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REVIEW

The impact of personalised therapies on respiratory medicine

J. Stuart Elborn

ABSTRACT: Stratified approaches to treating disease are very attractive, as efficacy is maximised by identifying responders using a companion diagnostic or by careful phenotyping. This approach will spare non-responders from potential side-effects. This has been pioneered in oncology where single genes or gene signatures indicate tumours that will respond to specific chemotherapies. Stratified approaches to the treatment of asthma with biological therapies are currently being extensively studied. In cystic fibrosis (CF), therapies have been developed that are targeted at specific functional classes of mutations. Ivacaftor, the first of such therapies, potentiates dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) protein Class III mutations and is now available in the USA and some European countries. Pivotal studies in patients with a G551D mutation, the most common Class III mutation, have demonstrated significant improvements in clinically important outcomes such as spirometry and exacerbations. Sweat chloride was significantly reduced demonstrating a functional effect on the dysfunctional CFTR protein produced by the G551D mutation. Symptom scores are also greatly improved to a level that indicates that this is a transformational treatment for many patients. This stratified approach to the development of therapies based on the functional class of the mutations in CF is likely to lead to new drugs or combinations that will correct the basic defect in many patients with CF.

KEYWORDS: Cystic fibrosis, personalised medicine, potentiator therapy

Treatment approaches for respiratory diseases have generally involved all patients with a given condition receiving the same therapy. This assumes that the underlying disease pathophysiology is similar for all patients and that all patients will have the same treatment response to a therapy. As this is invariably not the case, there are increased efforts to develop personalised therapies. The series of articles in the current issue of the *European Respiratory Review* has explored this approach in some detail, describing its application to respiratory diseases, in general, and cystic fibrosis, in particular [1–4].

Early examples of personalised or stratified medicine mostly stem from the field of oncology [2]. An archetypal example is trastuzumab, better known as Herceptin®, for adjunctive treatment of patients with human epidermal growth factor receptor 2 (*HER2*) gene-amplified breast cancer [5]. Two clinical trials have shown that trastuzumab was associated with a 33% reduction in the risk of death ($p=0.015$) [6] and improved 3-yr recurrence-free survival [7], compared to patients who did not receive therapy. In the field of

endocrinology, PEARSON *et al.* [8] reported that diabetic patients with mutations in the gene encoding a subunit of the pancreatic ATP-sensitive channel responded better to sulfonylurea therapy treatment than insulin.

Examples of personalised medicine in the field of respiratory medicine are also mostly in the area of oncology, where knowledge of tumour-related mutations has been used to refine the selection of chemotherapy. The kinase inhibitor crizotinib was specifically developed to treat nonsmall cell lung cancer (NSCLC) patients who have a chromosomal transformation that activates the anaplastic lymphoma kinase (*ALK*) gene [9]. Updated results of a phase I trial assessing crizotinib in *ALK*-positive NSCLC patients showed that 87 (60.8%) out of 143 patients had an objective response (95% CI 52.3–68.9%) and median progression-free survival was 9.7 months (95% CI 7.7–12.8 months) [10].

Extending these approaches to non-malignant respiratory disease presents exciting possibilities, and has already led to new approaches to phenotyping in areas such as chronic obstructive

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TABLE 1 Mechanism of action and targets of emerging cystic fibrosis transmembrane conductance regulator (CFTR) modulators

Mutation class	Nature of defect	Example mutations	Pancreatic function [#]	Modulator strategy	Agents in development
I	Biosynthesis	G542X	Insufficient	Suppressor Suppressor and potentiator [†]	Ataluren
II	Trafficking	F508del	Insufficient	Corrector Corrector plus potentiator	VX-809 plus ivacaftor ⁺ VX-661 plus ivacaftor ⁺
III	Channel gating	G551D	Insufficient	Potentiator	Ivacaftor (FDA approved, G551D) Other gating mutations? [†]
IV	Channel conductance	R117H	Sufficient	Potentiator? [†]	No clinical data available
V	Low transcript levels	3849+10kb C->T	Sufficient	Potentiator? [†]	No clinical data available

FDA: US Food and Drug Administration. [#]: when *in trans* with a non-functional CFTR mutation; [†]: theoretical approach based on nature of defect and known drug mechanism; ⁺: currently in phase II trials. Reproduced from [15] with permission from the publisher.

pulmonary disease, asthma, lung fibrosis or cancer using, for example, serum markers, blood count, clinical phenotypes, somatic genotype, germinal genotype and co-morbidities. Not all of these approaches will necessarily end up being applicable in practice, but they are worthy of investigation. Multiple genome-wide association studies (GWAS) have been published in respiratory medicine, mostly relating to genes associated with asthma development or susceptibility to chronic obstructive pulmonary disease [11]. Recently, there has been increased interest in the role of interleukin (IL)-33 in asthma. IL-33 is associated with promoting a type-1 T-helper cell response and may play a role in chronic inflammation and airway remodelling [12]. Moreover, IL-33 gene polymorphisms have been identified in various asthma GWAS analyses [2, 13, 14].

The recent identification of the ability of ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) modulator, to treat some patients with cystic fibrosis (CF) is the first example in which a stratified medicine approach has resulted in a major change in therapy for patients with this disease who carry the gating channel mutation, *G551D* [15].

CFTR MODULATORS: A POTENTIAL PARADIGM FOR "PERSONALISED RESPIRATORY MEDICINE"

Ivacaftor, formerly known as VX-770, was identified from a library of 228,000 diverse drugs using high-throughput screening [13]. The candidate agent was subsequently shown to increase the channel opening probability of *G551D* CFTR by approximately six-fold and to partially restore fluid regulation and cilia beating in cultured CF human bronchial epithelia with the *G551D/F508del* genotype [3, 16]. These results provided convincing evidence and rapidly advanced into clinical trials.

The efficacy and safety of ivacaftor was evaluated in two 48-week, randomised, double-blind, placebo-controlled trials in patients aged 6–11 yrs (ENVISION study) and patients aged ≥12 yrs (STRIVE study) who have at least one copy of the *G551D-CFTR* mutation [4].

Ivacaftor was shown to result in a rapid and sustained improvement in lung function through to week 24 and this effect continued through to week 48. Sweat chloride concentration significantly decreased in both trials to levels below the diagnostic cut-off point for CF. Moreover, treated patients in the ENVISION

and STRIVE studies demonstrated significant improvements in body weight. The most common reported adverse events were abdominal pain, diarrhoea, dizziness, rash, upper respiratory tract reactions, headache and bacteria in sputum.

A separate phase II trial, DISCOVER, assessed the efficacy of ivacaftor in patients homozygous for the *F508del-CFTR* mutation [17]. No observed clinical effect was measured between the treatment and placebo arms, suggesting that CFTR potentiation with ivacaftor alone will not benefit CF patients who are homozygous for *F508del-CFTR*. The reason for this is clear; ivacaftor is a CFTR potentiator that targets gating defects in *G551D-CFTR* channels. *F508del* mutation defects, however, can only be repaired through use of a CFTR corrector, such as VX-808 [3].

Emerging CFTR modulators

Ivacaftor, the first CFTR modulator to be approved for clinical use, can be only prescribed to approximately 4–5% of CF patients who have the *G551D* mutation. If successful, other emerging CFTR therapies will hold greater promise to treat many more CF patients (table 1).

The read through agent, ataluren, is undergoing clinical trials to treat CF in patients with mutations caused by premature stop codons. Ataluren was linked to improvement in cough over 3 months and increases in CFTR activity, as measured by the nasal potential difference [18, 19]. Results of a phase III pivotal trial are expected soon and are eagerly awaited.

VX-809 (or lumicaftor) is a CFTR corrector that has been assessed in a phase IIa study of patients homozygous for the *F508del-CFTR* mutation. The drug, which was well tolerated with no significant safety signals, caused a moderate reduction in sweat chloride compared to placebo [20]. Surprisingly, no other clinically significant improvements were measured. Nevertheless, the trial provided a basis for investigation into the safety and efficacy of lumicaftor plus ivacaftor combination therapy in CF patients homozygous or heterozygous for the *F508del-CFTR* mutations [21].

Impact of personalised medicine on CF care

Based on experience with ivacaftor, the potential for CFTR modulators (alone or combined) to transform the lives of a significant number of CF patients is exciting. This optimism must

also be guarded: many trials of promising drug candidates are still in their infancy and the long-term effect of these therapies is still unknown. Nevertheless, as personalised therapies, CFTR modulators truly represent a milestone in CF treatment.

CONCLUSION

The theoretical benefit of personalised respiratory medicine is almost beyond reproach. However, despite an increasing number of success stories, such as crizotinib, trastuzumab, imatinib and ivacaftor, the development of personalised therapies remains a significant challenge; one that is perhaps above and beyond those typically faced by the pharmaceutical industry, which also has to consider how to recoup the not-insignificant development costs in a specialised and limited market. Overcoming these challenges will involve input and consensus from funders, scientists, providers, patients and regulatory authorities. Nevertheless, personalised medicine has the genuine potential to revolutionise healthcare as we know it.

STATEMENT OF INTEREST

J.S. Elborn has received fees for consultancy and speaking from Vertex. He received payment as a grant for three clinical trials (€50,000).

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