Cystic fibrosis transmembrane conductance regulator biomarkers in 'real life': can we evaluate individual efficacy of cystic fibrosis transmembrane conductance regulator therapy?

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Silke van Koningsbruggen-Rietschel and Lutz Naehrlich

Ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, is approved for the treatment of patients with cystic fibrosis (CF) with the *G551D* mutation aged 6 years or older. To evaluate the efficacy of this CFTR-modulating therapy (CFTR-MT) biomarkers such as sweat chloride (SC), nasal potential difference (NPD) and intestinal current measurement (ICM) have been implemented.

All three biomarkers play a crucial role in diagnosing CF, especially in questionable cases. Experiences in applying several CFTR measurements in individual patients to evaluate a CFTR-MT have been scarce so far.

SC is a highly feasible biomarker for assessing CFTR function in an organ not involved in chronic inflammation/infection and can reflect even small changes. NPD has the advantage of representing CFTR function in the respiratory system, the organ most responsible for survival in CF. ICM is feasible, but does not represent CFTR in the respiratory system and some patients are reluctant to undergo rectal biopsies [DeBoeck, 2013].

A review article by DeBoeck and colleagues provided useful information to support the promotion of these CFTR biomarkers to surrogate endpoints in clinical trials and to guide further research in this area [DeBoeck *et al.* 2013]. We discuss the practical use of these biomarkers in 'real-life' situations for evaluating the efficacy of personalized CFTR-MT in a specific patient. We report the results of these biomarkers in a small sample size survey of eight patients with CF receiving ivacaftor and discuss the difficulty in identifying clear responders to CFTR-MT in view of the fact that long-term side effects are still unknown.

Eight patients (*G551D* heterozygotes; aged 11–41 years) were treated with ivacaftor as a CFTR-MT. To evaluate efficacy, we implemented a surveillance protocol including forced expiratory volume in 1 second (FEV_1) and the biomarkers described above (EC-approved; NPD-performance [after certification] according to the standard operating procedures [SOP] of the Therapeutics Development Network [TDN], Bethesda, MA, USA; ICM [only Giessen] [after certification] according to the European Cystic Fibrosis Society-TDN-SOP).

All patients showed marked, constant improvement in SC; seven patients changed their category of CF (chloride $>$ 60 mmol/L) to intermediate (30–60 mmol/L) or normal ($<$ 30 mmol/L) (Table 1). In ICM, two patients demonstrated an improvement in CFTR function from CF category to the normal category. Further ICM measurements were denied. In NPD, slight improvements within the pathological category were observed in three patients. In six patients the absolute FEV_1 improved by more than 5%.

We observed marked improvements in SC and ICM with changes in category (pathological to intermediate or normal in SC and pathological to normal in ICM), whereas NPD did not show this clear improvement (at most, slight improvement within the pathological category); however, the evaluation of ICMs has to be interpreted cautiously as only two measurements could be performed. In the ivacaftor trials, FEV_1 and SC showed marked improvements [Ramsey *et al.* 2011], but changes in SC were more

Correspondence to:
Silke van Koningsbruggen-Rietschel, MD
CF-Center, Children's Hospital, University of Cologne, Kerpener Str. 62, 50924 Cologne, Germany
Silke.vanKoningsbruggen@uk-koeln.de

Lutz Naehrlich, MD
Department of Pediatrics, Justus-Liebig-University Giessen, Giessen, Germany

Table 1. Demographics and clinical CFTR-response in eight patients with one G551D mutation receiving ivacaftor treatment.

Age (years)	Mutation	Gender	*Pseudomonas aeruginosa* status	FEV_1 predicted (%)	Sweat chloride (mmol/L) Cut-off < 60 mmol/L	NPD CFTR response average $\Delta 0Cl^-$ + Iso (mV) Cut-off < –7.7 mV	ICM CFTR response average ΔIsc ($\mu A/cm^2$) Cut-off >20 $\mu A/cm^2$
11	*R709X*	Male	Negative	116 / **121** / 111	113 / **56 / 32**	–3.24 / 2.77 / –2.63	NA
16	*G542X*	Female	Negative	83 / 71 / 78	89 / **15 / 17**	2.64 / 1.62 / 5.36	NA
18	*F508del*	Male	Negative	102 / **121 / 114**	92 / **12** / NA	–2.95 / NA / –4.56	NA
20	*E60X*	Female	Positive	81 / 83 / 52*	113 **/ 43 / 52**	8.80 / **4.09 / 2.26**	NA
25	*F508del*	Male	Negative	76 / **84** / 77	94 / **36 / 41**	3.88 / **0.31 / 0.05**	17.9 / **28.0** / NA
26	*N1303K*	Male	Negative	85 / **102 / 104**	100 **/ 44 / 46**	6.20 / 4.83 / 6.18	NA
30	*F508del*	Male	Positive	60 / 61 / **67**	102 / 61 / 67	4.87 / 8.36 / 5.56	NA
41	*F508del*	Female	Positive	48 / 52 / **53**	97 / **41 / 48**	6.41 / **1.84 / 1.30**	–2.12 / **43.2** / NA

In cells with three values the first value represents the baseline measurement; the second and third values represent results at 1–3 months and 6–15 months, respectively.
Pseudomonas aeruginosa status: negative or positive during time interval of survey.
NPD CFTR response: the sum of the response to zero chloride + isoproterenol (both nostrils averaged). ICM CFTR response: the sum of the response to Forskolin/3-isobutyl-1-methylxanthine (IBMX) + carbachol + histamine.
Bold face numbers represent improvements in absolute FEV_1% pred. that were more than 5% from baseline, noncystic fibrosis reference ranges for sweat chloride (< 60 mmol/L), improvement of NPD ($\Delta 0Cl^-$ + Iso < - 3 mV; noncystic fibrosis range < -7.7 mV) and of ICM (> 20 $\mu A/cm^2$) [Bagheri-Hanson *et al.* 2014].
*pulmonary exacerbation.
CFTR: cystic fibrosis transmembrane conductance regulator; FEV1: forced expiratory volume after 1 second; ICM: intestinal current measurement; NPD: nasal potential difference; NA: not applied.

impressive than changes in NPD. None of the NPD measures correlated with changes in FEV_1 nor did SC [Rowe *et al.* 2013]. ICM was not performed.

When SC improves, particularly with a change in category, we tend to be convinced of clinical efficacy because SC reflects CFTR function without confounding factors. We might even conclude that SC may reflect compliance because pharmacokinetics are not routinely measured clinically. One patient remained in the pathological category (chloride 61 + 67 mmol/L) and stopped ivacaftor after some months due to severe anxiety about future side effects. We hypothesized that reduced compliance could explain the lack of marked SC improvement.

FEV_1 is influenced by 'physiological', 'genetic' and 'environmental' factors which are not influenced by CFTR-MT [DeBoeck *et al.* 2013]. Only 50% of FEV_1 variability can be explained by inherited factors, including CFTR [Stanke *et al.* 2011]; other important factors include genetic modifiers, epigenetic effects and environmental determinants. Our inconsistent FEV_1 results may reflect this individual course of disease. The lack of improvement in NPD (respiratory epithelium) could also be explained by these factors, for example, inflammation, scarring or passive cigarette-smoke exposure. Wilschanski and colleagues examined healthy controls, men with congenital bilateral aplasia of the vas deferens, pancreatic-sufficient CF and pancreatic-insufficient CF patients according to the genotype–phenotype relationship between SC and NPD, and demonstrated that SC seems to be more sensitive than NPD towards the severe end of the spectrum [Wilschanski *et al.* 2006].

Several questions remain, including: which biomarker(s) should be used to suggest clinical benefit? How many biomarkers should show which degree of improvement or even a change in category? Fortunately, standardization of these techniques has advanced with SOPs and certification processes, but we lack validated standards for interpreting the results, for example, for NPD and ICM [Naehrlich *et al.* 2014]. In some studies, group-specific differences may be statistically significant, but how can we define clinical relevance in individual patients during CFTR-MT?

To date, no biomarker has been found to correlate with FEV_1. Previous attempts to correlate SC with

FEV_1 have been unsuccessful; random variation or environmental factors were considered possible explanations [Davis *et al.* 2004]. In addition, it still remains to be determined whether changes in biomarkers can be translated into individual patient mortality. Simmonds and colleagues showed that neither NPD nor SC was associated with increased survival on examining long-term survival in patients with homozygous F508del [Simmonds *et al.* 2011] Furthermore, different biomarkers may be relevant in different pathophysiological processes and disease stages [Ramsey *et al.* 2011]. So how often should we measure biomarkers?

Finally, the question remains: how can we translate results into the efficacy/nonefficacy of an individual therapy, in terms of mortality or even long-term survival? Even when more biomarkers are added to the surveillance protocol, such as body mass index, mucociliary clearance, beta-adrenergic sweat secretion rate, gastrointestinal pH and sputum inflammation [Rowe *et al.* 2014], this question remains unanswered. Novel emerging clinical endpoints such as lung clearance index measurements, intestinal organoids, chest computed tomography scans or nasal cell banks might contribute to more insight in the future. However, clinical-relevant differences for each method remain to be defined.

Up to now, a change in category with at least one biomarker might seem convincing to patients and CF teams to justify continuing ivacaftor, independent of changes in FEV_1. Longitudinal monitoring of CF patients receiving ivacaftor by applying all CFTR functional tests might allow further insights into the evaluation of clinical effects until we have proven the relationship between biomarkers and survival or at least long-term benefit.

Conflict of interest statement

SKR has participated in clinical trials of Vertex Pharmaceuticals. LN has received lecture and advisory board honoraria from Vertex Pharmaceuticals GmbH (Germany) and participated in clinical trials of Vertex Pharmaceuticals.

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