Rare Diseases Day 2022
Hope for New Treatments in Cystic Fibrosis

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Rare Disease Day

Rare Disease Day aims to raise awareness and create change for the 300 million people worldwide living with a rare disease.

Since rare conditions are often difficult to diagnose, patients and their families can endure a long odyssey, involving many specialist doctors, tests, and numerous misdiagnoses.

Today provides us with an opportunity to #SHAREYOURCOLOURS to raise awareness, reflect on the achievements in this space to date and address the challenges for the future.

Hope for New Treatments in Cystic Fibrosis

I have to confess, Cystic Fibrosis (CF) is a condition I had not really thought about much until I became aware of the additional stress experienced by patients with CF as a result of the COVID-19 pandemic.

My knowledge of the disease is rooted back in school biology classes when being taught genetics and how CF is the most common autosomal recessive disease in the Caucasian population. We were also taught that CF affects multiple organ systems including the lung, pancreas, liver, gut, and reproductive organs.

At the time I went to medical school in the 1970s, most patients with CF usually did not survive to adulthood. So, what's been happening over the last four decades? The good news is that the mean predicted life expectancy has dramatically increased to almost 50 years of age. It is important to note that this is a mean value, and some people with CF will live into their 70s or even their 80s, if treatments continue to improve.

Like many diseases, progress in CF treatment and management has been incremental based on a 'team' approach to treat the person and the disease as a whole rather than respiratory or gastrointestinal issues separately.

The mainstay of treatments responsible for this steady improvement in survival (in chronological order) are; pancreatic enzymes, airway clearance, oral anti-staphylococcal and anti-pseudomonal antibiotics, recombinant DNase and inhaled antibiotics including tobramycin, azithromycin, aztreonam lysine and tobramycin inhalation powder.

However, until recently the treatments introduced did not target the underlying pathology i.e., the CF transmembrane conductance regulator (CFTR) gene that encodes the CFTR protein. This anion channel, which conducts chloride and bicarbonate ions at the apical membrane of different epithelia, regulates water and ion transport and maintains epithelial surface hydration. In CF, epithelial cell functions are impaired resulting in thickened mucus, impaired mucociliary clearance/antimicrobial enzyme activity which promotes a pro-inflammatory environment, mediated by recurrent infections, that leads to lung damage.

Based on those distant biology lessons, one might assume there is a single mutation in the CFTR gene, but there are approximately 2,000 different mutations. The amount and functionality of the CFTR protein produced varies dependent on the mutation within the gene. The protein may be virtually absent, significantly reduced, or is in an unstable form that results in premature recycling and degradation in lysosomes.

At present, three oral drugs, known as CFTR modulators, have been approved by both the European Medicines Agency and Food and Drugs Administration to treat the underlying defect in CF. The approvals were based on improvements in forced expiratory volume in 1 second (FEV1) and in the risk of pulmonary exacerbations. These drugs are: ivacaftor, lumacaftor plus ivacaftor, tezacaftor plus ivacaftor, and triple the combination of elexacaftor/tezacaftor/ivacaftor. Ivacaftor is a potentiator that improves the CFTR channel opening so that more ions flow through the pore to improve protein access. Tezacaftor and lumacaftor are correctors which improve CFTR protein folding and trafficking so that more mature CFTR protein appears at the cell membrane. Elexacaftor is considered a next-generation CFTR corrector as it possesses both a different structure and mechanism as compared to first generation correctors like tezacaftor (NCBI 2022). As CFTR) modulator therapies are designed to correct the malfunctioning protein made by the CFTR gene, they do not work in all patients, for example patients who do not produce any CFTR protein. As a result CFTR modulators are licensed for use in patients with specific CF gene mutations.These are examples of mutation-specific therapies. In addition, testing CFTR function and its rescue by CFTR modulators in vitro, in patient-specific tissue, opens the pathway to personalised therapy.

Although CFTR modulators bring enormous promise for the future and immediate clinical and quality of life benefits for current patients (less infections, longer time between exacerbations and thus less rapid progressive lung damage), other corrective strategies continue to be explored. Replacing the genetic mutation with a 'correct version' of the CFTR gene would be the holy grail of treatment for CF patients, as it offers a potentially permanent cure.

There have been several gene therapy trials conducted but most studies were conducted in small numbers of patients and for short durations. They were not designed to assess clinical benefit, but to establish safety and proof-of-concept for gene transfer using molecular end points, such as the detection of recombinant mRNA or correction of the ion transport (Griesenbach, Pytel, and Alton 2015).

Great progress in the treatment of CF has been made over the last 40 years.

In 2015, the UK Cystic Fibrosis Gene Therapy Consortium tested a liposome-based plasmid DNA encoding the CFTR gene, in a Phase 2b gene therapy trial, but it only improved lung function by a few percentage points and never advanced to the market, (Khamsi 2020). However, Wave 2, now known as BI 3720931 (Boehringer Ingelheim exercised its option to license Oxford Biomedica's lentiviral vector technology) is development is now underway (Oxford Biomedica Press release).
This new gene therapy treatment is an important step as it brings hope to the whole CF community and in particular to those who don't benefit from the currently available medicines.

There are many challenges facing successful gene therapy for CF, even if it was a single mutation disease, including (but not limited to):

1. Ability to repeatedly deliver the gene therapy as progenitor cells of the airways do not sustain expression during cell turnover.
2. Low efficiency of targeting of the donor gene to the CF airways due to the highly inflammatory microenvironment.
3. The inability to deliver large DNA fragments of the CFTR gene effectively with current delivery methods.
4. Concerns of 'off-target' safety that can result in insertional mutagenesis.

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Continuing research efforts and collaborations promise further improved treatments in the future.

There is now renewed interest in gene therapy in CF because of the new gene editing techniques, such as clustered regularly interspaced short palindromic repeats, (CRSPR), Zinc Finger Nucleases and transcription activator-like effector nucleases and Base editing (Lee et al. 2021). Other strategies include the addition of normal mRNA or influencing gene expression and protein production by small interfering ribonucleic acid.

I have been both enlightened and encouraged after reading the paper by De Boeck (De Boeck 2020). Maybe one of my professors at medical school was partially wrong when he stated: *'Don't have a rare disease because you'll spend your life talking to medical students and there* will be no treatment available*'*.

Summary

Great progress in the treatment of this disease has been made over the last 40 years. Continuing research efforts and collaborations, such as the UK CF Gene Therapy Consortium[#] (UK GTC. 2022), promise further improved treatments in the future.

References

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[#]UK CF Gene Therapy Consortium comprises: Imperial College London, the University of Oxford, the University of Edinburgh, and the pharmaceutical companies Boehringer Ingelheim and Oxford BioMedica.