

## COMMENTARY

## Suicidal risk with isotretinoin treatment – a never-ending story

Since 2000, there is an ongoing discussion about the potential risk of suicide ideations and real suicide correlated with the isotretinoin therapy of moderate-to-severe acne. The starting point was the suicide of a 17-year-old son of an US Congressman who blames Accutane and called the federal regulators to strengthen warnings to the public about the drug's possible psychiatric side-effects.<sup>1</sup> Bart Stupak Jr. shot himself in the head with his father's gun in the early hours of 14 May 2000. Stupak was popular in school, a football player, and killed himself after a prom-night party. This event leads to the ongoing discussion about a potential risk of suicides when taking isotretinoin for acne, and at PubMed, you will find 91 papers about the special topic. But it is not that easy to answer the question about a real cause of isotretinoin leading to depression and potential suicide when you look with a scientific point of view to the question. Even in 1998, warnings about depression and other psychiatric side-effects were added to the drug's patient information leaflet. In section four, it states that 'some people have had thoughts about hurting themselves or ending their own lives (suicidal thoughts), have tried to end their own lives (attempted suicide) or have ended their lives (suicide). These people may not appear to be depressed'. Roaccutane, a brand name of the drug isotretinoin, is used by about 30 000 people in the UK each year. Data from NHS Digital show prescriptions for isotretinoin rose from 34 283 to 69 040 between 2008 and 2018. Ten of 12 recorded deaths by Roaccutane users in 2019 were suicide.

It is well known that the psychogenic impairment in acne patients correlates despite of which therapy is used with social anxieties and depression.<sup>2,3</sup> One of the first papers due to acne impairment was already pointed out 1948 by Sulzberger and Zaidens<sup>4</sup> who published their statement: 'There is probably no single disease which causes more psychic trauma, more maladjustment between parents and children, more general insecurity and feeling of inferiority and greater sums of psychic suffering than does acne vulgaris'. Furthermore, a study by physicians in Yorkshire, UK, reveals that nine of 18 dermatologic patients who committed suicide over a 20-year span were males who suffered from severe acne.<sup>5</sup>

In a review by Marqueling and Zane,<sup>6</sup> they found nine studies that met the qualifying criteria for their analysis. Rates of depression among isotretinoin users ranged from 1% to 11% across studies, with similar rates in oral antibiotic control groups. Overall, studies comparing depression before and after treatment

did not show a statistically significant increase in depression diagnoses or depressive symptoms. Some studies demonstrated a trend towards fewer or less severe depressive symptoms after isotretinoin therapy. This decrease was particularly evident in patients with pretreatment scores in the moderate or clinical depression range. No correlation between isotretinoin use and suicidal behaviour was reported.<sup>6</sup>

So, a recently large population-based study by Droitcourt *et al.* (7/8) in this journal gives new evidence for answering the important question about isotretinoin treatment and suicidal attempts. Droitcourt *et al.* performed a comprehensive case series of suicides and SAs under isotretinoin, and a case-control study, using Nationwide French Health Insurance database. They conclude that there is no higher risk of suicide during isotretinoin treatment of acne in comparison with the controls in 328 018 subjects started a course of isotretinoin between 1 January 2010 and 31 December 2014. A total of 184 patients were hospitalized for a suicidal attempt, and more than 50% of them continued the medication. The authors demonstrate a clear high correlation with risk-prone profile of psychiatric disorders or anxiety detectable at the time of treatment initiation.<sup>7</sup>

The main two questions that remained are the following: first: is there a higher correlation of suicidal attempts in patients after the beginning of isotretinoin treatment? and second is the risk of suicidal attempts in not treated severe acne with isotretinoin higher regarding suicides in comparison with those who are treated.

The discussion is still controversial, and many studies with large sample sizes are looking to the question. Jick *et al.*<sup>9</sup> analysed 7195 isotretinoin users and compared them with 13 700 oral antibiotic users with acne from the Canadian Saskatchewan Health Database and for 340 isotretinoin users and 676 oral antibiotic users with acne from the United Kingdom General Practice Research Database. The relative risk estimate for suicide and attempted suicide was 0.9 (95% confidence interval, 0.3–2.4) when comparing current isotretinoin exposure with non-exposed.<sup>8</sup> So, they found the same results as the new study of the French patients by Droitcourt *et al.*<sup>7</sup> and a very similar study from Erdogan *et al.*<sup>10</sup> both isotretinoin and antibiotic treatments were shown to improve the quality of life, social anxiety and obsessive-compulsive symptoms in acne patients. The authors stated, however, clinicians should be careful about psychiatric side-effects in patients using isotretinoin.<sup>10</sup>

Despite numerous case reports linking isotretinoin to depression, suicidal ideation and suicide, there is, as yet, no clear proof of an association.<sup>11</sup> But van Broekhoven *et al.*<sup>12</sup> published that

although any causal relationship has not been identified, such a relationship cannot be ruled out.

In contrast, other authors who reviewed the literature for case reports and database studies and showed a clear association, came to the result that this association is biologically plausible.<sup>13</sup> Since isotretinoin crosses the blood–brain barrier, it affects the expression of a broad spectrum of genes in the limbic structures, thus affecting the function of the dopaminergic, serotonergic and noradrenergic neurons involved in the regulation of mood and emotion. Borovaya *et al.*<sup>14</sup> suggested that isotretinoin in high concentrations inhibits hippocampal neurogenesis and induces apoptosis of hippocampal cells. However, some studies do not confirm this pathogenic role, and isotretinoin was even reported to have a therapeutic effect in acne-associated depression.<sup>14</sup> Although prospective studies have opposite results, limitations might make them unsuitable to identify a subgroup of patients who may be at risk of developing depression or suicidal ideation with ITT.<sup>13</sup> Kellett and Gawkrödger<sup>15</sup> looked in a prospective study to the different treatment phases with isotretinoin (week 1–week 8) and compared to the second phase (week 9–week 16). Patients reported significant improvements in the cognitive–affective features of depression during the first phase of treatment, but not during the second phase. Corresponding improvements in the somatic symptoms of depression and hopelessness were not found.<sup>15</sup>

The Australian dermatologist recognized the risk of suicidal attempts more seriously than other countries and published their guidelines, while the possible causal association between isotretinoin and mental illness remains a controversial topic, a systematic review has presented evidence to support this relationship. But on the other hand, Rowe *et al.*<sup>16</sup> stated that successful treatment of acne can improve the quality of life and reduce levels of anxiety and depression in these individuals. The current treatment of choice for severe or refractive acne is isotretinoin, a retinoid, and they suggest the safe prescribing of isotretinoin in adolescents.<sup>16</sup>

Interestingly, some other psychiatric aspects occur together with isotretinoin treatment. Patients with bipolar disorder had possibly an increased risk for a clinical exacerbation of symptoms undergoing treatment with isotretinoin. A few studies also seem to suggest a possible link between isotretinoin and psychosis. Nonetheless, studies point out a link between retinoid dysregulation and schizophrenia through modulation of dopamine receptors.<sup>17</sup> Another case report of nine patients who were reported to the department and treated with affective disorders (AD) while undergoing isotretinoin (INN) therapy. The predictors of occurrence of psychiatric disorders included a family history of AD and a prior episode of mental disorders.<sup>18</sup>

A recent retrospective study evaluated reports of psychiatric adverse events with isotretinoin as the primary suspect drug in the US Food and Drug Administration's Adverse Event Reporting System from 1997 through 2017. Publicly available data on

number of patients enrolled in the iPLEDGE program were used to calculate rates of completed suicide per 100 000 patients enrolled in iPLEDGE in 2009 and 2010. All data were analysed between 1 July 2018 and 31 January 2019. Between 1997 and 2017, 17 829 psychiatric adverse events with isotretinoin use were reported to the US Food and Drug Administration, with depressive disorders, emotional lability and anxiety disorders reported most frequently. More than half (52.5%) of all events occurred in 10- to 19-year-old individuals. The rates of completed suicide were 8.4 in males and 5.6 in females' suicides per 100 000 patients enrolled in iPLEDGE in 2009 and 2010, respectively. These data suggest that the rate of completed suicide in patients taking isotretinoin may be lower than that of the general US population. The authors demonstrate that although no causal link between isotretinoin and psychiatric risk has been established, patients taking the drug appear vulnerable to psychiatric concerns. They emphasize the frequent consultation together with looking for psychiatric side-effects in those patients.<sup>19</sup>

If this risk of suicides in acne patients with isotretinoin is compared to, for example, body dysmorphic disorder patients where suicidal reactions occur in about 15% of the cases,<sup>20,21</sup> The risk of suicide in high traditional masculinity is 2.4 times higher in comparison with other male behaviour.<sup>22</sup>

A recent article outlines the advantages and disadvantages of standard, high-dose and low-dose isotretinoin regimens; discusses the current status of controversies surrounding isotretinoin also including depression/suicide, pregnancy, and inflammatory bowel disease and reviews monitoring recommendations and treatment for hypertriglyceridemia and elevated transaminase levels; and discusses common adverse effects seen with isotretinoin, along with their treatment and prevention.<sup>23</sup>

Suicide is fortunately rare, and it seems that following the FDA, isotretinoin use is one-fifth the number expected by looking at rates in the general population. But every suicide who must not be is one too many. Depressed persons need not avoid isotretinoin with regard to all the studies. Severe acne itself often lowers mood and reduces self-esteem, so effective treatment can improve emotional health.

So, for dermatologists who treat acne patients with isotretinoin with regard to common guidelines should have the potential risk of psychiatric disorders in acne patients in general, especially depression and anxiety disorders that correlate highly with suicidal attempts in mind. Useful very short questionnaires for practical use are the patient health questionnaire-2 and the patient health questionnaire-9 are validated instruments that enable dermatologists to efficiently screen for depression before and after isotretinoin is initiated.<sup>24</sup> Karakulo-Juchnowicz *et al.*<sup>18</sup> showed in their case study about psychiatric disorders in acne patients during isotretinoin therapy the onset of AD was in most cases preceded by prodromal symptoms such as headaches, sleep disorders, fatigue, drowsiness or general weakness that could be asked in the routine follow-ups.

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### Conflicts of interest

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