hospitalisation with no supplemental oxygen, 30 (20·3%) required hospitalisation with ventilation or supplemental oxygen, and 21 (14·2%) died. Text entry diagnoses for this group were only present for nine (6·1%) patients (four had Takayasu's arteritis, one had Cogan's syndrome, one had cryoglobulinaemic vasculitis, one had isolated pulmonary capillaritis, one had deficiency of adenosine deaminase 2 vasculitis, and one had relapsing polychondritis). Given the heterogeneity of diagnoses, ordinal regression models were not constructed.

Discussion

To our knowledge, we report the largest study to date of COVID-19 outcomes in patients with primary systemic vasculitis or polymyalgia rheumatica. Older age, a higher number of comorbidities, higher disease activity, and taking 10 mg/day or more of prednisolone were associated with worse COVID-19 outcomes. In disease-specific analyses, we observed unique factors associated with poor outcomes in individual primary systemic vasculitis categories. Reassuringly, patients with COVID-19 submitted to the registry later in the analysis period (ie, Oct 1, 2020, to April 12, 2021) had a lower rate of poor outcomes than those submitted earlier in the analysis period (ie, on or before June 15, 2020).[11]

These data extend previous observations from smaller cohort studies to a large and well characterised international cohort of patients with primary systemic vasculitis who had COVID-19. In the pooled cohort, almost half (49·8%) of patients were hospitalised and 15·2% had died. Compared with a recent (2021) study done in the UK and Ireland, which found that 59 (91%) of 65 patients with primary systemic vasculitis were admitted to hospital and 18 (28%) died, our results are reassuring and could reflect an improvement in outcomes over time.[11,12] The cause of this change is not known, but it could plausibly be related to more experience with managing COVID-19 or the use of fewer experimental interventions over time.[13] As with the general population, both comorbidities and age were important risk factors for poor outcomes, emphasising the importance of public health measures, risk mitigation, and prioritisation of vaccination in these individuals. Consistent with previous studies, higher doses of glucocorticoids and moderate or high disease activity were associated with worse outcomes; however, no interaction between these two variables was found.[3,4]

	Odds ratio (95% CI)*	p value
Age, per decade of life	1·44 (1·31–1·57)	<0·001
Sex		
Female	1·00 (ref)	..
Male	1·38 (1·05–1·80)	0·020
Time period		
June 15, 2020, or before	1·00 (ref)	..
June 16, 2020, to Sept 30, 2020	0·80 (0·54–1·19)	0·27
Oct 1, 2020, to April 12, 2021	0·39 (0·30–0·51)	<0·001
Number of comorbidities	1·39 (1·23–1·58)	<0·001
Smoking status		
Never smoker	1·00 (ref)	..
Ever smoker	1·01 (0·70–1·46)	0·95
Body-mass index, mg/kg^2		
<30	1·00 (ref)	..
≥30	1·07 (0·78–1·46)	0·16
Glucocorticoid (prednisolone equivalent) use, mg/day		
0	1·00 (ref)	..
1–5	1·14 (0·83–1·57)	0·41
6–9	1·22 (0·75–1·97)	0·43
≥10	2·14 (1·50–3·04)	<0·001
Disease activity		
Remission or low	1·00 (ref)	..
Moderate, or high or severe	2·12 (1·49–3·02)	<0·001

This analysis excludes 182 patients with missing outcome data. *Adjusted for age, sex, time period, number of comorbidities, smoking status, obesity, glucocorticoid use, disease activity, region, and medication category.

Table 3: **Multivariable logistic regression analysis of factors associated with ordinal COVID-19 severity outcomes in patients with primary systemic vasculitis or polymyalgia rheumatica**

	Giant cell arteritis (n=149)		ANCA-associated vasculitis (n=266)		Polymyalgia rheumatica (n=291)	
	OR (95% CI)*	p value	OR (95% CI)*	p value	OR (95% CI)*	p value
Age, per decade of life	1·89 (1·27–2·83)	0·0019	1·60 (1·33–1·91)	<0·001	2·75 (2·00–3·80)	<0·001
Sex						
Female	1·00 (ref)	..	1·00 (ref)	..	1·00 (ref)	..
Male	1·20 (0·56–2·55)	0·64	1·37 (0·83–2·26)	0·21	1·54 (0·89–2·67)	0·12
Time period						
June 15, 2020, or before	1·00 (ref)	..	1·00 (ref)	..	1·00 (ref)	..
June 16, 2020, to Sept 30, 2020	0·72 (0·22–2·34)	0·59	0·82 (0·39–1·71)	0·59	0·59 (0·24–1·44)	0·25
Oct 1, 2020, to April 12, 2021	0·28 (0·13–0·62)	0·0015	0·47 (0·27–0·81)	0·0062	0·28 (0·16–0·47)	<0·001
Medication						
No DMARD	1·00 (ref)	..	1·00 (ref)	..	1·00 (ref)	..
Methotrexate	0·97 (0·34–2·71)	0·95	0·79 (0·31–1·99)	0·61	1·61 (0·85–3·07)	0·15
Leflunomide	4·93 (0·34–72·07)	0·24	..	..	..	..
IL-6 inhibitor	0·52 (0·20–1·33)	0·17	..	..	..	..
Azathioprine	..	..	1·10 (0·54–2·24)	0·79	..	..
Rituximab	..	..	2·15 (1·15–4·01)	0·016	..	..
Cyclophosphamide	..	..	4·30 (1·10–16·75)	0·036	..	..
Number of comorbidities	1·48 (1·06–2·07)	0·021	1·13 (0·89–1·42)	0·31	1·27 (0·98–1·63)	0·068
Smoking status	..	..	..	..	..	..
Never smoker	1·00 (ref)	..	1·00 (ref)	..	1·00 (ref)	..
Ever smoker	0·93 (0·42–2·06)	0·86	1·12 (0·61–2·05)	0·71	0·80 (0·39–1·62)	0·52
Body-mass index, mg/kg^2						
<30	1·00 (ref)	..	1·00 (ref)	..	1·00 (ref)	..
≥30	2·98 (1·18–7·55)	0·021	1·35 (0·73–2·51)	0·34	1·06 (0·55–2·05)	0·87
Glucocorticoid (prednisolone equivalent) use, mg/day						
0	1·00 (ref)	..	1·00 (ref)	..	1·00 (ref)	..
1–5	0·96 (0·39–2·34)	0·92	1·67 (0·92–3·03)	0·091	1·29 (0·60–2·79)	0·52
6–9	1·75 (0·44–7·04)	0·43	0·60 (0·21–1·69)	0·33	1·30 (0·50–3·38)	0·58
≥10	2·89 (1·16–7·21)	0·023	2·80 (1·36–5·79)	0·0054	1·27 (0·52–3·12)	0·60
Disease activity						
Remission or low	1·00 (ref)	..	1·00 (ref)	..	1·00 (ref)	..
Moderate, or high or severe	3·14 (0·71–13·97)	0·12	2·16 (1·01–4·31)	0·028	1·99 (0·81–4·89)	0·13

This analysis includes only patients with studied factors (ie, medications). ANCA=antineutrophil cytoplasmic antibody. DMARD=disease-modifying antirheumatic drug. IL-6=interleukin 6. OR=odds ratio. *Adjusted for age, sex, time period, medication use category, number of comorbidities, smoking status, obesity, glucocorticoid use, disease activity, and region.

Table 4: **Multivariable logistic regression analysis of factors associated with ordinal COVID-19 severity outcomes in patients according to disease type**

Among the identified patients with ANCA-associated vasculitis and COVID-19, almost two-thirds were hospitalised and approximately one-fifth died. These results should be interpreted with caution. First, a provider-reported registry is biased toward accumulating patients with severe COVID-19. Second, COVID-19 outcomes have improved over time, and this study includes patients from the early months of the COVID-19 pandemic. Nevertheless, this is the first study to evaluate a large and well characterised population of patients with ANCA-associated vasculitis who had COVID-19. Our results are supported by a smaller published case-series,[14] which also reported high rates of poor outcomes in patients with ANCA-associated vasculitis. Our study builds on these previous results by further identifying risk factors associated with poor outcomes. In a sensitivity analysis, patients with chronic kidney disease had worse COVID-19 outcomes than those who did not have chronic kidney disease, which is consistent with other studies done in the general population.[1,13] Glucocorticoid use and having received rituximab or cyclophosphamide were also associated with worse outcomes, which is similar to the results of previous studies in other rheumatic diseases.[3] Whether this observations reflects the immunosuppressive effects of these drugs or the selection bias related to the patients who receive them cannot be ascertained from this study.

Similar to patients with ANCA-associated vasculitis, a high proportion of patients with giant cell arteritis reported in this registry had poor COVID-19 outcomes, including death. In addition to the aforementioned limitations of these data, the high mortality rates observed

in patients with giant cell arteritis could reflect the importance of age in COVID-19 mortality.[15] The high COVID-19 mortality rates could also be associated with an increased risk or severity of cardiometabolic comorbidities, which have been associated with poor outcomes in COVID-19.[16–18] Few cohorts of patients with giant cell arteritis are available to further verify these findings. A study done in France reported eight cases of COVID-19 among 148 patients with large vessel vasculitis, only one of whom died.[19] A similar study done in Italy reported four cases of COVID-19 among 151 patients with large vessel vasculitis, none of whom died.[20] Given some of the unmodifiable risk factors for outcomes in patients with giant cell arteritis, attention to other factors, such as the prescription of high-dose glucocorticoids, is crucial. Patients with polymyalgia rheumatica in our study had less severe COVID-19 outcomes and lower mortality rates than did patients with giant cell arteritis and ANCA-associated vasculitis. In patients with polymyalgia rheumatica, poor outcomes were associated only with age, which is a known risk factor for the general population. Despite a similar age distribution in this group as in the group of patients with giant cell arteritis, these differences could potentially highlight the role of other important factors, such as the use of higher glucocorticoid doses and obesity.

Overall, few patients with Behçet's syndrome in our cohort had severe COVID-19 outcomes, with only a third of patients requiring hospitalisation and two patients who died. Patients with Behçet's syndrome were younger than those with other disease types. Despite the evident concern of an increased risk of thrombosis associated with both Behçet's syndrome and COVID-19,[21] which is associated with poor outcomes, our results showing less severe outcomes in these patients than in those with other disease types are reassuring and consistent with those reported by small case-series.[22,23] Due to a low number of events, patients with Behçet's syndrome who had COVID-19 were not included in the regression analysis. The mortality rate in patients with other types of vasculitis was lower than in those with giant cell arteritis and ANCA-associated vasculitis, but given the smaller sample size, reduced diversity of diagnoses, and absence of information on specific diagnoses, this patient group was not included in regression analyses.

In addition to the limitations already noted, the following factors should also be acknowledged. First, cross-sectional, physician-entered, case-reporting registries might be subject to selection bias toward patients with more severe COVID-19. In particular, the mortality rate should be considered a case fatality rate as opposed to an infection fatality rate, as we have probably overestimated the true mortality risk among patients with primary systemic vasculitis who develop COVID-19. Second, given the nature of the COVID-19 Global Rheumatology Alliance physician registry, participation is dependent on a COVID-19 diagnosis, and particular covariates (eg, age) that were accounted for can lead to a collider bias (by affecting both condition and outcomes).[24] Third, the time periods between COVID-19 diagnosis and clinical outcomes were not fully collected, and the attribution of clinical outcomes to COVID-19 was based on the treating physician's opinion. However, the results from this registry are consistent with findings from other data sources, verifying the information collected and the interpretation of our results. Fourth, although we were able to analyse multiple factors associated with COVID-19 outcomes in our models, we cannot exclude other confounders as potential explanations for our findings. We therefore caution against making causal inferences from our data. Finally, the absence of an interaction between prednisolone treatment and disease activity, as well as other medication associations, could have been due to low power rather than an absence of an association.

In conclusion, in this study of patients with primary systemic vasculitis or polymyalgia rheumatica who had COVID-19, we report high rates of severe COVID-19 outcomes, particularly in patients with giant cell arteritis and ANCA-associated vasculitis. Important predictors of poor COVID-19 outcomes include older age, a higher number of comorbidities, moderate, or high or severe disease activity, and the use of specific medications, including high-dose glucocorticoids. Our study identifies risk factors associated with poor COVID-19 outcomes in this patient population and in those with specific disease phenotypes, and stratifies outcomes by specific disease phenotypes. These observations could guide risk mitigation strategies in the treatment of patients with these conditions. Further studies should address the reasons for these concerning outcomes in patients with primary systemic vasculitis who develop COVID-19.

Contributors

SES, RC, MSP, AMS, MAG, KB, CH, DL, SLM, PM, LN, JY, ZSW, and PCR contributed to the study design and the original idea for the manuscript. SES, RC, MSP, AMS, MAG, and JY had full access to and verified the underlying study data, developed the figure and tables, and vouch for the data analyses. AMS and MAG did the statistical analysis and contributed to data quality control, data analysis, and data interpretation. SES, RC, MSP, AMS, MAG, KB, CH, DL, SLM, PM, LN, JY, ZSW, PCL, GG, MIHS, FNM, HAM, SAdSS, NCA, AK, DR, LQ, MSa, SBa, ATJM, PC, RH, UM-L, BFH, RV, RPT, ML, SLER, SA-E, JAS, TY-TH, KMD'S, NJP, LW, EG, MVA, MU-G, LJ, ZI, AS, EFM, KLH, LG, LC, SL-T, LK-F, ES, JSH, PS, SBh, JWL, and PMM contributed to data collection, data analysis, and data interpretation. SES, RC, MSP, JY, and PCR directed the study, data collection, data analysis, and interpretation of the methods, and had final responsibility for the decision to submit the publication. All authors contributed intellectual content during the drafting and revision of the manuscript and approved the final version to be published.

Declaration of interests

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All other authors declare no competing interests.

Data sharing

Researchers interested in performing additional analysis from the COVID-19 Global Rheumatology Alliance provider registry are invited to submit proposals through the COVID-19 Global Rheumatology Alliance at https://rheum-covid.org. Data are currently available on reasonable request. For approved projects, after review by the COVID-19 Global Rheumatology Alliance steering committee, summary tables and data analyses will be provided as requested. Raw data is not available to other researchers.

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3.8 Einstellung der RheumatologInnen gegenüber der COVID-19 Impfung

Originalarbeit 15:

Hasseli R, Pfeil A, Krause A, Schulze-Koops H, Müller-Ladner U, Specker C; COVID-19 Task Force of the German Society for Rheumatology (DGRh). *A survey to evaluate knowledge, perceptions and attitudes toward COVID-19 vaccinations among rheumatologists in Germany.*
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Zur Bewältigung der Pandemie wurden weltweit verschiedene Strategien entwickelt, spezifische Therapeutika und Impfstoffe zu entwickeln. Die Entwicklung von spezifischen Therapeutika war Mitte 2020 noch nicht ausreichend erfolgversprechend, so dass der Fokus auf der Entwicklung eines Impfstoffes lag. Ende des Jahres 2020 stand der Impfstoff von Biontech/Pfizer zur Verfügung. Die neuartigen Impfstoffe stießen jedoch nicht nur auf Akzeptanz innerhalb der Bevölkerung. Die bisherigen Impfquoten gegen Influenza und Pneumokokken bei PatientInnen mit ERE legten nahe, dass eine adäquate Kommunikation und Aufklärung notwendig waren, um eine hohe Impfquote und somit Herdenimmunität zu erreichen. Dies setzt jedoch auch voraus, dass die behandelnden RheumatologInnen eine Impfung befürworten und den PatientInnen entsprechend Empfehlungen aussprechen. Für eine adäquate Empfehlung sind evidenzbasierte Daten notwendig. Bis März 2021 und somit lediglich gut drei Monate nach Start der Impfkampagne lagen noch keine ausreichenden Daten bezüglich der Effektivität und Sicherheit der Impfstoffe bei ERE-PatientInnen vor. Dennoch sprach sich die Ständige Impfkommission des Robert-Koch-Instituts für eine COVID-19-Impfung bei ERE-PatientInnen mit den damals zur Verfügung stehenden Impfstoffen aus, da es sich um keine Lebendimpfstoffe handelte [209].

Dies führte jedoch nicht nur in der Allgemeinbevölkerung, sondern insbesondere auch bei ERE-PatientInnen verständlicherweise zur Unsicherheit und Zweifel. Um dies zu beheben, veröffentliche die Adhoc-Kommission COVID-19 der DGRh bereits im Dezember 2020 eine Empfehlung zum Umgang mit dem COVID-19-Impfstoffen [210]. Die Hauptpunkte der Empfehlung waren, dass alle bisher zur Verfügung stehenden Impfstoffe bei ERE einsetzbar sind. Eine Impfung sollte bei Remission/geringer Krankheitsaktivität erfolgen. Eine Therapieunterbrechung der Immunmodulation zur Verbesserung der Impfantwort wurde nicht empfohlen. Lediglich unter Therapie mit Rituximab sollte eine Impfung 4-6 Monate nach der letzten Rituximab-Therapie erfolgen und frühestens 14 Tage nach Abschluss der Impfung sollte die Therapie mit Rituximab wieder eingeleitet werden. Die Entscheidung gegen eine Therapieunterbrechung basierte auf der fehlenden Evidenz diesbezüglich und dem möglichen Risiko einer Aktivitätszunahme der ERE durch eine Therapiepause. Trotz dieser schnellen

Reaktion der DGRh herrschte sowohl unter den PatientInnen als auch ÄrztInnen weiterhin Zweifel bezüglich des Einsatzes der COVID-19-Impfstoffe bei ERE.

Aus diesem Grund wurde eine bundesweite anonyme Befragung unter RheumatologInnen initiiert, um das Meinungsbild bezüglich der COVID-19-Impfstoffe zu erfassen und mögliche Informationsdefizite aufzudecken.

Hierfür wurde ein Online-Fragebogen mit 21 Fragen entwickelt (Originalarbeit *15*). Die Umfrage erfolgte von Anfang Februar bis Mitte März 2021. Zu diesem Zeitpunkt war bereits die COVID-19-Impfkampagne in Deutschland angelaufen. Mithilfe verschiedener Kommunikationswege, wie z.B. Newsletter der DGRh, Soziale Medien, diversen Mailverteilern, und direkter Interaktion, konnten 214 RheumatologInnen für die Umfrage gewonnen werden. Die größte Altersgruppe stellten Personen zwischen 51-60 Jahren dar (41%), gefolgt von Personen zwischen 41-50 Jahren (21%). Über 80% der Befragten hatten mehr als 11 Jahre Berufserfahrung und waren mehrheitlich auch wissenschaftlich (59%) oder/und in der Lehre (46%) tätig. In rheumatologischen Schwerpunktpraxen waren 61% der Befragten tätig.

Trotz der fehlenden Daten bezüglich der Sicherheit und Effektivität der zur Verfügung stehenden COVID-19-Impfstoffe, sprachen sich 99% der Befragten für eine COVID-19-Impfung bei ERE aus und ca. 90% gaben an, dass sie sich sicher im Umgang mit COVID-19-Impfungen bei ERE fühlen würden. Entsprechend der Empfehlung gab die Mehrheit der Befragten an, dass sie die Immunmodulation aufgrund der Impfung nicht pausieren würden. Nur im Falle von Rituximab wurde eine Therapiepause in Erwägung gezogen. Trotz der Option des Einsatzes der Vektorimpfstoffe und der fehlenden Datenlage bezüglich der Präferenz eines COVID-19-Impfstoffs, bevorzugten über 70% der Befragten den Einsatz von mRNA-Impfstoffen bei ERE.

Somit spiegelte sich die Entscheidung der Befragten mit der Empfehlung im Umgang mit den COVID-19-Impfstoffen seitens der DGRh wider.

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OBSERVATIONAL RESEARCH

A survey to evaluate knowledge, perceptions and attitudes toward COVID-19 vaccinations among rheumatologists in Germany

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Abstract

The objective is to evaluate the attitude of rheumatologists regarding the use of COVID-19 vaccination in patients with inflammatory rheumatic diseases (IRDs). From February 2nd until March 15th, 2021, rheumatologists from Germany were asked to participate anonymously in a survey addressing their attitude with respect to COVID-19 vaccinations of IRD patients. The survey was completed by 214 participants (107 men, 103 women, 4 unspecified). More than half of the physicians (61%) were working in rheumatologic private practices and 62% had more than 20 years of experience in rheumatology. 90% reported to be at least confidential in handling issues of COVID-19 vaccination and 99% would recommend COVID-19 vaccination for IRD patients. The majority would not recommend to stop or reduce immunomodulatory drugs for vaccination except for rituximab. More than 70% would prefer vaccination with a mRNA vaccine for their IRD patients. This study shows that almost all rheumatologists in Germany support the COVID-19 vaccination for their IRD patients without reducing or terminating the actual immunomodulatory medication to potentially improve the response to the vaccine. This attitude is in accordance with the current recommendations of the German Society of Rheumatology regarding COVID-19 vaccination in IRD patients, and indicates that these have been well accepted and work in everyday clinical practice.

Keywords Immunmodulatory drugs · Rituximab · Inflammatory rheumatic diseases · Glucocorticoids · COVID-19 vaccines

Introduction

For more than 1 year, the world is struggling with the coronavirus SARS-CoV-2 disease (COVID-19). The available COVID-19 vaccines are offering light at the end of the pandemic tunnel by achieving a so-called 'herd immunity'. Herd immunity works through achieving a threshold immunity at the population level that is able to interrupt the transmission chain of a given infectious disease, either by wild virus infection or by vaccination [1]. An optimal herd immunity is achieved by a high immediate and long-term vaccine efficacy [1]. For a vaccine with an efficacy of 95%,

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the required herd immunity level would be 63–76% [1]. In addition to a fundamental skepticism toward vaccinations, concerns prevail in Germany among patients and many physicians about the effectiveness and safety of vaccinations in inflammatory rheumatic diseases (IRDs), especially with respect to triggering flares. In addition, the so far unsurpassed rapid development of several new vaccines and the respective new technologies used to develop COVID-19 vaccines raised additional doubts and concerns in the population and among physicians [2].

Although until March 15th, 2021, no data on the safety and efficacy of the COVID-19 vaccines specifically in patients with IRDs were available, the Standing Committee on Vaccination (STIKO) of the Robert Koch Institute (RKI) recommends vaccination against COVID-19 of IRD patients [3]. The caveat, that live vaccines should not be administered in patients under immunosuppressive therapy, is not an issue for vaccination against COVID-19 since all currently licensed vaccines are non-live vaccines. Nevertheless, this has been and still is questioned repeatedly by patients and physicians.

To overcome the concerns and fears, both of the patients with IRD and their caring rheumatologists, the German Society for Rheumatology released the first recommendations for handling COVID-19 vaccinations in IRD patients in December 2020 [4, 5]. The recommendations were based also on the recommendations of the German National Authorities for vaccination strategies (Robert Koch Institute (RKI) and Paul Ehrlich Institute) and phase three clinical trials of the SARS-CoV-2 vaccines [3]. The main statements were that all available vaccines against COVID-19, including those using viral vectors (since they are non-replicating) are non-live vaccines and the use of nucleic acid technologies for the development of messenger RNA-vaccines does not imply threat or harm to the genetic integrity of the recipient [4, 6]. Therefore, these vaccines can and should be used without restriction in IRD patients, especially under immunosuppressive/immunomodulating therapy. Vaccinations should preferably be given when the IRD is in remission or a state of low activity. Moreover, to avoid disease flares, it is not recommended to reduce the dose or terminate immunomodulators in general [4]. In case of rituximab, if possible, an alternative treatment strategy should be considered to facilitate an adequate vaccination response without risking a flare [4]. However, the assumption to develop protective immune response upon vaccination was derived from other vaccines, as this aspect has not been evaluated specifically for COVID-19 vaccination. Similarly, derived from a markedly impaired immune response to established vaccinations during B cell depletion therapy, vaccination against COVID-19 is recommended not earlier than 4–6 months after the last application of rituximab [7–9]. Vice versa, the vaccination should be completed at least 2 weeks prior to the next rituximab infusion. The (so far unproven) idea to reduce immunosuppressive therapy in patients with IRD to facilitate or enhance the immune response upon vaccination was explicitly discouraged to avoid the risk of disease flares.

To increase the vaccination rate, rheumatologists should provide their patients with sufficient and consistent information. This study aimed to evaluate the attitude and knowledge of rheumatologists regarding the use of COVID-19 vaccination in patients with IRDs and thus examine the implementation of recommendations and identify any further needs.

Methods

An online questionnaire with 21 questions, including baseline characteristics of the participants (e.g., age, work experience) and questions focusing on their attitude toward COVID-19 vaccination in IRD patients, was developed and announced to the German rheumatologists on a nationwide basis in a cross-sectional design using computer software SoSci Survey (version 3.1.06, Leiner [10], available at https://www.soscisurvey.de). The questions were designed as a selection of only one answer or selection of multiple answers. For pretest validation of the survey, a pilot test was run by a group of rheumatology staff members. Answers of the participating rheumatologists and health professionals were recorded by transferring the submitted data into an excel sheet. Only fully completed questionnaires were evaluated. Duplicate entries and incomplete questionnaires were excluded.

The study was open from February 2nd until March 15th, 2021. At this time, the nationwide vaccination campaign in Germany started with healthcare workers, especially healthcare workers involved in the treatment of COVID-19 patients, along with people aged 80 and over. Vaccination for IRD patients younger than 80 years were not available at that time period. Participants had to be specialized rheumatologists, trainees in clinical departments of rheumatology, or physicians treating mainly IRD patients. Participation was voluntary, anonymously, and without any reimbursement. Therefore, the ethics committee of the University of Giessen certified that no additional ethical approval was required for this study (January 26th, 2021) and the study was performed based on the rules of the ethics committee of the University of Giessen in accordance with the Declaration of Helsinki. Written informed consent was not required. This work was conducted in accordance to the recently published primer for author guidelines for reporting survey-based studies [11].

Statistical analysis

The analysis was based on a descriptive statistic and additional exact binomial tests were used to assess differences between physicians' characteristics and COVID-19-related answers using SPSS (version 26 IBM SPSS Statistics, Chicago, Illinois, USA). P values were 2-sided with a significance level set at $p \leq 0.05$.

Results

Baseline characteristics (details see Table 1)

In total, 214 physicians (Table 1) from all federal German states participated and 90% were rheumatologists (specialists and residents). Most of them were middle aged with an equal distribution of males and females and had considerable work experience as rheumatologists (more than 80% between 11 and more than 30 years). Almost half of the participants were involved in teaching (46%) and/or science (59%). The majority of the physicians were working in private practices (61%), 37% in academic or university hospitals (Table 1).

Physicians' attitudes to vaccination against COVID-19 (details see Table 2)

Participants reported following the aforementioned recommendations of the German Society of Rheumatology (84%), recommendations of the Robert Koch Institute (82%) and its STIKO (74%). In addition, own online research (72%), online training (72%), personal communication among colleagues (69%), and public media [(television and radio) 61%] were used to stay informed. Only 35% of the participants reported informing themselves via the official association of panel doctors. The majority of physicians reported feeling at least confident with counseling their patients regarding vaccination (90%) and two-thirds that almost every patient spontaneously addressed questions regarding COVID-19 vaccination. Only 1.4% of the rheumatologists would not recommend COVID-19 vaccination for IRD patients. Half of the participants had already undergone vaccination

Table 1 Baseline characteristics of participating physicians

Age (years)						
< 30	31–40	41–50	51–60	61–70	> 70	No answer
7 (3.3%)	40 (18.7%)	45 (21%)	87 (40.7%)	29 (13.6%)	4 (1.9%)	2 (0.9%)
Gender						
Male					107 (50%)	
Female					103 (48.1%)	
Unspecified					2 (0.9%)	
No answer					2 (0.9%)	
Specialty						
Internal medicine and rheumatology					174 (81.3%)	
Internal medicine					6 (2.8%)	
Orthopedics					2 (0.9%)	
Orthopedics with specialization in rheumatology					2 (0.9%)	
Residency in rheumatology					20 (9.3%)	
Residency in internal medicine					5 (2.3%)	
Other					5 (2.3%)	
Workplace						
Private practice	Outpatient clinic	Hospital without teaching assignment	Academic teaching hospital	University hospital		
130 (60.7%)	16 (7.5%)	7 (3.3%)	38 (17.8%)	41 (19.2%)		
Work experience (years)						
< 5	5–10	> 10	> 20	> 30		
17 (7.9%)	16 (7.5%)	48 (22.4%)	85 (39.7%)	48 (22.4%)		
Involvement in teaching				Involvement in science		
98 (45.8%)				126 (58.9%)		

Table 2 Questions regarding COVID-19 vaccination

Information sources for COVID-19 vaccination	
Training	154 (72%)
German Society for Rheumatology	179 (83.6%)
Robert Koch Institute	176 (82.2%)
Standing vaccination commission	159 (74.3%)
Online research	154 (72%)
Communication among colleagues	147 (68.7%)
General media (TV, radio)	131 (61.2%)
Association of panel doctors	76 (35.5%)

Self-assessment regarding handling COVID-19 vaccination and IRD				
Very uncertain	Uncertain	Undecided	Confident	Very confident
4 (1.9%)	4 (1.9%)	14 (6.5%)	136 (63.6%)	56 (26.2%)

How many patients are asking for further information about COVID-19 vaccination?			
No	< 50%	> 50%	Nearly every patient
3 (1.4%)	17 (7.9%)	55 (25.7%)	139 (65%)

Recommendation of COVID-19 vaccination for IRD patients	Self-vaccination against COVID-19
211 (98.6%)	211 (98.6%)

Under which dose of prednisolone (mg/day) would you recommend COVID-19 vaccination in IRD patients? (multiple selection possible)	
< 5 mg/day	116 (54.2%)
5–10 mg/day	121 (56.5%)
11–15 mg/day	40 (18.7%)
> 15 mg/day	15 (7%)
No influence of GC on recommendation for COVID-19 vaccination[a]	71 (33.2%)

Which type of COVID-19 vaccine do you prefer for IRD patients? (multiple selection possible)	
Moderna (COVID-19 Vaccine Moderna®)	153 (71.5%)
Biontech/Pfizer (Comirnaty®)	169 (79%)
AstraZeneca/Oxford (AZD1222®)	62 (29%)
Dead vaccine	2 (0.9%)
No opinion yet[a]	41 (19.2%)

Changes in therapy due to COVID-19 vaccination?						
	Pause before vaccination	Pause after vaccination	Pause before and after vaccination	Reduction of dose before vaccination	No change	No answer
csDMARDs	6 (2.8%)	26 (12.1%)	19 (8.9%)	3 (1.4%)	158 (73.8%)	2 (0.9%)
Azathioprine	3 (1.4%)	5 (2.3%)	17 (7.9%)	1 (0.5%)	183 (85.5%)	5 (2.3%)
Mycophenolate	4 (1.9%)	9 (4.2%)	20 (9.3%)	2 (0.9%)	165 (77.1%)	14 (6.5%)
TNF-inhibitors	4 (1.9%)	10 (4.7%)	18 (8.4%)	5 (2.3%)	172 (80.4%)	5 (2.3%)
IL-17-inhibitors	4 (1.9%)	10 (4.7%)	18 (8.4%)	4 (1.9%)	172 (80.4%)	6 (2.8%)
IL-6-inhibitors	5 (2.3%)	10 (4.7%)	22 (10.3%)	5 (2.3%)	166 (77.6%)	6 (2.8%)
IL-1-inhibitors	3 (1.4%)	10 (4.7%)	21 (9.8%)	5 (2.3%)	166 (77.6%)	9 (4.2%)
Abatacept	8 (3.7%)	13 (6.1%)	36 (16.8%)	5 (2.3%)	142 (66.4%)	10 (4.7%)
Rituximab	54 (25.2%)	7 (3.3%)	124 (57.9%)	6 (2.8%)	19 (8.9%)	4 (1.9%)
JAK-inhibitors	7 (3.3%)	14 (6.5%)	24 (11.2%)	1 (0.5%)	160 (74.8%)	8 (3.7%)

[a]Multiple selections were possible except for this item

themselves, 49% planned to do so and 1.4% stated that they would not get vaccinated.

Rheumatology treatment strategy during vaccination (details see Table 2)

One-third of the participants reported that their recommendation for COVID-19 vaccination would be independent of the use of glucocorticoids (GC). More than half of the physicians would recommend vaccination at a maximum dose of 10 mg prednisolone daily, 19% up to a maximum dose of 15 mg prednisolone, and 7% even at higher doses. More than 80% reported checking the vaccination status of their patients routinely. More than 70% would recommend vaccination with Comirnaty® (79%) and COVID-19 Vaccine Moderna® (72%), while only 29% would recommend vaccination with Vaxzevria® (AstraZeneca). At least 19% reported having no clear opinion about which type of vaccine to recommend.

More than 70% of the physicians would not recommend changing therapy with conventional synthetic (CS) disease-modifying anti-rheumatic drugs (DMARDs), and around 80% would recommend to continue TNF-, interleukin(IL)-1-, IL-6-, IL-17-, and JAK-inhibitors (Table 2). However, one-third would pause the therapy with abatacept, and only 9% would recommend vaccination during ongoing therapy with rituximab. Rituximab was considered to be rather paused before vaccination whereas abatacept was rather recommended to be withheld after vaccination.

Overall, the answers regarding the handling of immunotherapy and COVID-19 were independent of the gender of the respective physician, and whether the physicians worked in private practices or rheumatology departments.

Discussion

To our knowledge, this study is the first to investigate the opinion of rheumatologists on COVID-19 vaccines in IRD patients and it illustrates the attitude of physicians toward the actually licensed vaccines in Germany. For IRD patients as well as for their rheumatologists, it is important to know if vaccination against COVID-19 will be effective, even under immunomodulating therapy, and does not induce disease flares. At the time of the survey, no data on the effectiveness and safety of COVID-19 vaccines in IRDs patients were available. The first paper to address this important issue was published at the end of March 2021 and covered selected immunosuppressants in a relatively small group of patients with chronic inflammatory diseases (mainly RA) [12]. Even though these primary results affirmed a sufficient immune response and no safety issues upon vaccination in IRDs under glucocorticoids (up to 15 mg daily), selected csDMARDs (mainly leflunomide) and biologics (mainly TNF-inhibitors), reliable data for the whole spectrum of IRDs and especially for many other immunomodulatory drugs are still lacking. Therefore, recommendations on vaccination against COVID-19, released by national and international societies rely on opinions of experts and adoptions from (even sparse) evidence from vaccination against other diseases [13]. The results of the survey indicate that more than 90% of the participating rheumatologists recommend vaccination against COVID-19 for their IRD patients, which is in line with the recommendation of the German society for rheumatology and STIKO [3, 5].

Despite the use of new platforms for development and lacking data in special diseases or under certain therapies, the administration of all available vaccines against COVID-19 is recommended for IRDs and also under immunosuppression by different official health institutions and rheumatological societies with some restrictions, mainly with respect to the use of rituximab. Concerns of potentially promoting disease flares through vaccination were outweighed unequivocally by the risk of COVID-19 in light of its pandemic nature.

The fact that the vast majority (99%) of German rheumatologists recommend their patients with IRDs to get vaccinated can be considered a success of the information policy of the German Society for Rheumatology. In a survey to explore the perspective of Egyptian Rheumatology staff members 70.1% agreed that they will recommend vaccination for IRD patients [14]. This is also reflected by the willingness of physicians to get vaccinated themselves (Table 2). The rate of physicians to get vaccinated themselves was higher compared to the results of a survey of healthcare workers in Turkey [15]. In this survey, only 68.4% of the physicians reported their willingness to get vaccinated against COVID-19 [15]. However, it is possible that more physicians with positive attitudes toward vaccines against COVID-19 completed the questionnaire, as participation was voluntary.

Regarding the use of different vaccines, the majority of participating rheumatologists in Germany prefers one of the mRNA vaccines for their IRD patients, only 29% would use the vector vaccine from AstraZeneca (Table 2). This is notable since the first warning due to reported cerebral sinus vein thromboses in the context of vaccination with the AstraZeneca vaccine came up in Germany shortly after closing our survey. There is no explanation for these results, as in the survey no further questions regarding the use of different vaccines were asked.

As immunomodulation might influence the response to vaccination, the question was if physicians would recommend to change treatment with immunomodulatory drugs with the intention to achieve a better immune response. On the contrary, discontinuation enhances the risk of disease

flares, which might require the use of GC in higher doses. For pneumococcal vaccination, it could be observed that the use of prednisolone higher than 10 mg daily was associated with an impaired antibody response [16]. Therefore, physicians were asked, up to which dose of GC they would recommend COVID-19 vaccination in their IRD patients. In this survey, one-third reported that the use of GC would not have any impact on their advice for COVID-19 vaccination, 7% reported accepting dosages of more than 15 mg prednisone daily, 19% up to 15 mg, and most accepted doses of up to 10 mg (Table 2).

Compared to normal controls, a lower response to pneumococcal or influenza vaccines was reported for IRD patients under leflunomide, sulfasalazine, azathioprine, and hydroxychloroquine. However sufficient seroprotection was achieved in all cases [16–21]. This holds also true for the use of mycophenolate, of which immune response to vaccinations was investigated in organ-transplanted patients [21]. Likewise, under treatment with methotrexate, a moderately impaired humoral response to pneumococcal and influenza vaccines could be detected [21–25]. Discontinuation for up to 4 weeks after vaccination increased vaccine titres, however, such a long period off therapy might provoke disease flares [23, 25]. Three-quarters of the physicians reported not to change csDMARD therapy due to COVID-19 vaccination followed by 12% of the physicians who would recommend to pause csDMARD treatment for a while after vaccination. For practicability reasons, our survey did not differentiate between different csDMARDs.

For so-called targeted therapies, exact differentiation regarding the underlying mode of action was applied instead. Treatment with TNF-, IL-17-, and IL-6-inhibitors was not reported to be changed by the treating rheumatologists because of COVID-19 vaccination. This is justified by some studies revealing that immune response upon vaccination is not impaired under these treatments [17, 25–31]. Although to our knowledge, no data regarding IL-1 inhibition and immune response upon vaccinations are available yet, 78% of our physicians would not pause this around COVID-19 vaccination in IRD patients. In the survey of Egyptian Rheumatology staff members 71.7% of the participants reported to avoid treatment with biologics before vaccination [14]. This is contrary to our results, possibly due to national differences in the use of immunomodulation regarding COVID-19 vaccination or due to the availability of recommendations at this time.

For the use of abatacept, data are inconsistent regarding vaccination response. In a study of RA patients, subcutaneously administered abatacept with background csDMARDs did not alter an appropriate immune response to pneumococcal and influenza vaccines [32]. On the other hand, abatacept given intravenously (again with csDMARDs, mainly methotrexate) significantly reduced the humoral response to influenza A/H1N1 vaccine in RA patients during a pandemic in 2009 [33]. Therefore the 'American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases' recommends withhold of subcutaneous abatacept 1 week before and 1 week after the first vaccination dose but not for the second [34]. Even though this was not recommended in the German recommendations [5], 33% of rheumatologists in our survey advised pausing of abatacept around COVID-19 vaccination, the highest percentage of pausing among DMARDs except for rituximab. The latter was withhold by more than 90% of rheumatologists. Patients are advised to pause abatacept rather after than prior to vaccination, in contrast to the opposite way for rituximab. This is interesting, given the mode of action of these two compounds and the huge difference in biological half-time. Due to the known and markedly impairment of humoral responses to influenza and pneumococcal vaccines after administration of rituximab [22, 34–37], it is suggested performing vaccination against COVID-19 not earlier than 4–6 months after rituximab treatment [5, 8, 9].

Regarding JAK-inhibitors and vaccination responses, data are even more sparse. For tofacitinib a satisfactory response to the influenza vaccine could be observed, but response to pneumococcal vaccines was decreased [8, 38]. In this survey, three-quarters of the physicians reported not to change treatment with JAK-inhibitors due to COVID-19 vaccination, and if, this would rather be paused after than before vaccination (Table 2).

A limitation of our study is the absence of a control group, e.g., physicians treating other inflammatory diseases or general practitioners. Of the participating physicians, only 1.4% of rheumatologists would not recommend COVID-19 vaccination for IRD patients. The possible reasons for this decision were not further evaluated. As the survey was announced among members of the German society for Rheumatology, the results cannot be generalized to other specialities. As the sampling of our study was voluntary, the possibility of a selection bias (i.e., rheumatologists with special interest in vaccination or COVID-19) could not be eliminated. This survey was conducted during a single period of time during the third wave of the pandemic. Information, thoughts, decisions and perceptions may be a matter of change during the ongoing pandemic.

Conclusions

Taken together, our study supports the idea that the timely recommendations of the German Society for Rheumatology regarding the handling of COVID-19 vaccination in patients with IRDs were well perceived by rheumatologists

in Germany, providing high confidence in counseling their patients regarding COVID-19 vaccination.

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Availability of data and material All data relevant to the study are included in the article.

Declarations

Conflict of interest The other authors declared no competing interests.

Patient and public involvement Not applicable.

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3.9 Einfluss der erhobenen Register-Daten auf Handlungsempfehlungen hinsichtlich COVID-19 und ERE

Originalarbeit 16:

Specker C, Aries P, Braun J, Burmester G, Fischer-Betz R, **Hasseli R**, Holle J, Hoyer BF, Iking-Konert C, Krause A, Krüger K, Krusche M, Leipe J, Lorenz HM, Moosig F, Schmale-Grede R, Schneider M, Strangfeld A, Voll R, Voormann A, Wagner U, Schulze-Koops H.

Updated recommendations of the German Society for Rheumatology for the care of patients with inflammatory rheumatic diseases in the context of the SARS-CoV-2/COVID-19 pandemic, including recommendations for COVID-19 vaccination.

Z Rheumatol. 2021 Dec;80(Suppl 2):33-48. doi: 10.1007/s00393-021-01055-7

Originalarbeit 17 (Übersichtsarbeit):

Hasseli R, Müller-Ladner U.

COVID-19 and inflammatory rheumatic diseases

Dtsch Med Wochenschr. 2021 Nov;146(23):1564-1568. doi: 10.1055/a-1616-8742

Bereits im März 2020 wurden erste Handlungsempfehlungen für den Umgang von COVID-19 bei ERE seitens der DGRh ausgesprochen [211]. Diese basierten vor allem auf Expertenkonsens. Bereits im Juli 2020 flossen die erhobenen Daten aus dem COVID19-Rheuma.de-Register und den bis dahin international zur Verfügung stehenden Daten in die aktualisierten Handlungsempfehlungen ein [212]. Durch weitere wichtige Erkenntnisse, die aus den Daten des COVID19-Rheuma.de-Registers sowie aus den internationalen Kooperationen abgeleitet werden konnten, erfolgte im Juli eine erneute Aktualisierung[197]. Neben spezifischen Risikofaktoren für einen schweren COVID-19-Verlauf bei ERE, wurde auch Bezug auf den Einsatz von COVID-19-Impfungen genommen.

Die Kernaussagen der Empfehlung beinhalteten folgende Punkte (*Originalarbeit 16* und Originalarbeit *17*):

1) Ziel des Erreichens einer Remission der ERE mithilfe steroidfreier Immunmodulation
2) erhöhte Krankheitsaktivität und der Einsatz von Prednisolon über 5 mg/Tag kann einen schweren Verlauf einer SARS-CoV-2-Infektion begünstigen
3) PatientInnen unter Therapie mit Rituximab weisen ein höheres Risiko für schwere COVID-19-Verläufe auf
4) alle zur Verfügung stehenden Impfstoffe sind bei ERE und unter Immunmodulation einsetzbar
5) es besteht keine Präferenz bezüglich eines COVID-19-Impfstoffes
6) eine Therapieunterbrechung der Immunmodulation aufgrund der COVID-19-Impfung wird nicht empfohlen, außer bei Rituximab

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Updated recommendations of the German Society for Rheumatology for the care of patients with inflammatory rheumatic diseases in the context of the SARS-CoV-2/COVID-19 pandemic, including recommendations for COVID-19 vaccination

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Supplementary Information

The online version of this article (https://doi.org/10.1007/s00393-021-01055-7) contains a summary of these recommendations composed for patients.

The German version of this article can be found under https://doi.org/10.1007/s00393-021-01056-6

All authors are writing on behalf of the Executive Board of the German Society for Rheumatology

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Extended author information available on the last page of the article.

Core recommendations

Table 1.

1 Introduction

Even after more than one year, the COVID-19 pandemic is a great challenge for patients with inflammatory rheumatic diseases (IRD) as well as for rheumatologists. The recommendations of the German Society for Rheumatology (Deutsche Gesellschaft für Rheumatologie e. V.; DGRh) of March 2020 were intended to provide initial, rapid guidance on specific concerns in the care of patients with IRD in the face of the threat posed by SARS-CoV-2. These were based primarily on expert consensus [1–3]. The first update in July 2020 [4, 5] already relied on scientific data from registries, cross-sectional studies, case reports, and case series [6, 7]. In the meantime, we have further results from scientific publications on COVID-19 in IRD, from which much more precise statements on disease- or therapy-related risks can be derived. An important reason for updating the recommendations for action again is the fact that vaccinations against SARS-CoV-2 are now available and are thus increasingly being administered to patients with IRD. This raises many questions, also and especially for patients with IRD, but also for the physicians and medical professionals caring for them.

2 To whom should these recommendations apply?

The statements and recommendations made here refer to patients with inflammatory rheumatic diseases (IRD), especially in consideration of the medicinal antirheumatic therapy. Where appropriate or necessary, comparisons are also made with SARS-CoV-2 infections and COVID-19 in the general population. The statements have to be relativised—at least partially—for IRD patients who have

Table 1 Core recommendations of the DGRh for the care of patients with inflammatory rheumatic diseases in the context of the SARS-CoV-2/COVID-19 pandemic

#	Recommendation	LoA[a] (± SD)	GoR
1	Patients with inflammatory rheumatic diseases (IRD) should follow the behavioural and precautionary measures described by the Robert Koch Institute to avoid infections. This also applies in the case of a positive SARS-CoV-2 IgG antibody detection. Special additional measures are not necessary	9.9 (± 0.43)	⇑
2	To interrupt chains of infection and contain a new possible wave of infection, patients may be advised to use the "Corona Warning App" or similar digital applications	8.95 (± 1.25)	⇔
3	The individual risk for infection or severe disease progression can be estimated based on general (such as age, multimorbidity, obesity, smoking) and disease-specific (e.g. high activity of IRD, severe systemic disease) risk factors	9.43 (± 0.85)	⇑⇑
4	Initiation or change of antirheumatic therapies should neither be omitted nor delayed due to the COVID-19 pandemic	9.9 (± 0.43)	⇑⇑
5	Before administering rituximab, an individual risk–benefit assessment should be carried out due to the increased risk of a severe COVID-19 course, and the use of alternative therapies should also be examined	9.81 (± 0.5)	⇑
6	In patients without signs of infection, even with contact with SARS-CoV-2 positive persons, the existing antirheumatic therapy should be continued unchanged. This also applies to the therapy with glucocorticoids in the therapeutically necessary dose	9.76 (± 0.53)	⇑
7	In patients tested positive for SARS-CoV-2 by PCR without signs of infection, pausing or delaying ts- or b-DMARD therapy for the duration of the mean incubation period of SARS-CoV-2 infection (e.g. 5–6 days) should be considered. Generally, csDMARDs should not be discontinued in the absence of signs of infection	9.38 (± 0.72)	⇑
8	In patients with confirmed active COVID-19, DMARD therapy should be paused and leflunomide washed out if necessary. Continuous GC therapy ≤ 10 mg/day used for the treatment of the rheumatological disease should be continued at the same dose	9.43 (± 0.85)	⇑
9	Rheumatologists should always be involved in the decision to maintain, reduce or pause antirheumatic therapy in the context of COVID-19	9.89 (± 0.31)	⇑
10	A general recommendation for screening patients with IRD for SARS-CoV-2 antibodies after infection cannot be given at present due to a lack of data on antibody formation and persistence (especially under immunosuppression)	9.33 (± 1.21)	⇑
11	Patients with IRD and positive test for SARS-CoV-2 (PCR, rapid antigen test, antibody test) should be documented in the COVID-19 registry of the DGRh (COVID19-rheuma.de)	9.76 (± 0.61)	⇑
12	Patients with IRD should be vaccinated against SARS-CoV-2 following the vaccination recommendations of the STIKO	10 (± 0)	⇑⇑
13	The presence of IRD alone does not imply a preference for one of the vaccines approved in Europe. With the aim of rapid immunisation in urgently needed rituximab therapy and in patients over 60 years of age with confirmed APS or immune thrombocytopenia, the use of an mRNA vaccine should be considered as a precaution in these situations	9.48 (± 0.85)	⇑
14	General discontinuation of DMARD therapy solely due to vaccination—as DMARDs and immunosuppressants can attenuate the measurable humoral immune response after COVID vaccination (with this most clearly affecting rituximab and least affecting anti-cytokine biologics)—is not recommended, as it is not known to what extent this affects actual vaccination protection	9.71 (± 0.55)	⇑⇑
15	Pausing methotrexate for 1–2 weeks after each vaccination, JAK inhibitors for 1–2 days before and 1 week after each vaccination, and abatacept for 1 week before and after each vaccination can be considered if IRD is in stable remission. But this is not mandatory. Good disease control has priority over a possibly attenuated immune response, even in the context of vaccination	9.1 (± 0.92)	⇔
16	The vaccination series should begin at least 4 months after the last rituximab administration and rituximab should ideally be given at the earliest 4 weeks after completion of the vaccination series. In individual cases and patients at risk, this may be deviated from	9.29 (± 0.93)	⇑
17	SARS-CoV-2 antibody titres should not be determined regularly to monitor vaccination success. It is not yet clear to what extent the results are predictive of protection against infection or disease	9.48 (± 0.79)	⇑

[a] *LoA* Level of Agreement (± standard deviation) after consultation in the author group with 21/21 votes for every item. *GoR* Grade of recommendation. ⇑⇑ strong recommendation, ⇑ recommendation, ⇔ open recommendation (according to 3-level grading of the AWMF regulations). Although level 2b or 3b evidence was also available for individual recommendations, only evidence level (LoE) 5 is used for the consensus recommendations and is not shown individually in the table

APS antiphospholipid syndrome

Table 2 General risk factors for a severe course of COVID-19
Higher age
Male gender
Smoking
Obesity
Multimorbidity, especially pre-existing lung disease, renal insufficiency, diabetes mellitus, hypertension, coronary heart disease

been vaccinated against COVID-19 or who are protected after a SARS-CoV-2 infection. However, there is still no clarity as to whether and how a vaccination's success or protection after a previous infection can be investigated with sufficient reliability and when booster vaccinations may be necessary. It should also be pointed out that these recommendations cannot cover all situations that justify or even suggest a deviation from them in individual cases.

3 What is the risk for patients with IRD for infection with SARS-CoV-2 and a severe course of COVID-19?

An idea of the significance of age for the risk of COVID-19 for hospitalisation and death, also in relation to various concomitant diseases, is given in **Fig. 1** in the appendix from a comprehensive so-called "Umbrella Review" of the Robert Koch Institute (RKI) [8].

3.1 General risk factors for COVID-19 and a severe course

Risk factors in the general population for a severe course of COVID-19 (**Table 2**; [9]) also apply to patients with IRD [10–20].

3.2 Specific risk factors of inflammatory rheumatic diseases for SARS-CoV-2 infection and severe course of COVID-19

3.2.1 Risk for infection

Whether patients with IRD have an increased risk of COVID-19 compared to the normal population is not conclusive. While some studies report an increased risk of COVID-19 compared to the normal population or compared to a "matched" population without IRD in certain patient populations, e.g. in patients with systemic sclerosis [20–22], others indicate a comparable risk to the normal population [23–25].

3.2.2 Risk of a severe course

Current data from registries and a meta-analysis [20] mostly confirm results from early case series [26], according to which the risk of a severe course (defined here and in the following as inpatient admission and/or the need for ventilation and/or death) is generally not increased in patients with IRD in total compared to the normal population or compared to "matched" cohorts without IRD. As in the normal population, the risk is increased above all in the presence of comorbidities [12–15, 27]. Only a few cohort studies found an enhanced risk for a severe course in patients with rheumatoid arthritis [28, 29] or in the total cohort of IRD patients compared to the normal population or to "matched" cohorts without IRD. These publications show a high proportion of patients with connective tissue disease and vasculitides (**Table 5** in the appendix), which could possibly contribute to a more severe course (see [28]). Subgroup analyses from recent registry and cohort studies support this finding: systemic diseases such as vasculitides, SLE, systemic sclerosis, Sjögren's syndrome, as well as autoinflammatory diseases possibly carry a higher risk for a severe COVID-19 course or death compared to the normal population or a matched non-IRD population or rheumatoid arthritis used as a reference [12, 13, 18, 19, 28–30]. When interpreting these data and drawing conclusions from them, it must be taken into account that only relatively small numbers of cases of these IRD subpopulations have been recorded in the registries and cohort studies to date. It is also unclear whether the increased risk for a severe course is caused by the disease itself or by certain organ involvement (e.g. lung or kidney involvement) or the intensity of immunosuppression.

In analyses from the German and global COVID-19 registries, high disease activity of the respective IRD was clearly identified as a risk factor for a severe course of COVID-19, with an odds ratio (OR) of 1.96 (95% confidence interval [CI] 1.02–3.76) and 1.87 (95% CI 1.27–2.77), respectively, compared to patients with low or no disease activity [14, 15].

4 Influence of immunosuppressive/immunomodulatory drugs on the course of COVID-19

4.1 Glucocorticoids

Long-term therapy with glucocorticoids (GC) is a known risk factor for infections and also for a more severe course of infections in IRD [31, 32]. Cohort studies and registry data have shown that this also applies to COVID-19: Therapy with GC was already associated with an increased COVID-19 infection rate from a dose of 2.5 mg daily in a large northern Italian cross-sectional study of over 2000 IRD patients [33]. GC use at doses of 10 mg (prednisone equivalent) daily and above resulted in an increased risk of severe COVID-19 compared with a matched non-IRD population at an OR of 1.97 (95% CI 1.09–3.54) in a cohort study of 694 patients with IRD [13]. In the global registry study of 3729 IRD patients, the OR for COVID-19-associated mortality was 1.7 (95% CI 1.18–2.41) for GC above 10 mg daily versus no systemic GC intake [15]. In the German registry of 468 IRD patients, the OR for GC > 5 mg was 3.67 (95% CI 1.49–9.05) versus no glucocorticoid therapy [6].

The interpretation of this risk increase must be made with caution since an increase in the glucocorticoid dose in most cases occurs due to increased disease activity leading to "confounding by indication". In a further evaluation of the global registry, it could be shown that in remission or low disease activity, even GC in a dosage of > 10 mg daily versus no glucocorticoid therapy are not associated with a higher risk of a more severe course or death [34]. Therefore, the data suggest that higher disease activity is the main risk factor compared to the GC dose, but since the strength of the association with a more severe course within the subgroups of different disease activity increased with higher GC doses, it cannot be ruled out that GC exert an additional negative influence.

4.2 Conventional DMARDs[1], immunosuppressants, and immunomodulators

In the analysis of the global IRD registry with data up to July 2020, ongoing therapy with immunosuppressants overall (azathioprine, cyclophosphamide, ciclosporin, mycophenolate, tacrolimus) was significantly associated with a lethal outcome of COVID-19 with an OR of 2.22 (95%CI 1.43–3.46), as was therapy with sulfasalazine with an OR of 3.6 (95%CI 1.7–7.8) [15]. In the French registry, of the immunosuppressants, mycophenolate was conspicuous for a severe course (ventilation or death) with an OR of 6.6 (95%CI 1.47–29.6), while no signal was found for methotrexate, leflunomide, and azathioprine (although the number of cases for azathioprine was very small) [13]. In the evaluation of the global registry, "no DMARD therapy" was also associated with an increased OR for a lethal course of 2.11 (95%CI 1.48–3.01) compared to methotrexate monotherapy. In the aforementioned northern Italian cohort study, there was no increased risk of COVID-19 infection either in the group of conventional synthetic DMARDs (csDMARDs) or in the group of biological or targeted DMARDs (b/tsDMARDs), although an analysis by individual substances was not carried out [33].

4.3 Biologics and JAK inhibitors

There is increasing evidence that B-cell depletion, or possibly only significant hypogammaglobulinemia, are risk factors for a severe course of COVID-19. Initially, individual cases were reported [35–38] of a more severe course of COVID-19 after or during therapy with rituximab. Rituximab therapy was significantly associated with a fatal course of COVID-19 in the global COVID-19 registry on IRD [15] with an OR of 4.04 (95%CI 2.32–7.03) and in the French registry [13] with an OR of 4.21 (95%CI 1.61–11.0). In another analysis of the French registry [39], a total of 137 (13%) severe courses and 89 (8%) deaths were found in 1090 patients with IRD (mean age 55 ± 16 years; 734 [67%] female). Of 63 patients treated with rituximab, 13 (21%) died compared to 76 (7%) of the 1027 patients without rituximab. Although the risk of death adjusted for the above-mentioned parameters was not significantly increased in the rituximab group (effect size 1.32, 95% CI 0.55–3.19, $p = 0.53$), severe courses were significantly more frequent with rituximab ($n = 22$) than in the control group ($n = 115$), even after adjustment (effect size 3.26, 95% CI 1.66–6.40, $p = 0.0006$).

The Global Rheumatology Alliance (GRA) evaluated 2869 of 6132 RA patients in the global COVID-19 registry (as of mid-April 2021) who were on treatment with the biologics abatacept ($n = 237$), rituximab ($n = 364$), IL-6R inhibitors ($n = 317$), TNF inhibitors ($n = 1388$) or JAK inhibitors ($n = 563$) at the time of infection. A higher rate of treatment with TNF and IL-6R inhibitors was found in nonhospitalised RA patients and a higher rate of treatment with rituximab in oxygen-dependent and deceased RA patients; the rate of treatment with JAK inhibitors was also slightly higher. In multivariate analysis adjusted for age, sex, region, season, obesity, smoking, csDMARDs, GC (±/dose), disease activity and the number of comorbidities, the OR for a severe course of COVID-19 versus treatment with TNF inhibitors was 4.15 (3.16–5.44) for rituximab and 2.06 (1.60–2.65) for the JAK inhibitor group [40]. Whether a protective effect of TNF or IL-6R inhibitors concerning severe courses of COVID-19 may also play a role here cannot yet be answered. Patients under TNF inhibitors were chosen as a reference in the multivariate analysis, and patients under IL-6R inhibitors did not show any difference. It should be mentioned, however, that even among the 571 patients treated with TNF blockers in the German registry so far, only two fatal courses of COVID-19 were recorded and the number of hospitalised cases was comparatively low at 52 patients (as of 23 May 2021). However, it must be taken into account that patients treated with TNF inhibitors were on average younger (53 vs. 59 years), received GC less frequently, and had less disease activity compared to patients not treated with TNF blockers.

In summary, due to an increased risk of a more severe course of COVID-19 during therapy with rituximab, we recommend that this therapy be carefully weighed up about possible alternatives or concerning the individual benefit and risk. Otherwise, the risk of increased disease activity for a severe course of COVID-19 is estimated to be higher than the risk of a severe course due to antirheumatic therapy. It is therefore not recommended to discontinue or reduce antirheumatic therapy as a precaution. Even a therapeutically necessary glucocorticoid dose should not be changed out of concern for a more severe course of COVID-19.

5 Prevention of infections and protective measures

Common behavioural and precautionary measures described and regularly updated by the Robert Koch Institute [41] and the Federal Centre for Health Education [42] for the general population and for persons at special risk apply. Special measures going beyond this are not recommended.

Weighing up the benefits and risks, there is no need to avoid visits to the doctor intending to reduce the risk of infection. Necessary inpatient treatment should not be delayed.

Appropriate behavioural and hygienic measures must continue to be ensured in out- and in-patient settings. Intelligent planning of consultation hours should be carried out (e.g. short waiting times, observance of distance rules, wearing of mouth and nose protection masks, minimisation of the number of accompanying persons, generous ventilation).

To prevent the spread of infection, patients should be informed in advance not to attend unannounced health facilities with symptoms of illness or after contact with people who are known to be infected with SARS-CoV-2. In such cases or after a stay in a high-risk or virus variant area ("variants of concern"), the practice should first be contacted by telephone.

Typical COVID-19 symptoms (see **Table 6** in the appendix) or contacts to infected persons can be asked for in

[1] The term Disease modifying antirheumatic drug (DMARD) is usually used only in the context of inflammatory joint diseases. In these recommendations, for simplicity, it is used for the drug groups regardless of the respective indication.

advance. In case of doubt, adequate testing is recommended. To break chains of infection and contain new possible waves of infection, patients can be advised to use the "Corona warning app" or comparable digital applications [43].

According to the recommendations of the Standing Commission on Vaccination (STIKO) of the Robert-Koch-Institute (RKI), the vaccination status should be updated: In addition to SARS-CoV-2 (see section 8), this primarily concerns vaccinations against pneumococci and influenza.

6 Antirheumatic therapy in the context of SARS-CoV-2 or COVID-19

In principle, rheumatologists should always be involved in the decision to maintain, reduce or pause antirheumatic therapy in the context of COVID-19. Counseling regarding antirheumatic therapy should be performed in a shared-decision manner between doctor and patient even in the context of the COVID-19 pandemic. To further improve the data situation, it is recommended that patients with IRD and COVID-19 (detected through positive PCR, rapid antigen test, or antibody test for SARS-CoV-2) are documented in the COVID-19 register of the DGRh (COVID19-rheuma.de).

The following specific recommendations continue to apply:

6.1 Patients without signs of infection

6.1.1 Existing antirheumatic therapy

- Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), biologic DMARDs (bDMARDs) and immunosuppressants (see section 4.2) should be continued unchanged as indicated by the IRD and should not be discontinued or reduced for fear of SARS-CoV-2 infection alone. The GC dose should be kept as low as possible—as is valid for all situations in IRD therapy—and a necessary increase above 10 mg daily should be accompanied by consistent protective measures.
- In the case of therapy with rituximab (RTX) in indications without potentially life-threatening manifestations, especially in uncomplicated RA in sustained remission, a postponement of RTX administration should be considered, also to enable a potentially more promising vaccination of the patient (see section 8). This should be done after weighing the risk of relapse against the individual risk of infection. Under no circumstances should the use of RTX for remission induction be delayed in cases of systemic diseases that pose a serious threat, e.g. ANCA-associated vasculitis (AAV).

6.1.2 Restarting or changing antirheumatic therapy

- The start of antirheumatic therapy should not be omitted or delayed because of the COVID-19 pandemic; the dose should follow the usual recommendations.
- A recommendation for or against a specific DMARD (for RTX see next point in the list) cannot currently be made for new patients.
- In the case of valid alternatives (e.g. in RA), the use of RTX should be critically questioned because of possible favouring a more severe course of COVID-19 (see section 4.3), the long B-cell depletion, and limited vaccination response. However, the use of RTX for remission induction in systemic diseases (e.g. in AAV) should not be omitted in concern of COVID-19.
- Protocols with reduced GC administration, e.g. in giant cell arteritis or AAV should be preferred [44, 45].

6.2 Patients with contact to SARS-CoV-2 positive persons and without own COVID-19 infection signs

- The therapy should be continued as described in section 6.1. If symptoms occur, a doctor or rheumatologist should be contacted (see section 6.3).

6.3 Patients with signs of infection after contact with SARS-CoV-2 positive persons

- A change in therapy should not be made if symptoms are mild and fever is absent.
- If there are clear signs of infection and especially fever (> 38 °C), the antirheumatic medication should be paused.
- GC therapy ≤ 10 mg prednisolone equivalent daily can be continued; for higher doses, the continuation of GC treatment must be decided on an individual basis.

6.4 Patients tested positive for SARS-CoV-2 and without signs of COVID-19 infection

- Pausing or delaying ts- or bDMARD therapy for the duration of the mean incubation period may be considered. As it is often not known when an infection has occurred, a pause for 5–6 days after smear may be considered if symptom-free conditions persist.
- GC therapy ≤ 10 mg prednisolone equivalent daily can be continued; at higher doses, the continuation of GC treatment must be decided on an individual basis.
- csDMARDs should not be discontinued.

6.5 Patients tested positive for SARS-CoV-2 and with signs of COVID-19 infection

- GC therapy ≤ 10 mg prednisolone equivalent daily can be continued; for higher doses, the continuation of GC treatment must be decided individually.
- DMARDs should be paused in this situation (leflunomide should be washed out, if necessary, because of the long half-life of this compound).
- In patients at risk for severe COVID-19 progression (e.g. severe immunosuppression with active IRD, primary immunodeficiencies), early passive immunisation with a combination of two neutralising monoclonal antibodies should be considered according to the COVRIIN/STAKOB/DGI statement

Table 3 COVID-19 vaccines licensed in the EU (as of 15 May 2021)

Company	Name	Vaccination type	Doses	Schedule	Application	EU approval
BioNTech/Pfizer	Comirnaty® (BNT162b2)	mRNA + LNP	2	Days 0, 21/6 weeks[a]	i.m.	21 Dec. 2020
Moderna	COVID-19-Vaccine Moderna (mRNA-1273)	mRNA + LNP	2	Days 0, 28/6 weeks[a]	i.m.	06 Jan. 2021
Astra-Zeneca/Oxford University	Vaxzevria® (AZD1222)	Vector-based ChAdOx1, nonreplicative	2	Days 0, 28–84/ 12 weeks[a]	i.m.	29 Jan. 2021
Janssen-Cilag International N.V.	Ad26.COV2.S	Adenovirus-26-Vector-based, nonreplicative	1	Single shot	i.m.	11 Mar. 2021

[a]Recommendation of the STIKO regarding the scheduling of the second vaccination [49]

(for current information including link to the list of therapy centres see [46] or explanation in the supplementary online information).

7 Proof of past infection with SARS-CoV-2

With the duration of the pandemic, the proportion of patients who have been exposed to SARS-CoV-2 increases, regardless of whether COVID-19 symptoms were present. In the future, it may become important to be able to estimate the individual risk of infection by knowing the patients' (possibly protective) immune status against SARS-CoV-2. At present, due to lack of data on antibody formation and persistence and the importance of T-cell immunity, especially under immunosuppression, and due to limited or unclear specificity and sensitivity of the different test methods, no recommendation can yet be made for screening patients with IRD for antibodies. A general screening before vaccination in the absence of clinical evidence of a previous infection is not recommended.

Furthermore, it cannot be assessed at present whether the risk of re-infection or contagiousness is reduced if IgG antibodies against SARS-CoV-2 are detected. Thus, even in the case of a positive antibody test, it is not recommended to loosen the measures for infection and foreign infection prophylaxis.

8 Vaccination against COVID-19

8.1 Introduction

Despite worldwide efforts to develop effective drugs for the treatment of COVID-19, there is as yet no therapeutic option that promises a cure with sufficient certainty. Thus, vaccination of large parts of the population as soon as possible is considered the decisive step to contain the pandemic [47].

Also for the accelerated assessment and approval procedures of the COVID-19 vaccines by the EMA, the safety standards required for approval applied without restriction [48]. Currently, four SARS-CoV-2 vaccines are available in Germany [49]. These are two messenger RNA (mRNA) vaccines and two vector vaccines (**Table 3**).

Patients with known or suspected immune dysfunction were excluded from the phase III trials of the vaccines, but because "healthy adults and those with stable pre-existing conditions" could be included [8], the pivotal trials with more than 43,000 [50] and more than 30,000 [51] subjects included also some with IRD [25].

Based on this situation, the DGRh had published the first recommendations for vaccination of patients with IRD or under immunomodulating therapies against SARS-CoV-2 in IRD and subsequently updated them (online) several times. These recommendations could not be based on studies on the safety and efficacy of SARS-CoV-2 vaccines in IRD patients so far but were consented based on findings with other vaccinations in IRD patients among the experts of the COVID-19 commission of the DGRh [52–54]. In addition to a continuous literature search, national [8, 47, 49] and international recommendations of other professional societies [55, 56] were also taken into account.

8.2 Type of vaccines and inflammatory rheumatic diseases

None of the vaccines against SARS-CoV-2 approved so far is a live vaccine. Therefore, all of them can be administered to patients with IRD, even under immunosuppressive/immunomodulatory therapy. Apart from extremely rare allergies to vaccine components, there are no contraindications to COVID-19 vaccination.

8.3 Vaccination against COVID-19 during pregnancy and lactation

From an ongoing study of more than 35,000 pregnant women vaccinated against COVID-19 with mRNA vaccines, a first interim evaluation of 827 completed pregnancies was carried out, in which no significant safety signals were seen [57]. The STIKO does not currently make a general vaccination recommendation for pregnant women. Pregnant women with previous illnesses and a resulting high risk of severe COVID-19 disease or with an increased risk of exposure due to their life circumstances can be offered vaccination with an mRNA vaccine from the 2nd trimester onwards after a risk–benefit assessment and detailed medical information [49]. The German Society for Gynaecology and Obstetrics recommends (as of 05/2021) that pregnant women are vaccinated with mRNA-based vaccine against COVID-19 in an informed participatory decision-making process and after exclusion of general contraindications [58]. To protect pregnant women indirectly, the prioritised vaccination of close contacts of pregnant women, especially their partners, as well as midwives and doctors, is also recommended. mRNA-based vaccination against COVID-19 should be offered and made available to breastfeeding women.

8.4 Are there differences in the effectiveness of COVID-19 vaccines?

The vaccines approved in Germany by BioNTech/Pfizer, Moderna, AstraZeneca, and Janssen (Johnson & Johnson) all offer protection against symptomatic infections. The efficiency data in the prevention of all infections determined by the clinical trials as percentages only reflect the effectiveness to a limited extent. All vaccines approved to date can largely prevent severe courses and deaths [49]. Current data on the vaccines can be found on the website of the Paul Ehrlich Institute (PEI) (https://www.pei.de/DE/arzneimittel/impfstoffe/covid-19/covid-19-node.html).

8.5 Efficacy of vaccines against SARS-CoV-2 variants

All vaccines licensed in Europe are considered to provide very good protection against symptomatic disease not only against the original "wild type" of SARS-CoV-2 but also against the alpha (B.1.1.7) and delta (B.1.617.2) variants currently prevalent in Germany, although a complete vaccination series seems to be important for protection against the delta variant [49].

8.6 To what extent does an inflammatory rheumatic disease or immunosuppressive/modulatory therapy change the entitlement to COVID-19 vaccination?

According to the Corona Vaccination Ordinance (CoronaImpfV) of the Federal Ministry of Health, patients with rheumatic diseases have so far been entitled to be vaccinated with increased priority, and in the case of certain organ manifestations also with high priority [59]. Concerning changes or cessation of prioritisation, reference is made to the current Corona Vaccination Ordinance in the official "Bundesanzeiger", the recommendations of the Robert Koch Institute, and the website of the DGRh. Even if prioritisation is discontinued, the DGRh would like to point out that patients with IRD should continue to be vaccinated preferentially.

8.7 Tolerance of vaccinations in rheumatic diseases

On the question of the tolerability of COVID-19 vaccinations in patients with IRD, an online survey of 325 patients [60] and two first prospective German studies with 29 and 84 patients [61, 62] have been published so far. Overall, good tolerability and no specific intolerance reactions were observed. However, only mRNA vaccines were used in all these studies. With more than 1.4 billion vaccinations administered worldwide (as of 15 May 2021) [63], there is currently no evidence that patients with IRD have a different spectrum of side effects or increased adverse reactions to the currently approved vaccines than the normal population. In principle, there is a recommendation not to administer elective vaccinations during a disease flare, but whether vaccination against COVID-19 should be made at all dependent on actual disease activity is controversial [55, 56].

8.8 Can COVID-19 vaccination trigger a flare of rheumatic diseases?

Theoretically, vaccines, like infections, could trigger relapses of known or even initial manifestations of IRD. This is not yet known for the currently approved vaccines against COVID-19. According to current knowledge, the benefit of vaccination clearly outweighs the theoretical risk of a usually only slight or temporary activation of the underlying disease. Studies on other vaccines showed no evidence that they trigger flares of IRD [64, 65]. In the first German study mentioned above, no effect on the activity of the underlying disease was found in association with the mRNA vaccination against SARS-CoV-2 [61]. Even if in individual cases "relapses" can occur in the context of the (desired) vaccination response, which can generally be controlled with symptomatic therapy, there are no hints for permanent activation of an IRD by vaccination against SARS-CoV-2. Therefore, concerns about the worsening of an IRD are no reason to refrain from vaccination.

8.9 Is there a vaccine to prefer for rheumatic diseases or immunomodulatory medication?

The STIKO does not derive any preference for a specific vaccine for the German population from the data available to date on the effectiveness of the available vaccines with regard to the virus variants known to date but assumes that all vaccines available to date are equally suitable for combating the pandemic [49].

No significant differences in the safety of these vaccines can be inferred from the controlled trials. Postmarketing surveillance for the AstraZeneca vaccine showed evidence of very rare immunologically mediated events, predominantly in younger female patients with thrombocytopenia, coagulation disorders, and unusual thromboses, including sinus vein thrombosis [66–68]. The EMA sees a probable connection with the vaccine, but continues to assume a clearly positive benefit–risk ratio due to the rarity of the events and has therefore not decided on any restrictions on the use of the AstraZeneca vaccine [69]. For Germany, the PEI and the STIKO came to a different conclusion and recommend its use, as well as that of the Johnson & Johnson vector vaccine due to similar complications, only for people under 60 years of age after detailed medical information [49].

Comparative data on the efficacy and safety of the vaccines currently used in Germany in patients with IRD is not available. This means that beyond the general differences described and the restrictions on use imposed by the PEI and the STIKO, there is no preference for patients with IRD in favour of a particular vaccine.

For two patient groups with IRD, namely patients in whom rapid complete immunisation is indicated because of urgent therapy with RTX and patients over 60 years of age with confirmed APS (antiphospholipid syndrome) or immunothrombocytopenia, the administration of an mRNA vaccine is recommended as a precautionary measure in view of the DGRh.

The mechanism of the very rare coagulation disorders, thrombopenias, and sinus vein thromboses is probably based on the formation of autoantibodies (VIPI: vaccine-induced prothrombotic immune

thrombocytopenia) [66]. The postmarketing surveillance data from Great Britain show comparatively more reported cases of APS and ITP under vaccination with the AstraZeneca vaccine [70] than with the Pfizer/BioNTech vaccine [71], although the number of cases cannot be analysed with statistical certainty. However, details on the cases of VIPI that have occurred so far are hardly available. Among 9 published cases, 2 were patients with pre-existing autoimmune disease, including 1 with positive antiphospholipid antibodies [66]. In a Norwegian study of healthcare workers, antibodies to platelet factor 4 (PF4) were detected in 6/492 cases after vaccination with the AstraZeneca vaccine. None of these cases developed thrombopathy or thrombosis [72].

If this does not delay vaccination, for patients with confirmed APS or immunothrombocytopenia, the use of an mRNA vaccine could represent a risk reduction. This does not apply to cases where only low-titre or single antiphospholipid antibodies are detectable or where there is no chronic immunothrombocytopenia.

With the mRNA vaccines, immunisation can be achieved within about 4–7 weeks: Currently, based on modeling by the RKI and the available data, a vaccination interval of 6 weeks is recommended for the mRNA vaccines, and 12 weeks for the AstraZeneca vaccine [49]. Immunity exists 2 weeks after the second vaccination (BioNTec, Moderna, AstraZeneca) or after the single vaccination (Johnson & Johnson), according to the respective technical information. Patients for whom therapy with RTX is urgent would benefit from rapid immunisation, as a significantly reduced vaccination response can be assumed after such anti-B cell therapy over a longer period of time. Under ongoing therapy with RTX, e.g. for remission maintenance in AAV, there may only be short time windows in which vaccination appears promising—at least with regard to anti-body formation. In these cases, too, patients would benefit from the use of an mRNA vaccine. There are no concrete data available on this procedure for IRD either. There is only a plausible analogy to other vaccinations.

For both case constellations, the DGRh concludes that vaccination should also be carried out with vector vaccines if, e.g. for reasons of availability, an mRNA vaccine cannot be used promptly, as the risk of a severe SARS-CoV-2 infection outweighs the possible vaccination risks.

8.10 Vaccinations following SARS-CoV-2 infection

Due to the immunity after a SARS-CoV-2 infection and because of the continuing vaccine shortage, immunocompromised persons who have undergone a SARS-CoV-2 infection confirmed by direct pathogen detection (PCR) should, in the opinion of the STIKO, receive a COVID-19 vaccination 6 months after recovery or diagnosis, taking into account prioritisation. Initially, one vaccine dose is sufficient for this, as high antibody concentrations can already be achieved, which cannot be further increased by a second vaccine dose. On the other hand, it must be decided on a case-by-case basis whether a single vaccination is sufficient or whether a complete vaccination series should be administered to persons with "impaired immune function" [49].

8.11 Is the effect of corona vaccination attenuated by antirheumatic therapy/ immunosuppressants/-modulants?

Immunomodulatory and immunosuppressive therapies can influence the response to vaccination. Previous studies investigated the antibody response after vaccination against tetanus, influenza, pneumococcus, and varicella in rather small cohorts and focused on the humoral immune reaction. Data on the immune response to vaccinations studied so far (no COVID-19 vaccinations) under different DMARDs are listed in **Table 7** (Appendix).

It is uncertain whether the results of these studies can be extrapolated to the SARS-CoV-2 vaccines and whether there is a difference between the mRNA and vector vaccines. It can also not be assumed that assessment of the humoral immune response alone is sufficient to assess the efficacy of the SARS-CoV-2 vaccination.

In the meantime, some studies on vaccination against SARS-CoV-2 have also been able to show that antibody formation depends on the existing immunosuppression. In the first study worldwide using a small cohort of IRD patients, mainly under biologic therapy, the Kiel working group led by B. Hoyer found an immune response in all of them after mRNA vaccination, although the antibody titres against SARS-CoV-2 were (slightly) reduced compared to healthy controls [61]. Colleagues from Erlangen were then able to show that a certain reduction in the humoral vaccination response can be observed, especially with methotrexate and also with JAK inhibitors [62]. Complete nonresponders were only observed in the Erlangen cohort, the explanation for this is still pending. In both the Kiel and Erlangen studies, it should be noted that the patient cohort was significantly older than the healthy controls and that in the Kiel cohort a large proportion of the differences were no longer statistically significant in an age-matched analysis, which could also be the case for the Erlangen data. This would be supported by the fact that in this study a reduction in the humoral vaccination response was also found in patients without immunosuppression, which would argue for immune senescence as an explanation. The reduction of antibody titres in the Kiel cohort was independent of whether the basic therapy was paused around the vaccinations or not—however, in this cohort, there were neither patients under JAK inhibitors nor under methotrexate.

For RTX, it could be shown in a study with 5 patients [73] and another with 30 patients [74] that antibody formation after COVID-19 vaccination is significantly suppressed depending on the time elapsed since the last administration of RTX. However, an antigen-specific T-cell response remained mostly present. In the second study, the detection of vaccine antibodies was also dependent on the presence of peripheral B cells in the blood. In another study, positive SARS-CoV-2 antibody titres were detected in a total of 94% of 404 IRD patients vaccinated with mRNA vaccines. While 100% of patients under TNF inhibitors showed a humoral vaccination response, this was only the case in 26% of patients under rituximab, albeit with an unclear time interval between the last administration and vaccination, and in 73% under mycophenolate [75].

Table 4 Expert consensus on *possible* adjustments of antirheumatic therapies in the context of vaccinations against COVID-19

Medication	Possible adjustments in the context of vaccinations	LoA (± SD)
Pauses or postponements are not generally recommended. In the case of a sustained remission, the following therapy adjustments can be considered in consultation with the rheumatologist in the context of vaccination		
Prednisolone ≤ 10 mg per day	No change	9.74 (± 0.55)
Prednisolone > 10 mg per day	If possible, reduction to lower doses (≤ 10 mg daily)	8.63 (± 2.25)
Hydroxychloroquine	No change	10 (± 0)
Methotrexate	Pause for 1(–2) weeks after each vaccination	7.79 (± 2.76)
Sulfasalazine, leflunomide, azathioprine, calcineurine inhibitors	No change	9.63 (± 0.67)
Belimumab	No change	8.84 (± 1.63)
TNF-I, IL-6-R-I, IL-1-I, IL-17-I, IL-12/23-I, IL-23-I	No change	9.95 (± 0.22)
JAK inhibitors	Pause for 1–2 days before to 1 week after each vaccination	7.74 (± 2.63)
Abatacept (sc)	Pause for 1 week before and 1 week after each vaccination	8.47 (± 1.67)
Abatacept (iv)	Vaccination in the interval between two infusions; if possible 4 weeks after an infusion with delay of the next infusion by 1 week	8.53 (± 1.63)
Rituximab	Consider alternative therapy and carry out vaccination	9.42 (± 1.27)
	Postponement of the first or next RTX cycle to 2–4 weeks after completion of the vaccination series	8.68 (± 1.92)
	If possible, vaccination at the earliest 4–6 months after the last RTX administration	9.53 (± 0.75)
	For patients at risk, earlier vaccination if necessary	9.11 (± 1.17)
Mycophenolate	Pause for 1 week after each vaccination	7.53 (± 2.11)
NSAIDs and paracetamol	Pause for 6–24 h (according to half-life of NSAID) before and 6 h after every vaccination	7.68 (± 2.77)

At the end of May 2021, a retrospective study from two cohorts located in New York and Erlangen was published, in which a reduced humoral and cellular response after vaccination with the Pfizer/BioNTech vaccine under methotrexate was reported in some of the vaccinated patients [76]. It remains questionable whether isolated subgroup analyses by age (comparison of those under 55 years of age, as methotrexate patients were 10 years older on average) and by COVID-19 already experienced (8% in the methotrexate group versus 15% in controls and 19% in patients on other therapies) were still statistically adequate. In addition, vaccination response was tested quite shortly after the second vaccination (8–14 days, assuming a vaccination interval of 21 days). So it cannot be ruled out that vaccination response is only delayed. The authors themselves also point out that it is not yet clear what level of immune response is sufficient for a vaccine to be effective. The arbitrarily defined cut-offs do not allow any conclusion as to whether the failure to achieve the desired humoral immune response is also associated with a higher risk of infection. The question of whether ongoing methotrexate therapy in fact weakens the immune response after SARS-CoV-2 vaccination in a relevant way cannot be answered with certainty based on the available data, and it is even less clear whether this reduces vaccine protection.

8.12 Should immunosuppressive/immunomodulatory therapy be reduced or paused because of vaccination?

Data on temporary pauses of DMARDs at the time of the SARS-CoV-2 vaccination is limited and refers predominantly to patients with inflammatory joint diseases. Controversy surrounds the study data on methotrexate, which showed an improved humoral immune response with a 2-week break after influenza vaccination. Other data show an increased rate of relapses of IRD with methotrexate paused > 2 weeks, without any further improvement in the immune response. For tofacitinib, it was shown that a 1-week therapy break before and after pneumococcal vaccination did not result in a better immune response. Comparable data on other DMARDs are not available.

For basic considerations of the effectiveness of vaccination, immunosuppression should be as low as possible at the time of vaccination, but not only with regard to vaccinations against SARS-CoV-2, the risk of reactivation of IRD after a longer pause or discontinuation of immunomodulatory/immunosuppressive therapy is estimated to be higher than the benefit of an even potential improvement of the vaccination response. Therefore, we do not recommend regularly changing an existing immunomodulatory/immunosuppressive therapy because of the vaccination. An exception is the administration of long-acting B-cell depleting substances (RTX). In this case, consideration should be given to postponing or switching to alternative therapies, taking into account the risk of reactivation of the underlying disease on the one hand and the improvement of a potential vaccine response on the other (see **Table 4**).

Good disease control is also a priority in the context of vaccination against COVID-19. Patients should be informed and involved in the decision-making process if there is even a temporary change in therapy. In order to optimise the vaccination response and in consultation

with the treating rheumatologist, a pause of methotrexate, mycophenolate, JAK inhibitors, and abatacept around the COVID-19 vaccination can be considered in the case of well-controlled IRD (Table 4).

8.13 Vaccination sequence

No specific restrictions or changes are seen compared to the time sequences of vaccinations given by the STIKO for patients with IRD. Depending on the urgency of an immunosuppressive therapy that impairs the vaccination response (i.e. especially in the case of planned administration of RTX), the shortest possible intervals between the first and second vaccination should be aimed for, as far as the approval permits, or a single vaccination with a vector vaccine (Johnson & Johnson) (see section 8.9). When administering RTX, a time window of 4 (in urgent cases at least 2) weeks after completion of the COVID-19 vaccination should be observed.

8.14 Can the success of a vaccination against COVID-19 be checked by titre testing?

Under any immunosuppression, the vaccination response may be reduced (see section 8.11). The antibody response after vaccination against COVID-19 can be checked by lab testing of antibody titre. However, routine determination of antibodies against SARS-CoV-2 is not recommended [77], as it cannot yet be assessed whether these are suitable as surrogate markers for existing immunity, even though there is increasing evidence that neutralising antibodies are predictive of protection against symptomatic infection [78]. With the currently available tests, it is not yet possible to give a precise statement at which antibody level there is actual protection against the disease. Even in the case of a complete absence of antibodies, a cellular immune response against the spike protein could exist and thus a vaccination protection could be present. This is not detected by antibody tests. In the case of low or negative antibodies, it should therefore not be concluded that the vaccination response against COVID-19 has completely failed and that patients are not protected against infection.

Even with a history of infection, routine titre control is not recommended prior to vaccination, as vaccination is recommended regardless of antibody findings.

However, it should be noted that the interpretation of humoral and cellular immunity is a dynamic process and a new assessment of the value of these tests, especially with regard to the evaluation of the need for a booster vaccination in immune suppressed persons with an insufficient vaccination response, may occur quickly. With regard to booster vaccination, a precise assessment will only be possible when criteria for an effective protective effect are defined and controlled studies on booster vaccination (including timing, quantity, active ingredient) are available.

8.15 Other vaccinations

Independent of the considerations on SARS-CoV-2, other vaccinations should be given according to the recommendations of the STIKO. Data on interactions between these and other known vaccines on the one hand and the SARS-CoV-2 vaccines on the other are not available. A minimum interval of 14 days before the start and after the end of the vaccination series against SARS-CoV-2 should be reserved for other vaccinations (with the exception of emergency vaccinations).

Appendix

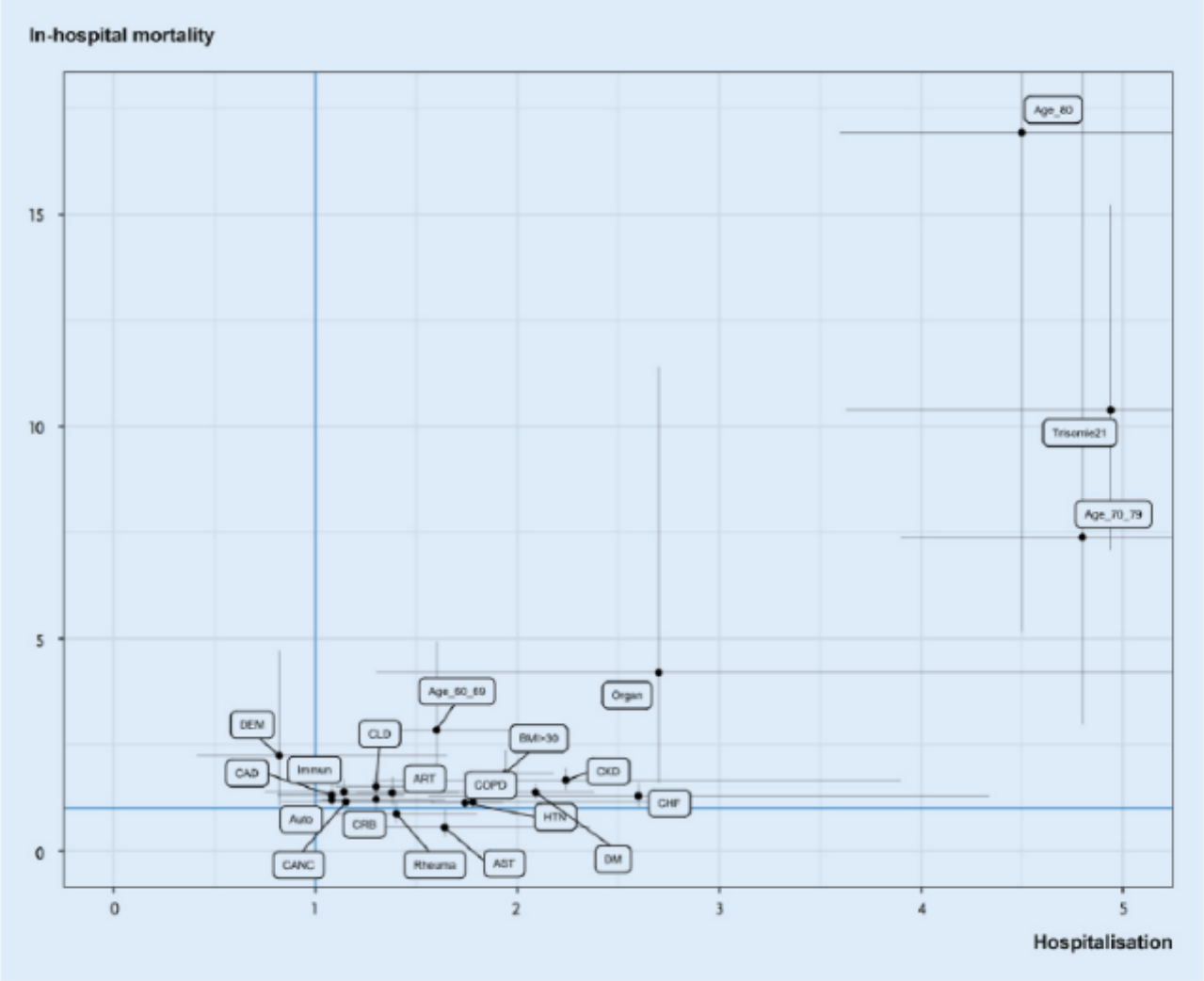

Fig. 1 ▲ Cluster-analysis—risk of different pre-existing conditions and age on hospitalisation and mortality in the context of COVID-19 (from [8]). *ART* arrhythmia or atrial fibrillation; *CHF* congestive heart failure; *CAD* coronary artery disease; *HTN* hypertension; *DM* diabetes; *BMI > 30* obesity & overweight; *CANC* cancer; *AST* asthma; *COPD* chronic obstructive pulmonary disease; *CKD* chronic kidney disease; *CLD* chronic liver disease; *CRB* cerebrovascular or stroke; *DEM* dementia; *Auto* autoimmune condition; *Immun* immunodeficiency or immunosuppressed state; *Rheuma* (inflammatory) rheumatic disease; *Organ* organ transplant history

Table 5 Various studies on the odds ratio (OR) of IRDs for a severe course, hospitalisation or death in association with COVID-19

Reference	Diagnosis	Number of patients/total IR-population	End point	OR (CI 95%)
Bachiller-Corral J, J Rheumatol 2020 [28] *(retrospective monocenter cohort study)*	SLE	254/4592	Hospitalisation	3.38 (1.28–8.95)
	Sjögren's syndrome	175/4592		4.9. (1.86–12.94)
	PMR	474/4592		2.71 (1.23–6.02)
	Vasculitis (vs. general population)	165/4592		3.9 (1.27–11.99)
Cordtz R, Rheumatology 2020 [29] *(Denmark, national cohort study)*	RA	29,440 (davon 69 hospitalisiert)/58,052	Hospitalisation	1.46 (1.15–1.86)[b]
	Vasculitis (vs. general population)	4072 (davon 8 hospitalisiert)/58,052 4.5 Million		1.82 (0.91–3.64)[b]
FAI²R, Ann Rheum Dis 2021 [13] *(France, registry data)*	Vasculitis	65/694	Serious course	2.25 (1.13–4.41)[a]
			Death	2.09 (0.93–4.56)[a]
	Autoinflammatory syndromes (vs. "matched cohort" of non-IRD COVID patients)	12/694	Serious course	7.88 (1.39–37.05)[a]
			Death	2.56 (1.15–5.95)[a]
Freitez-Nunez, Ann Rheum Dis 2020 [18] *(monocentric cohort study)*	Systemic autoimmune diseases (vs. RA)	123 (50 thereof with RA)	Hospitalisation	3.55 (1.30–9.67)
Pablos J, Ann Rheum Dis 2020 [12] *(multicentric cohort study)*	CTD[c] (vs. matched non-IRD cohort)	228 IRD-patients (40% with CTD)	Serious course	1.82 (1.00–3.30)

[a] adjusted OR

[b] hazard ratio

[c] CTD in this study with the following diagnoses: polymyalgia rheumatica, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, primary antiphospholipid-syndrome, giant-cell arteritis, myositis, other vasculitidies

Table 6 Common COVID-19 symptoms in patients with inflammatory rheumatic diseases in Germany. Data from the COVID-19 rheumatism registry [6]—with 2729 patients enrolled—(as of 23 May 2021)

Symptom	% (multiple answers)
Cough	55
Fatigue	52
Fever	49
Myalgia	36
Loss of taste	34
Headache	32
Loss of smelling	32
Dyspnoea	25
Common cold	22
Loss of appetite	22
Diarrhoea	13
Vertigo	12
Expectoration	10

Table 7 Studies on vaccination response under prednisone and DMARDs (no COVID-19 vaccinations)

Compound	Data on vaccination response
Prednisone [79–81]	> 10 mg Prednisone (dose-dependent) limited humoral response
csDMARDs	
Methotrexate [82–85]	Decreased humoral response (influenza, pneumococcus)
Mycophenolate [75]	Decreased humoral response
Other csDMARDs [86–89]	Limited, but acceptable humoral response
bDMARDs	
TNF inhibitors [81, 86, 90–92]	Limited, but acceptable humoral response (influenza)
IL-6-R inhibitors [93–95]	Unimpaired humoral response
Abatacept [95–97]	Inconsistent data
Rituximab [82, 98–100]	Significantly impaired humoral response (pneumococcus, influenza)
tsDMARDs JAK inhibitors [101–103]	Uninpaired humoral/cellular response (pneumococcus) Impaired humoral response (tetanus)

Research agenda

- Are patients with certain inflammatory rheumatic diseases (IRD) or organ involvement at increased risk of COVID-19 or severe progression?
- Are certain antirheumatic therapies/therapeutic principles associated with an increased risk of COVID-19 or severe progression?
- Are glucocorticoids also associated with an increased risk of COVID-19 or a severe course, independent of disease activity?
- To what extent do other vaccinations (e.g. against influenza, pneumococcus) have a positive effect on the course of COVID-19?
- Is pausing/discontinuing DMARD therapy before/after COVID-10 vaccination associated with an improved immune response? How long should the pause be for each therapy?
- What humoral or cellular immunity tests are useful to assess adequate protection against infection after infection or vaccination?
- What is the significance of SARS-CoV-2 antibody determinations with regard to protection against newly emerging virus variants?
- When and at what frequency are booster vaccinations useful?
- Is it useful to determine peripheral B cells before vaccination?
- Is there a preference for certain vaccines in the context of rheumatic diseases?
- How protective are vaccinations in terms of frequency and severity of COVID-19 in IRD?
- Is the influence of costimulation blockade particularly relevant in the primary response (first vaccination)?

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Declarations

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Ethical standards. For this article no studies with human participants or animals were performed by any of the authors.

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Thieme

COVID-19 und rheumatische Erkrankungen – bisherige Erkenntnisse der Pandemie

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WAS IST NEU?

COVID-19 bei Patienten mit entzündlich-rheumatischen Erkrankungen Eine erhöhte Entzündungsaktivität bei Patienten mit entzündlich-rheumatischen Erkrankungen ist mit schwereren COVID-19-Verläufen assoziiert. Der Einsatz von Glukokortikoiden (mehr als 5 mg Prednisolon/Tag) kann einen schwereren Verlauf von COVID-19 begünstigen. Glukokortikoide von > 10 mg über einen längeren Zeitraum müssen angesichts zahlreicher steroidsparender Alternativen sehr gut begründet sein.*

COVID-19 und Immunmodulation Bereits frühe Fallberichte deuteten auf einen negativen Einfluss von Rituximab auf den Verlauf von COVID-19 hin. Mittlerweile konnten in mehreren Arbeiten höhere Raten von Hospitalisierungen und COVID-19-assoziiertem Tod nachgewiesen werden. Ob ein vergleichbarer Effekt auch unter der Therapie mit Januskinase-Inhibitoren bei Patienten mit rheumatoider Arthritis besteht, wird derzeit untersucht.

COVID-19-Impfungen Alle in Deutschland zur Verfügung stehenden Impfstoffe gegen COVID-19 weisen bisher ein sehr gutes Sicherheitsprofil sowie kein relevant erhöhtes Risiko für Krankheitsschübe auf. Es wird keine generelle Pausierung oder Reduktion der Immunmodulation zum Erzielen einer besseren Impfantwort empfohlen. Eine Ausnahme stellt die Therapie mit Rituximab dar.

ABKÜRZUNGEN

ANCA	Antineutrophile Zytoplasma-Antikörper
DGRh	Deutsche Gesellschaft für Rheumatologie
ERE	Entzündlich-rheumatische Erkrankungen
MERS	Middle East Respiratory Syndrome
mRNA	Boten-Ribonukleinsäure
RA	Rheumatoide Arthritis
SARS	Schweres akutes respiratorisches Syndrom
SLE	Systemischer Lupus erythematodes
TNFi	Tumor-Nekrose-Faktor-Inhibitoren
WHO	Weltgesundheitsorganisation

Stand der Dinge

Seit dem 11. März 2020 spricht die Weltgesundheitsorganisation (WHO) von einer Coronavirus-Pandemie. Erstmalig wurde das Virus im Dezember 2019 in Wuhan in der Provinz Hubei beschrieben [1]. Die Infektion wird verursacht durch das neuartige („2"), ein schweres, akutes respiratorisches Syndrom auslösende Corona-Virus 2, abgekürzt SARS-CoV-2. Die Erkrankung wird COVID-19 genannt (Coronavirus Disease 2019). Trotz des wahrscheinlich zoonotischen Ursprungs war die Übertragung von Mensch zu Mensch verantwortlich für die schnelle und weltweite Verbreitung [2]. Die Übertragung erfolgt über den respiratorischen Trakt über Aerosole. Nach Eindringen in den Körper bindet das Virus an Rezeptoren und wird mithilfe von Endozytose oder Membranfusion intrazellulär aufgenommen [2]. Die Replikationsphase, die in der Regel wenige Tage beträgt, verläuft mehrheitlich asymptomatisch. In dieser Phase befällt das Virus den oberen Atemtrakt. Dies kann mit Symptomen wie Fieber, Abgeschlagenheit oder Husten einhergehen [2]. Bei ca. 20 % der Infizierten kommt es zu einer Beteiligung des unteren Atemtrakts [2], die in ein akutes vaskulär-entzündliches Lungenversagen münden kann [2]. Durch die Aktivierung des Immunsystems kann es zu einer überschießenden Immunantwort kommen, die mit einem lebensgefährlichen Zytokinsturm einhergehen kann [2].

Bereits zu Beginn der Pandemie wurden verschiedene antivirale Therapien im Einsatz gegen COVID-19 diskutiert, unter anderem der Einsatz von Hydroxychloroquin [3]. Dies führte zeitweise zu Lieferengpässen in der Behandlung von Patienten mit entzündlich-rheumatischen Erkran-

* In dieser Arbeit wird aus Gründen der besseren Lesbarkeit das generische Maskulinum verwendet. Weibliche und anderweitige Geschlechteridentitäten werden dabei ausdrücklich mitgemeint, soweit es für die Aussage erforderlich ist.

kungen (ERE). In den Studien konnte jedoch im Verlauf kein Benefit durch den Einsatz von Hydroxychloroquin gezeigt werden – weder als Prophylaktikum in Bezug auf die Infektion noch im Falle von schweren Verläufen von COVID-19 war die Substanz erfolgreich. Zytokinblocker wurden ebenfalls sehr früh im Einsatz gegen den Zytokinsturm diskutiert. Erste Daten weckten die Hoffnung eines möglichen Therapieansatzes durch Interleukin-6-Blocker im Rahmen von schweren COVID-19-Verläufen [4, 5]. Leider konnten in der COVACTA-Studie weder der primäre Endpunkt (Verbesserung des klinischen Status des Patienten bei COVID-19-assoziierter Pneumonie) noch der sekundäre Endpunkt (Reduktion der COVID-19-assoziierten Letalität) erreicht werden [4]. Auch in der EMPACTA-Studie zeigte sich keine Besserung der Überlebensrate [6]. Dagegen konnte in der REMAP-CAP-Studie durch den Einsatz von Interleukin-6-Blockern ein verbessertes Outcome sowie eine Reduktion der Letalität gezeigt werden [7], sodass die Frage offenbleibt, inwiefern der Einsatz von Interleukin-6-Blockern eventuell doch einen Vorteil im Rahmen von COVID-19 bringt. Unter der Therapie mit dem Januskinase-Inhibitor Baricitinib konnte zwar keine Verbesserung der Sauerstoffbehandlung gezeigt werden, es kam jedoch zu einem deutlichen Rückgang der Letalität, auch bei Patienten, die bereits mit Steroiden behandelt wurden [8]. Die AWMF empfiehlt daher, dass Januskinase-Inhibitoren bei Patienten mit COVID-19-Erkrankung ohne Sauerstoffbedarf oder mit Low-Flow-Sauerstoffbedarf unter Beachtung der Kontraindikationen eingesetzt werden – dies aber nicht in Kombination mit Tocilizumab. Auch unter der Kombination mit Remdesivir konnte eine Verbesserung des klinischen Status erreicht werden [9]. Dennoch bleibt auch hier die Frage offen, welche COVID-19-Patienten von einer Immunmodulation profitieren könnten.

Trotz Parallelen zu anderen Virusinfektionen wie SARS (schweres akutes respiratorisches Syndrom) oder MERS (Middle East Respiratory Syndrome), welche mit einer mit COVID-19 vergleichbaren initialen Klinik (Husten, Fieber, Zephalgien und Myalgien), demselben Übertragungsweg (Tröpfcheninfektion) und der sehr variablen Symptomatik (von symptomlos bis zu kurzfristig letalen Verläufen) einhergehen, gab es bis zu dieser Pandemie keine auf evidenzbasierten Daten basierenden Handlungsempfehlungen für ERE-Patienten. Dasselbe galt für die Bedeutung oder den Einfluss immunmodulierender Therapie bei diesen Patienten.

COVID-19 bei Patienten mit entzündlich-rheumatischen Erkrankungen

Aus diesem Grund initiierte die Deutsche Gesellschaft für Rheumatologie (DGRh) gemeinsam mit der Justus-Liebig-Universität, Campus Kerckhoff, ein Web-basiertes Register (▶ **Abb. 1**), um eine schnelle Datengewinnung zu ermöglichen und mithilfe dieser Daten Handlungsempfehlungen für die Betreuung von ERE-Patienten in Bezug auf die Pandemie abzuleiten. Diese Daten fließen zudem in das europäische (https://www.eular.org/eular_covid_19_registry.cfm) und globale (https://rheum-covid.org/) Register ein, um gemeinsam weltweit wichtige Erkenntnisse zu gewinnen. Das Register konnte bereits im März 2020 gestartet werden und 3151 Fälle bis zum 30.08.2021 erfassen. Lediglich bei 21 % war eine stationäre Behandlung notwendig. Es wurden 102 letale Verläufe berichtet. Somit liegt die Letalität bei 3,2 %.

▶ **Abb. 1** Für Ärzte: Eingabe von SARS-CoV-2-Fällen bei ERE-Patienten. www.covid19-rheuma.de.

In einer ersten Publikation zum Aufbau des Registers, in der die Fälle der ersten 4 Wochen nach Beginn des Registers ausgewertet wurden, ergaben sich schon Hinweise für eine höhere Rate COVID-19-assoziierter Hospitalisierungen unter Einsatz von Glukokortikoiden [10]. Bereits in einer Verlaufsanalyse bei 468 ERE-Patienten erwiesen sich – neben „allgemeinen" Parametern wie höheres Lebensalter, kardiovaskulären Erkrankungen und chronischen Lungenerkrankungen- die Krankheitsaktivität der ERE sowie der Einsatz von mehr als 5 mg Prednisolon/Tag als Prädiktoren für schwere COVID-19-Verläufe [11]. Ähnliche Resultate wurden bei der Auswertung der globalen Daten beschrieben [12, 13]. Diese Ergebnisse untermauern die Empfehlung der DGRh, durch den Einsatz von Immunmodulatoren eine Remission oder geringe Krankheitsaktivität zu erzielen, um das Risiko einer Infektion und somit auch das Risiko für schwere COVID-19-Verläufe zu minimieren [14]. Auf Basis einer steigenden Zahl an Publikationen zu COVID-19 bei ERE-Patienten sowie regelmäßigen Auswertungen des Registers konnten die Handlungsempfehlungen der DGRh aktualisiert werden [15].

Klinische Relevanz

Die bisherigen Daten untermauern die Empfehlungen der DGRh die Krankheitsaktivität der ERE möglichst mit dem Einsatz der zur Verfügung stehenden, Steroid-einsparenden Immunmodulatoren zu kontrollieren, um dadurch das Risiko einer Infektion sowie schwerer COVID-19-Verläufe zu reduzieren.

COVID-19 und Immunmodulation

Bereits zu Beginn der Pandemie wurde diskutiert, ob die verschiedenen immunmodulierenden Therapieoptionen den Verlauf von COVID-19 negativ beeinflussen könnten. Daher lag die Befürchtung nahe, dass Patienten ihre immunmodulierende Therapie beenden könnten. In einer longitudinalen Befragung von ca. 4000 Patienten im Zeitraum von März bis Juni 2020 gaben erfreulicherweise lediglich 3 % der befragten Personen bundesweit an, ihre Therapie zu beenden [16]. Dies war sehr beruhigend, da ein selbstständiges Absetzen der Therapie mit einer Zunahme der Krankheitsaktivität und der Notwendigkeit einer Therapie-Intensivierung einhergehen kann. Im Verlauf wurden jedoch einige schwere Fälle von COVID-19 unter Therapie mit Rituximab beschrieben [17]. Da Rituximab nicht zur Erstlinientherapie der rheumatoiden Arthritis gehört und bei den mit antineutrophilen Zytoplasma-Antikörpern (ANCA) assoziierten Vaskulitiden vor allem zur Remissionsinduktion gemeinsam mit höheren Dosen von Kortison eingesetzt wird, stellte sich die Frage, inwiefern diese Beobachtungen sich durch den alleinigen Einfluss von Rituximab untermauern lassen [18, 19]. Bezüglich der COVID-19-Todesfälle konnten international signifikant höhere Zahlen unter der Therapie mit Rituximab nachgewiesen werden [13]. In einer gemeinsamen Auswertung mit dem globalen Register wurde bei 2869 Patienten mit rheumatoider Arthritis eine signifikant höhere Rate von Hospitalisierungen und letalen Verläufen, sowohl unter der Therapie mit Rituximab als auch unter Therapie mit Januskinase-Inhibitoren, im Vergleich zu Tumor-Nekrose-Faktor-Inhibitoren (TNFi) festgestellt [20]. Trotz der hohen Fallzahl müssen diese Daten jedoch weiterhin vorsichtig interpretiert werden, da bei dieser Untersuchung nicht erfasst wurde, wie viele und welche Vortherapien die Patienten erhalten haben. Wichtig ist deshalb die Analyse des deutschen Registers. Die auf dem DGRh-Jahreskongress im September vorgestellten Daten und in der aktuellen Publikation (Regierer AC, Hasseli R, Schäfer M, Hoyer BF, Krause A, Lorenz HM, Pfeil A, Richter J, Schmeiser T, Schulze-Koops H, Strangfeld A, Voll RE, Specker C, Mueller-Ladner U. TNFi is associated with positive outcome, but JAKi and rituximab are associated with negative outcome of SARS-CoV-2 infection in patients with RMD. RMD Open. 2021 Oct; 7(3): e001896. doi:10.1136/rmdopen-2021-001896. PMID: 34670840; PMCID: PMC8529615) von 2979 Patienten und 100 Todesfällen zeigen, dass unter Rituximab 17 fatale Verläufe auftraten, unter (verschiedenen) Januskinase-Hemmern 12, wobei statistisch auch die anderen Immunsuppressiva wie Mycophenolate, Azathioprin, Cyclophosphamid und Ciclosporin mit einem höheren Risiko assoziiert waren – Hauptproblem waren nach wie vor die Glukokortikoide, die bei 64 der letalen Verläufe eingesetzt wurden.

Klinische Relevanz

Die bisherigen Daten deuten auf eine höhere Hospitalisierungsrate und Letalitätsrate unter der Therapie mit Rituximab hin. Auch unter dem Einsatz von weiteren Immunsuppressiva konnten bei Patienten mit rheumatoider Arthritis im Vergleich zu TNF-Blockern höhere Raten an schweren Verläufen und COVID-19-assoziierten Todesfällen beobachtet werden.

COVID-19-Impfungen

Die zur Verfügung stehenden Impfungen geben Hoffnung auf eine zeitnahe Bewältigung der Pandemie. Alle in Deutschland zugelassenen Impfstoffe sind nicht als Lebendimpfstoffe einzustufen und somit bei ERE-Patienten auch unter Immunmodulation einsetzbar. Ein generelles Absetzen der Immunmodulation zur Verbesserung der Impfantwort wird nicht empfohlen, da bislang unklar ist, inwieweit dies den tatsächlichen Impfschutz beeinträchtigt. Zudem birgt das Absetzen der Immunmodulation das Risiko einer Krankheitsaktivitätszunahme, sodass dies eine Intensivierung der Immunmodulation mit sich bringen könnte und dadurch auch das Risiko für eine Infektion und einen schweren Verlauf von COVID-19 erhöhen würde [15]. Eine Ausnahme stellt die Therapie mit Rituximab dar. Hier wird empfohlen, die Impfserie mit einem Abstand von mindestens 4 Monaten nach der letzten Rituximab-Gabe zu beginnen, und Rituximab idealerweise frühestens 4 Wochen nach Abschluss der Impfserie zu geben [15]. Im Einzelfall muss bei Risikopatienten hiervon abgewichen werden.

Da es bislang keine Erfahrung in Bezug auf die neuartigen mRNA-Impfstoffe (mRNA: Boten-Ribonukleinsäure) gab, herrschte sowohl seitens der Patienten als auch der behandelnden Rheumatologen Sorge in Bezug auf die Verträglichkeit der Impfungen. Aufgrund dessen initiierte die Kommission COVID-19 der DGRh auch hier eine Online-Erfassung (▶ **Abb. 2**) zur Untersuchung der Verträglichkeit, des Sicherheitsprofils und der Effektivität der Impfung bei ERE-Patienten. ERE-Patienten können freiwillig bereits nach der ersten Impfung an diesem Register teilnehmen und ihre Impferfahrung mithilfe eines Fragebogens teilen. Es erfolgt eine Verlaufsbefragung über insgesamt 12 bzw. 24 Wochen (abhängig vom Impfstoff) sowie eine letzte Befragung nach 12 Monaten, um zu erfahren, ob sich der Patient trotz Impfung mit SARS-CoV-2 infiziert hat und wie dann die Infektion verlaufen ist.

Bis zum 11. September 2021 nahmen 1842 Personen an dem Impfregister teil, 80 % waren weiblich und das Alter lag im Median bei 54 Jahren (18–104 Jahre). Mehrheitlich gaben die Personen an, an einer rheumatoiden Arthritis (RA, 50 %) zu leiden, gefolgt von Psoriasisarthritis (16 %), axialer Spondyloarthritis (11 %), systemischem Lupus erythematodes (SLE, 9 %) oder Sjögren-Syndrom (6 %). Zum Zeitpunkt der Impfung wurden 33 % mit Methotrexat behandelt, gefolgt von 30 % mit Glukokortikoiden, 22 % mit TNFi, 7 % mit Januskinase-Inhibitoren und 4 % mit Rituximab. Der Impfstoff von BioNTech/Pfizer wurde

▶ **Abb. 2** Für Patienten: Erfassung von allen COVID-19-Impfungen unabhängig von der Verträglichkeit. https://www.covid19-rheuma.de/patienten-information-impfung.

▶ **Abb. 3** Für Ärzte: Erfassung von schweren COVID-19-Impfnebenwirkungen. https://www.covid19-rheuma.de/arzt-sae.

als Erstimpfstoff bei 69 % eingesetzt, 22 % erhielten den AstraZeneca-, 9 % den Moderna-Impfstoff und 1 % andere Impfstoffe. Lediglich bei 2 % der Personen wurde eine SARS-CoV-2-Infektion vor der Impfung berichtet. Eine Zunahme der Krankheitsaktivität wurde bei 15 % der Personen berichtet, wohingegen dies lediglich bei 27 Personen in einer Änderung der Immunmodulation oder Erweiterung der Immunmodulation um ein weiteres Medikament resultierte. Bei 288 Personen wurden keinerlei Nebenwirkungen beschrieben. Erfreulicherweise wurden lediglich 3 Fälle von schwerwiegenden Nebenwirkungen nach Erstimpfungen erfasst:

- Ponsinfarkt bei einem RA-Patienten ohne Immunmodulation,
- Thrombose bei einem RA-Patienten unter Therapie mit Sulfasalazin,
- Thrombose bei einem Patienten mit SLE ohne Immunmodulation.

Das Nebenwirkungsprofil im Allgemeinen war vergleichbar mit der Allgemeinbevölkerung. Diese ersten Daten legen nahe, dass die Impfungen bei ERE-Patienten gut vertragen werden und zu keiner relevanten Zunahme der Krankheitsaktivität der ERE führen. Ähnliche Daten konnten auch in anderen Ländern beobachtet werden [21].

Nichtsdestotrotz werden in Fachkreisen Einzelfälle von schweren ERE-Reaktivierungen oder ERE-Erstmanifestationen diskutiert. Um dieser Frage nachzugehen, wurde eine Online-Erfassung für Ärzte initiiert, um diese Fälle standarisiert zu erfassen. Seit September 2021 können ERE-Patienten mit schweren Impfnebenwirkungen im Rahmen der COVID-19-Impfung durch die behandelnden Rheumatologen berichtet werden (▶ **Abb. 3**). Dies schließt auch Patienten ein, die zum Zeitpunkt der Impfung keine Immunmodulation erhalten haben.

Die Erfassung der rheumatologischen Patienten mit einer SARS-CoV-2-Infektion im COVID-19-Register ist und war nur durch die Arbeit der dokumentierenden Ärzte, der medizinischen Fachangestellten und Studienpersonal möglich. Aktuell dokumentieren 324 Kollegen, medizinische Fachangestellte und Studienpersonal aktiv in das COVID-19-Register. An dieser Stelle ist es der Ad-hoc-Kommission COVID-19-Register der DGRh ein ganz besonderes Anliegen, einen großen Dank an die Kollegen, medizinischen Fachangestellten und das Studienpersonal für die nicht vergütete Dokumentation der Patienten in das Register auszusprechen. Wir bitten Sie, uns weiterhin bei der Umsetzung des Registers und der COVID-19-Aktivitäten zu unterstützen.

Klinische Relevanz

In verschiedenen Studien zeigte sich unter der Therapie von Zytokinblockern wie TNF-Blockern bisher eine gute Immunantwort. Bisher konnte auch bei ERE-Patienten ein sehr gutes Sicherheitsprofil beobachtet werden. Inwiefern andere Immunmodulatoren die Impfantwort beeinflussen, ist derzeit Gegenstand der Forschung.

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4. Diskussion

4.1 Einfluss der COVID-19-Pandemie auf ERE-PatientInnen

Trotz vieler klinischer Parallelen zu anderen viralen Infektionen der Atemwege standen bis zur COVID-19-Pandemie nur eingeschränkt Daten zu Virusinfektionen bei ERE-PatientInnen zur Verfügung. Dasselbe galt auch für den Einfluss von Immunmodulatoren auf Virusinfektionen und den hierfür eingesetzten Impfstoffen. Basierend auf den Erfahrungen im Ursprungsland China zeigte sich, dass eine SARS-CoV-2-Infektion zwar häufiger bei Personen ab dem 60. Lebensjahr und bei relevanten Komorbiditäten komplikativ verlaufen kann, aber dass auch schwere Verläufe in jüngeren Altersgruppen zu beobachten waren [1]. Diverse Literaturquellen deuteten zu dieser Zeit auf ein erhöhtes Infektionsrisiko von ERE-PatientInnen mit oder ohne immunmodulierender Therapie hin [68,72,83,101,104,106,143,213]. Für das Abschätzen des Infektionsrisikos war und ist aber eine individuelle Betrachtung von Grunderkrankungen, immunmodulierender Therapie und Komorbiditäten notwendig.

Aufgrund der mangelnden Erfahrung mit Coronaviren und der noch ausstehenden Handlungsempfehlungen zu Beginn der Pandemie, war es notwendig, zu evaluieren, wie ERE-PatientInnen die damalige Situation in Bezug auf ihre ERE und immunmodulierende Therapie wahrnahmen und welche Konsequenzen daraus gezogen wurden.. In den beiden Studien der Originalarbeit *8* und Originalarbeit *8* konnte herausgearbeitet werden, dass die Mehrheit der ERE-PatientInnen sowohl in der Frühphase der Pandemie, als auch über einen Zeitraum von ca. drei Monaten während der ersten Welle ihre immunmodulierende Therapie weiterhin fortführten. Die individuelle Patientenentscheidung zur Fortführung der immunmodulierenden Therapie deckte sich in diesem Zeitraum mit den Expertenempfehlungen der DGRh, welche postulierten, dass durch Rezidive bzw. einen Schub der Grunderkrankung ein höheres Infektrisiko resultiere, da dadurch möglicherweise eine Intensivierung der Immunmodulation (z.B. durch Steroidstoß) notwendig gewesen wäre und somit eine größere Gefährdung der PatientInnen bestehen würde [94].

Diese Daten waren für die erste Einschätzung der Versorgung von ERE-PatientInnen sehr wichtig, da Bedenken bestanden, dass möglicherweise ERE-PatientInnen ihre immunmodulierende Therapie zur Risikoreduktion einer SARS-CoV-2-Infektion bzw. eines schweren Infektionsverlaufs selbstständig pausieren würden. Zudem war die medizinische Versorgung in diesem Zeitraum auf die Versorgung von COVID-19-PatientInnen fokussiert, so dass elektive fachsepzifisch-rheumatologische ärztliche Vorstellungen häufig ausblieben und somit auch eine aufklärende Arzt-Patienten-Kommunikation nicht möglich war.

Diese Ergebnisse deckten sich auch mit einer Studie aus Australien, in der auch über 90% der Befragten mit rheumatischen Erkrankungen angaben, ihre immunmodulierende Therapie fortzuführen [214].

In einer weiteren Studie zur Untersuchung von virtuellen ärztlichen Visiten in Nordamerika gaben jedoch ca. 14% der Befragten an, dass sie ihre immunmodulierende Therapie während der ersten Welle der Pandemie unterbrochen hätten [215]. Diese geographisch unterschiedlichen Studienergebnisse dürften am ehesten durch anders strukturierte Gesundheitssysteme oder Aufklärungsstrategien begründet sein.

4.2 Darstellung des Verlaufs einer SARS-CoV-2-Infektion bei ERE-PatientInnen

Die multiplen Therapieoptionen bei ERE mit neuen Therapieansätzen, wie z.B. bei JAKi, stellten eine Herausforderung dar, da unklar war, welchen Einfluss spezifische Therapieoptionen auf den Verlauf der SARS-CoV-2-Infektion haben würden. Es bestanden insbesondere Bedenken, dass aufgrund der Immunmodulation schwere Verläufe einer Infektion begünstigt werden könnten.

Die Grundlage zur Beantwortung der Frage nach den Verläufen einer SARS-CoV-2-Infektion bei ERE bildet das seit März 2020 etablierte deutsche COVID-19-Register für PatientInnen mit ERE, welches weltweit zu den größten Registern zur Erfassung von COVID-19 bei ERE zählt.

Ausgangspunkt des COVID19-Rheuma.de-Registers war die mangelnde Datenlage hinsichtlich Virusinfektionen der Atemwege bei ERE sowie die Notwendigkeit der schnellen Datengenerierung zur Ableitung von Handlungsempfehlungen für medizinisches Fachpersonal in der Pandemie. Bereits in der Anfangsphase der Pandemie entschied sich die Deutsche Gesellschaft für Rheumatologie, das COVID19-Rheuma.de-Register zu unterstützen und die Schirmherrschaft hierfür zur übernehmen. Diese Kooperation führte auch seitens der RheumatologInnen bundesweit zu einer hohen Akzeptanz des Registers, was sich in den Fallzahlen und Zahlen aktive beitragender ÄrztInnen im Register widerspiegelt.

Der Aufbau eines Registers war auch deshalb notwendig, da keine Sekundärdaten von Krankenkassen, Gesundheitsämtern oder kassenärztlichen Vereinigungen zur Verfügung standen, die für eine Einschätzung der COVID-19-Verläufe bei ERE hätten genutzt werden können.
Aufgrund des potenziell hohen Arbeitsaufwands hinsichtlich der Dokumentation seitens des medizinischen Personals stellte das Design eines solchen Registers ebenfalls eine

Herausforderung dar. Die Datenerfassung im Register musste im Rahmen der Patientenversorgung erfolgen, so dass bereits bei Aufbau des Registers die erfragten Parameter kritisch hinsichtlich der Notwendigkeit abgewogen wurden, um möglichst viele ÄrztInnen für das Register zu gewinnen, aber zeitgleich niemanden durch eine zu lange Eingabedauer der Registerdaten von einer erneuten Nutzung des Registers abzuhalten. Dies hatte neben der Sicherstellung der internationalen Vergleichbarkeit auch das Ziel, eine hohe Datenqualität sicherzustellen.

Die webbasierte Umsetzung des Registers ermöglichte, neben einer dezentralisierten Eingabemöglichkeit durch die NutzerInnen, die Reaktion auf dynamische Prozesse, die sich während der COVID-19-Pandemie regelmäßig ereignen, so dass diese im Register abgebildet werden konnten. Hierzu gehört z.B. die Erfassung bezüglich des Vorliegens einer Virusmutation oder COVID-19-Impfung.

Bereits 4 Wochen nach Etablierung des Registers erfolgte eine erste Auswertung von 104 Fällen (Originalarbeit *8*). In 32% der Fälle wurde eine COVID-19-assoziierte Hospitalisierung berichtet und die Letalität lag bei ca. 6%. Diese Daten deuteten zudem daraufhin, dass der Einsatz von Glukokortikosteroiden mit einem schweren COVID-19-Verlauf assoziiert sein könnte, wohingegen eine Biologikatherapie weniger häufig bei hospitalisierten ERE-PatientInnen berichtet wurde. Die Letalität sowie die COVID-19-assoziierte Hospitalisierung sank innerhalb eines Jahres von initial 6% auf 3,9% (Letalität) bzw. von initial 32% auf 22% (COVID-19-assoziierte Hospitalisierung) (Originalarbeit *8*).

Diese ersten Daten deckten sich mit Auswertungen des globalen Registers hinsichtlich Hospitalisierung und Letalität [216] sowie des Einflusses von Glukokortikosteroiden und Biologika bei ERE-PatientInnen auf eine SARS-CoV-2-Infektion [206].

4.3 Einfluss der Immunmodulation zur Behandlung der ERE im Kontext einer SARS-CoV-2-Infektion

Da der Einfluss einer SARS-CoV-2-Infektion auf PatientInnen mit ERE noch unklar war, zählten sie initial zur vulnerablen Patientengruppe. Daten aus Italien und den Vereinigten Staaten von Amerika deuteten dahingegend daraufhin, dass der Einsatz von Biologika nicht mit einem erhöhten Risiko für einen schweren COVID-19-Verlauf assoziiert ist [194,195]. In diesen Auswertungen wurde nicht innerhalb der Gruppe von Biologika differenziert, so dass auch der Einfluss von Rituximab entsprechend interpretiert wurde. Diese Schlussfolgerung deckte sich jedoch nicht mit den Beobachtungen aus dem deutschen COVID-19-Register. Aus diesem Grund wurden zwei letale COVID-19-Verläufe unter Therapie mit Rituximab veröffentlicht

(Originalarbeit *8* und Originalarbeit *8*). Die Erkenntnis, dass der Einsatz von Rituximab mit einem schwereren Verlauf einer SARS-CoV-2-Infektion assoziiert sein kann, hat dazu geführt, dass das Nutzen-Risiko-Profil vor Einleitung oder Wiederbeginn der Therapie stärker im Kontext der COVID-19-Pandemie abgewogen wurde und PatientInnen unter Therapie mit Rituximab intensiver bei einer SARS-CoV-2-Infektion ärztlich betreut wurden und weiterhin werden. Dies wirkte sich auch auf die internationale Betreuung von ERE-PatientInnen unter Therapie mit Rituximab aus. Zudem profitierten Rituximab-PatientInnen auch selbst von dieser Erkenntnis, da sie sich über das mögliche Risiko einer schweren Infektion informieren konnten und somit eigenverantwortlich entscheiden konnten, inwiefern sie sich einem möglicherweise gesteigerten Risiko aussetzen, aber auch wie konsequent sie Hygienemaßnahmen zur Vermeidung einer Infektion umsetzen.

Durch die frühe Kooperation mit nationalen und internationalen Arbeitsgruppen waren gemeinsame Auswertungen und vergleichende Analysen möglich. Diese gemeinsamen Auswertungen ermöglichten Analysen von Erkrankungen mit niedrigerer Prävalenz sowie Therapieoptionen mit geringerer Anwendungszahl. Dies führte bereits in der ersten Welle der Pandemie zu einer aussagekräftige Datenauswertung hinsichtlich der Rolle von Rituximab. In einer gemeinsamen Auswertung mit dem globalen Register konnte die Assoziation von Rituximab mit schweren COVID-19-Verläufen bzw. COVID-19-assoziierter Letalität nachgewiesen werden. In der ersten Welle der Pandemie war der Einsatz von Rituximab hierbei viermal stärker mit einer Letalität assoziiert als eine Monotherapie mit Methotrexat (Originalarbeit *8*). Auch andere Arbeitsgruppen konnten eine Assoziation von Rituximab mit schweren COVID-19-Verläufen nachweisen [217].

In einer weiteren Analyse wurde der Einfluss einer Therapie mit Abatacept, Interleukin-6-Inhibitoren, TNF-Hemmern, JAKi oder Rituximab im Kontext einer SARS-CoV-2-Infektion bei PatientInnen mit einer rheumatoiden Arthritis untersucht. Im Vergleich zu TNF-Hemmern war der Einsatz von JAKi und noch deutlicher der Einsatz von Rituximab mit COVID-19-bedingter Hospitalisierung und Letalität assoziiert (Originalarbeit *8*). Diese Daten untermauern, dass der Einsatz von Abatacept und Interleukin-6-Inhibitoren ein vergleichbares Risiko wie TNF-Hemmer aufweisen und somit eher nicht mit schweren COVID-19-Verläufen assoziiert sind (Originalarbeit *8*).

Bei der Interpretation der Daten hinsichtlich des Einsatzes von JAKi und Rituximab muss jedoch beachtet werden, dass JAKi erst seit 2017 im Einsatz sind und Rituximab leitliniengerecht erst nach Versagen eines TNF-Hemmers bei der rheumatoiden Arthritis zum

Einsatz kommt. [218]. Somit könnte es sein, dass diese PatientInnen per se eine höhere Krankheitsaktivität der ERE aufweisen und dadurch auch ein höheres Infektionsrisiko.

In der globalen Auswertung konnte zudem gezeigt werden, dass der Einsatz von Sulfasalazin mit schweren Verläufen einer SARS-CoV-2-Infektion assoziiert ist (Originalarbeit *8*). Dies ließ sich jedoch bei der Auswertung der deutschen Daten nicht bestätigen (Originalarbeit *12*). Ein möglicher Grund hierfür könnten länderspezifischen Verschreibungsverhalten und Verfügbarkeiten alternativer Therapieoptionen sein und untermauert eine nationale Datenerhebung zur Feststellung solcher Unterschiede.

Mit Voranschreiten der Pandemie ergaben sich weitere Erkenntnisse in Bezug auf den Einsatz von verschiedenen Immunmodulatoren. Sowohl in einer nationalen Auswertung als auch in einer globalen Auswertung konnten mildere Verläufe unter dem Einsatz von TNF-Hemmern nachgewiesen werden (Originalarbeit *8* und Originalarbeit *8*. Diese Resultate wurden ebenfalls von anderen Arbeitsgruppen beschrieben [21,23]. TNF-Hemmern werden sowohl bei inflammatorischen Arthritiden als auch bei Psoriasis und chronisch-entzündlichen Darmerkrankungen eingesetzt [204,205,218]. Diese Daten deuten auf ein gutes Sicherheitsprofil der Präparate im Rahmen einer SARS-CoV-2-Infektion hin.

Bei PatientInnen mit systemischem Lupus erythematodes oder einer Vaskulitis (Originalarbeit *8* und Originalarbeit *8* waren, neben den allgemeingültigen Risikofaktoren wie Alter und Komorbiditäten, dieselben Faktoren mit schweren COVID-19-Verläufen assoziiert wie in den Gesamtauswertungen. Dies schließt eine erhöhte Krankheitsaktivität, den Einsatz von Glukokortikosteroiden in höherer Dosierung sowie Immunsuppressiva, wie z.B. Cyclophosphamid und Rituximab, ein. Trotz der unterschiedlichen Pathomechanismen zeigt sich aus allen Daten, dass die beste Prävention vor einem schweren Verlauf von COVID-19 die Krankheitskontrolle der ERE darstellt, vor allem durch den Einsatz von steroidfreien Immunmodulatoren.

4.4 Handlungsempfehlungen zur bestmöglichen Betreuung von ERE-PatientInnen im Kontext der Pandemie

Die zunehmenden Erkenntnisse aus den Registerdaten führten zu einer Aktualisierung der Handlungsempfehlungen seitens der DGRh für die Betreuung von PatientInnen mit ERE im Rahmen der Pandemie. Dies resultierte konkret u.a. in folgenden Empfehlungen (*Originalarbeit 16)*:

- Die Einleitung oder Umstellung antirheumatischer Therapien sollten aufgrund der COVID-19-Pandemie weder unterbleiben noch verzögert werden

- Vor der Gabe von Rituximab sollte aufgrund des erhöhten Risikos für einen schweren COVID-19-Verlauf eine individuelle Nutzen-Risiko-Abwägung erfolgen und auch der Einsatz alternativer Therapien geprüft werden

4.5 Veränderungen des Infektionsgeschehens im Laufe der Pandemie unter Einsatz der Impfungen bei

Aufgrund der webbasierten Umsetzung war es zeitnah möglich, auf Änderungen im Pandemiegeschehen zu reagieren. Somit wurde das Register im Verlauf um weitere Parameter erweitert, die sich im Laufe der Pandemie als relevant erwiesen hatten,, beispielsweise der Nachweis einer Virusmutation oder die Darstellung von Infektionen trotz COVID-19-Impfung sowie der Einsatz von COVID-19-spezifischen Therapieoptionen.

Somit konnte gezeigt werden, dass seit Beginn der Pandemie in Phasen des Auftretens neuer Virusvarianten eine Zunahme der dokumentierten Infektionen bei ERE-PatientInnen festzustellen war. Im Jahr 2021 war gegenüber 2020 ein Rückgang von Hospitalisierungen und letalen COVID-19-Verläufe zu verzeichnen, am ehesten zu erklären durch die Verfügbarkeit der Impfung und milderen Virusvarianten. Diese Daten zeigen, dass sich bei PatientInnen mit ERE die gleichen zeitlichen Abläufe der Coronapandemie wie in der Allgemeinbevölkerung finden. Das Auftreten von Virusmutanten und die Verfügbarkeit von Impfungen hatten somit bei PatientInnen mit ERE einen vergleichbaren Einfluss auf die Auswirkungen der Pandemie wie in der Allgemeinbevölkerung (s. Abbildung 1).

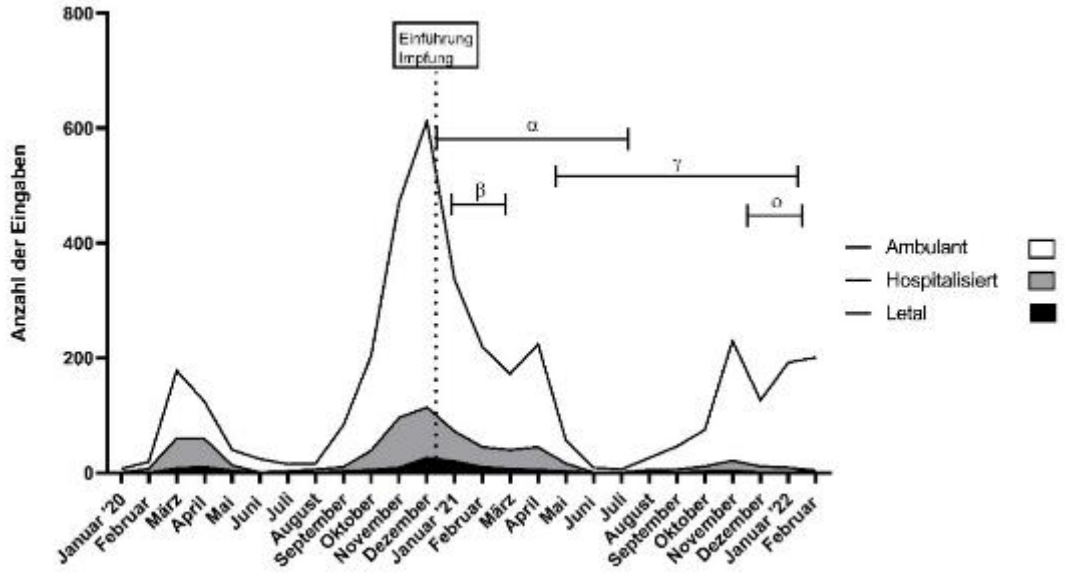

Abbildung 1: Verlauf der Daten im Register
Ambulante Fälle (weiß), hospitalisierte Fälle (grau) und letale Fälle (schwarz) wurden im zeitlichen Verlauf seit Januar 2020 dargestellt. Der Zeitraum der Dominanz der einzelnen Virusmutationen (α,β,γ,o) in Deutschland wurden eingefügt(↔).

5. Vorteile des Registers

Basierend auf der Registerplattform wurden weitere Projekte generiert, die sich mit der Thematik der COVID-19-Pandemie und ERE befassen.

Hierzu gehören:

1) Die Untersuchung des psychosozialen Einflusses der COVID-19-Pandemie auf PatientInnen mit ERE
2) Das COVID-19-Impfregister für PatientInnen mit rheumatischen Erkrankungen
3) Die Erfassung von schwerwiegenden Impfnebenwirkungen oder neuen Immunphänomenen bei ERE-PatientInnen in Bezug auf COVID-19-Impfungen
4) Das COVID-19-Register für PatientInnen mit neuromuskulären Erkrankungen (www.COVID19-NME.com)

Die deutschen Daten stellen inzwischen 23% der Daten aus dem europäischen Register dar und sind somit die größte Kohorte (Stand September 2022). Dies verdeutlich nochmals den hohen Stellenwert des COVID19-Rheuma.de-Registers zur nationalen und internationalen Pandemiebewältigung.

6. Limitationen des Registers

Eine Limitation des Registers stellt die nicht erfasste Darstellung des Krankheitsverlaufs der ERE vor der Infektion dar. Wie bei Registerdaten üblich, handelt es sich hier um retrospektive Datenanalysen. Es konnte somit keine Randomisierung erfolgen. Die Auswertung der Daten lässt daher nur eine Untersuchung von Korrelationen und Assoziationen zu.

Bei der Eingabe der Daten wird die Krankheitsdauer und die Anzahl und Art der Vortherapien nicht erfasst. Somit konnte nicht beurteilt werden, ob es Unterschiede innerhalb der Gruppe der PatientInnen gibt, die zum Zeitpunkt der Infektion eine moderate/hohe Krankheitsaktivität der ERE aufweisen. Dies ist ein wichtiger Faktor, der bei der Interpretation der Daten beachtet werden muss. Somit könnten diese PatientInnen insgesamt einen komplikativeren Verlauf der ERE aufweisen. Ein weiterer Faktor ist die Verfügbarkeit der eingesetzten Therapeutika. JAKi werden erst 2017 in Deutschland zugelassen. Auch hier könnte es sein, dass beispielsweise zuvor austherapierte PatientInnen unter diesen „neuen“ Therapie standen und somit bereits eine vielfache Immunmodulation in Vergangenheit erhalten haben.

Zudem ist bei der Dateneingabe auch ein Selektionsbias möglich. Die Dateneingabe erfolgt freiwillig und ohne finanzielle Honorierung des Aufwands, weshalb dies als möglicher Anreiz zur konsequenten Dokumentation wegfällt. Die Eingabe von mehrheitlich asymptomatischen bzw. milden Verläufen entkräftigt jedoch den Aspekt des Selektionsbias in gewissen Maße.

Um zumindest einen Vergleich mit SARS-CoV-2-infizierten Personen ohne ERE zu ermöglichen, wurde bereits in der Frühphase des Registers eine Kooperation mit dem LEOSS-Register initiiert. Die Limitation im Rahmen der Kooperation ist jedoch, dass im LEOSS-Register mehrheitlich hospitalisierte SARS-CoV-2-Infizierte aus universitären Zentren erfasst wurden und somit nur ein Vergleich der hospitalisierten PatientInnen aus beiden Registern möglich war bzw ist.

Um noch spezifischer den Einfluss spezifischer Immunmodulatoren untersuchen zu können, wäre daher ein prospektiver, randomisierter Studienansatz notwendig, welcher derzeit nicht umsetzbar ist, da Gesundheitsdaten nicht zentral gespeichert werden und somit keine eindeutige Aussage zur ERE vor Infektion getätigt werden kann. Durch eine prospektive Datenerhebung wäre zudem der Infektionsverlauf detaillierter zu erfassen.

7. Zusammenfassung und Ausblick

Klinisch-epidemiologische Registerdaten zur Untersuchung des Einflusses von ERE und Immunmodulation auf Infektionsgeschehen sind wichtige Werkzeuge für eine evidenzbasierte Formulierung von Handlungsempfehlungen. Aus den dargestellten Arbeiten in Bezug auf COVID-19 bei ERE lassen sich daher folgende Schlussfolgerungen ableiten:

1) Für ERE-PatientInnen gelten im Allgemeinen dieselben Risikofaktoren wie in der Allgemeinbevölkerung hinsichtlich schwerer COVID-19-Verläufe. Hierzu zählen u.a. das Alter, männliches Geschlecht und Komorbiditäten
2) ERE-PatientInnen mit pulmonaler Manifestation in Form einer interstitiellen Lungenerkrankungen weisen ein höheres Risiko für schwere COVID-19-Verläufe auf
3) Eine erhöhte Krankheitsaktivität, und damit verbunden der Einsatz von Glukokortikosteroiden, ist mit schweren COVID-19-Verläufen assoziiert, unabhängig von der Art der ERE
4) Zur Reduktion des SARS-CoV-2-Infektionsrisikos sowie des Risikos schwerer COVID-19-Verläufe sollte eine bestmögliche Krankheitskontrolle der ERE erzielt werden
5) Eine Krankheitskontrolle sollte mit steroidfreien Immunmodulatoren angestrebt werden

6) Rituximab und Cyclophosphamid, und in geringerem Maße auch JAKi, sind mit schweren COVID-19-Verläufen assoziiert
7) TNF-Hemmer sind mit milderen COVID-19-Verläufen assoziiert

Die Arbeit am Register verdeutlich die Notwendigkeit weiterer Untersuchungen von Infektionen im Kontext von ERE. Diesbezüglich sind weitere Projekte im nationalen und internationalen Austausch geplant. Unter anderem sollen die gewonnen Erkenntnisse im Rahmen von Influenza untersucht werden. Die bereits etablierten web-basierten Plattformen sollen hierfür erweitert werden.
Dadurch sollen weitere Erkenntnisse zu folgenden zukünftigen Forschungsansätzen gewonnen werden:

1) Einsatz von Immunmodulatoren im Kontext von COVID-19 bei bereits immunmodulierten ERE-PatientInnen
2) Einfluss der Immunmodulation und ERE auf andere Virusinfektionen der Atemwege bei ERE-PatientInnen
3) Verträglichkeit, Effektivität und Sicherheitsprofil von Impfungen im Allgemeinen bei ERE-PatientInnen

Um die Dateneingabe attraktiv zu gestalten, soll in Zukunft auch eine finanzielle Honorierung des Dokumentationsaufwands erfolgen. Durch eine Kooperation mit verschiedenen Zentren sollen zudem Virusinfektionen prospektiv und longitudinal analysiert werden.
Um eine doppelte Erfassung der Daten zu verhindern, wäre es sinnvoll, zukünftige Register in einer gemeinsamen Plattform zu vereinen. Die Etablierung einer studienorientierten Anpassung des Datenschutzes stellt jedoch noch eine Herausforderung dar.

8. Danksagung

Ich möchte mich bei allen sehr herzlich bedanken, die mir die Möglichkeiten und die Unterstützung gegeben haben, die Voraussetzungen der Habilitation zu erfüllen und die vorliegende Arbeit zu erstellen.

Mein Dank gilt meinem Mentor und Förderer Herrn Prof. Dr. Ulf Müller-Ladner, welcher mich nicht nur in der Etablierung des Registers unterstützte, sondern mir auch andere erfolgreiche Forschungsprojekte ermöglichte und mir mit Rat und Tat zur Seite steht. Er hat maßgeblich zu meiner Begeisterung für die Rheumatologie beigetragen.

Ein großer Dank gilt auch der Deutschen Gesellschaft für Rheumatologie, welche vom ersten Tag an das Register tatkräftig unterstützte. Insbesondere möchte ich hier Herrn Prof. Dr. Christof Specker sowie Herrn Prof. Dr. Hendrik Schulze-Koops danken, welche durch ihre hervorragende Unterstützung und wissenschaftliche Expertise zum Erfolg des Registers maßgeblich beigetragen haben.

Mein Dank gilt auch allen teilnehmenden RheumatologInnen, den PatientInnen und Patientenvereinigungen (hier sei insbesondere die RheumaLiga e.V. erwähnt). Dank ihres Engagements und ihrer Mitarbeit konnten all diese Daten im Register erfasst werden und somit wichtige Erkenntnisse gewonnen werden.

Ein großer Dank gilt meiner Mutter und meinem Bruder, die mich bei meinem Wunsch des Medizinstudiums uneingeschränkt unterstützt haben und mir auf dem bisherigen Weg mit allen zur Verfügung stehenden Mitteln zur Seite standen.

Zudem möchte ich mich bei meinen Freunden bedanken, die mir seelisch und moralisch in den letzten Jahren zur Seite standen und Verständnis dafür hatten, wenn ich aufgrund der Registerarbeit zeitlich eingebunden war.

Abschließend möchte ich mich bei meinem Ehemann Dr. Christian Fräbel bedanken, welcher mich bedingungslos begleitet und meine berufliche und wissenschaftliche Karriere unterstützt. Dank seiner Motivation sowie seine seelische und moralische Unterstützung war die Umsetzung des Registers erst möglich. Vielen Dank für die wertvollen Ratschläge und Mitarbeit am Register zu jeder Tages- und Nachtzeit.

Diese Habilitationsschrift stellt eine wunderbare Teamarbeit auf privater und beruflicher Ebene dar, die mich hoffentlich weiterhin begleiten wird.

9. Erklärung der Habilitationsleistung

Hiermit erkläre ich, dass ich die vorliegende Arbeit bzw. die mir zuzuordnenden Teile im Rahmen einer kumulativen Habilitationsschrift, selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nichtveröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Ich versichere, dass ich für die nach §2 (3) der Habilitationsordnung angeführten bereits veröffentlichten Originalarbeiten als Erst- oder Seniorautor fungiere, da ich den größten Teil der Daten selbst erhoben habe, für das Design der Arbeiten verantwortlich bin und die Manuskripte maßgeblich gestaltet habe. Für alle von mir erwähnten Untersuchungen habe ich die in der „Satzung der Justus-Liebig-Universität zur Sicherung guter wissenschaftlicher Praxis“ niedergelegten Grundsätze befolgt. Ich versichere, dass alle an der Finanzierung der Arbeiten beteiligten Geldgeber in den jeweiligen Publikationen genannt worden sind. Ich versichere außerdem, dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Weise einer anderen Prüfungsbehörde vorgelegt wurde oder Gegenstand eines anderen Prüfungsverfahrens war. Mit der Überprüfung meiner Arbeit durch eine Plagiatserkennungssoftware bzw. ein internetbasiertes Softwareprogramm erkläre ich mich einverstanden.

Giessen, den 21.09.2022

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10. Erklärung zu anderweitigen Habilitationen oder Habilitationsversuchen

Hiermit erkläre ich, dass ich an keiner Universität, weder im Inland noch im Ausland, bisher einen anderweitigen Habilitationsversuch oder eine anderweitige Habilitation unternommen habe. Ferner wird hiermit erklärt, dass ich mich nicht vor Abschluss des Habilitationsverfahrens an anderer Stelle zur Habilitation melden werde.

Giessen, den 21.09.2022

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