Personalised medicine for cystic fibrosis: Treating the basic defect


Published in:
European Respiratory Review

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
Copyright ERS 2013.
This is an open access Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits use, distribution and reproduction for non-commercial purposes, provided the author and source are cited.

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.
EDITORIAL

Personalised medicine for cystic fibrosis: treating the basic defect

J. Stuart Elborn

THE RIGHT TREATMENT, FOR THE RIGHT PATIENT, AT THE RIGHT TIME

The concept of personalised or stratified therapies is not a new one. For centuries, physicians have observed that the manifestation of a disease and its response to intervention can vary according to many factors including age, sex, ethnicity, diet and the type of administered drug [1]. Hippocrates, for example, observed over 2,000 years ago that patients can respond very differently to various medications [2].

It wasn’t until 1998, however, that the term “personalised therapy” was first used [3]. This can be defined as a therapy prescribed using molecular profiling technologies to tailor the right therapeutic strategy for the right person at the right time. The therapy is typically accompanied by a “companion test” or clinical biomarker to identify responders whilst assessing therapeutic response.

Personalised medicine is often used synonymously with the expression “stratified medicine”. There are, however, subtle differences between both of these terms as illustrated by the patient therapeutic continuum described by Trusheim et al. (fig. 1) [4].

Most of today’s medical practice is empirical, with drug development targeted at treating large populations of patients; an example is non-steroidal anti-inflammatory drugs, which have high efficacy in almost the entire population (fig. 1).

Other agents, however, may have a significant number of non-responders, as is the case with selective serotonin-reuptake inhibitors for the treatment of depression. Identifying and specifically treating this subpopulation of patients is stratified medicine [5]. A well-known example is the monoclonal antibody trastuzumab, which represents one of the first targeted adjunctive therapies for the treatment of breast cancer in patients who overexpress HER2/neu, the gene for human epidermal growth factor receptor 2 [6].

The most specific level in the patient therapeutic continuum of care is personalised or individualised medicine. An extreme example of this is development of a vaccine for an individual patient. Oncophage and provenge are both examples of therapeutic “cancer vaccines” for the treatment of renal cell carcinoma and prostate cancer, respectively [7]. Both therapies are tailor made to raise a specific immune response against the molecular profile of the patient’s cancer.

PERSONALISED MEDICINE AND RESPIRATORY DISEASE

Respiratory medicine is at the forefront of personalised medicine, as exemplified by recent advances in asthma research. Asthma, as a complex multifactorial disease, poses a significant challenge for genomics-led drug discovery. The disease pathophysiology involves the interaction of multiple genes with each other, and with a plethora of environmental factors, such as allergens, pathogens and air pollution [8]. Nevertheless, over the past few years there has been significant progress in identifying asthma-associated genes, primarily driven by genome-wide association studies [9, 10]. Gene expression profiling will not only allow accurate profiling of responders and non-responders to particular therapies, but will also aid identification of novel therapeutic targets for drug discovery. Ultimately, this could lead to asthma management plans tailored to individual patients.
Editorial: Personalised Medicine in CF

J.S. Elborn

Cystic Fibrosis as a Paradigm for Prospective Personalised Drug Development

Cystic fibrosis (CF) is an inherited disease affecting the respiratory, digestive and reproductive systems [11]. The disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, colloquially referred to as the CF gene. When CF was first described in 1938, the predicted survival age of patients was only 6 months [12]. Over the decades the prognosis has incrementally increased due to the introduction of multiple therapies that treat the symptoms of CF (fig. 2). Despite these improvements, however, the predicted survival age of CF patients was reported as only 37 yrs as recently as 2009 [12].

CF as a disease area is well positioned to take advantage of personalised medicine. It is a monogenic disorder (i.e. is the result of mutation(s) in a specific gene) and has a well-characterised pathophysiology with clear therapeutic targets [13]. Furthermore, diagnosis of CF often utilises genetic testing, leading to a high rate of mutation identification in the CF population [14]. Research into CFTR gene mutations continues to reveal correlations between various CFTR genotypes and disease severity [15].

Recently, a first-in-class disease-modifying CF treatment was approved in the USA and Europe for patients with a specific mutation in their CFTR gene. The clinical development of this small molecule CFTR modulator (ivacaftor) serves as a promising example of how personalised therapies can transform the therapeutic landscape.

This series of articles has been developed based on the symposium “Personalized medicine: Treatment advances and the genetic medical revolution”, which was held during the 2012 European Respiratory Society Congress in Vienna, Austria. The articles in this series will discuss the potential impact of personalised medicine approaches on respiratory medicine in light of the recent development of CFTR modulators.

The prospects of developing personalised therapies in the field of respiratory medicine look promising, as illustrated by the ivacaftor clinical development programme in CF. Nevertheless, the challenges faced by researchers developing personalised therapies remain significant, especially in more complex polygenetic diseases, such as asthma. Overcoming these challenges will require collaboration between public bodies, such as academic institutions, regulatory authorities and clinical networks, and commercial organisations, such as pharmaceutical and diagnostic companies [19].

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).

References


What next?

<table>
<thead>
<tr>
<th>Age yrs</th>
<th>CF gene identified</th>
<th>CF protein identified</th>
<th>Sweat chloride test developed</th>
<th>Discovery of high salt in sweat</th>
<th>Airway clearance</th>
<th>Pancreatic enzymes</th>
<th>Antipseudomonal antibiotics</th>
<th>RhDNase</th>
<th>Aztreonam for inhalation solution</th>
<th>Tobramycin for inhalation solution</th>
<th>First successful pregnancy</th>
<th>Inhaled tobramycin</th>
<th>First pathologic description</th>
<th>CFTR gene identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1940</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1950</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1960</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1970</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 2. Schematic illustration of how the introduction of novel cystic fibrosis (CF) therapies influenced patient survival over the decades. HTS: high throughput screening; AZLI: aztreonam for inhalation solution; TIP: tobramycin inhalation solution.


