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REVIEW

Recent advances in cystic fibrosis

F. Ratjen*

Hospital for Sick Children, Toronto, Canada

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Summary Considerable advances in cystic fibrosis (CF) research have translated into improved patient care, reflected by a continuing trend of improving life expectancy in CF patients. This review summarises some of the major findings of CF research that have occurred in the past year. The review specifically focuses on those developments that have direct implications for patient care or those in which clinical trials suggest benefits that may impact on the treatment of CF patients in the near future.

Major improvements in cystic fibrosis (CF) care have been achieved over the past 2 decades. Many CF centres now have a larger patient population in their adult compared with their paediatric clinics, which signifies how life expectancy has improved over the years. This is also highlighted by the recently published data from the UK CF registry, which demonstrate the continued improvement in prognosis over the past 30 years.[1] Even though an extrapolation of life expectancy based on slopes derived from patients who have been followed over limited time periods are problematic, it is expected that, with our current therapeutic armamentarium, most CF patients will reach the fourth or fifth decade of life.[1] Multiple factors are important for this achievement, but the early and aggressive therapy of airway infections is thought to be a major reason for this ongoing trend.

Early intervention with therapeutic strategies is considered to be a key factor to avoid permanent damage to the lung, and this can be best achieved when CF is diagnosed prior to the development of symptoms.[2] Multiple studies have provided a rationale for neonatal screening in CF, which has led to its implementation in many countries.[3–5] While evidence for better nutritional outcome has been convincing, it was largely unclear whether the costs of a newborn screening programme would outweigh the higher treatment costs of patients being diagnosed on the basis of symptoms as these patients often require expensive interventions including hospital admissions for intravenous antibiotic treatment. Sims *et al.*[6] have provided convincing evidence that a newborn screening programme for CF can actually save money and is therefore not only beneficial for patients' outcome, but also cost-effective.[6] This information should be very helpful for the future implementation of newborn screening in countries that are currently reluctant to include CF in their screening programme.

Besides newborn screening, it is important to consider the key factors that are important in predicting a decline in lung function in CF patients. Konstan *et al.*[7] have used data from an epidemiological data registry to assess risk factors that can predict lung function decline in a large cohort of CF patients.[7] While female gender and *Pseudomonas aeruginosa* infection were confirmed as important factors negatively affecting lung function evolution, the major factor continues to be baseline lung function, thereby confirming earlier findings.[7,8] While this finding could partially be explained by a statistical phenomenon (regression to the mean), it could signify that patients with good lung function may continue to be undertreated. Part of this may be explained by the lack of sensitivity of current lung function tests such as forced expiratory volume in 1 second (FEV_1) to pick up early abnormalities in CF.

There is a wide variety of potential outcome parameters in CF for both clinical use and clinical trials, but most will

* Division of Respiratory Medicine, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada. Tel.: +1 416 813 6167; Fax: +1 416 813 6246.
E-mail address: felix.ratjen@sickkids.ca.

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require further validation before they can be used in routine clinical care.[9] One of the more promising techniques to assess lung function in CF is the use of gas-mixing techniques that assess the clearance of an inhaled inert gas.[10,11] Gustafsson *et al.*[10] have recently shown that the lung clearance index, a measure of ventilation homogeneity, has a higher sensitivity than other lung function tests to predict bronchiectasis in patients with CF.[12] Admittedly, limited information is available on how such tests will detect changes after a therapeutic intervention. However, the early data support other data obtained by high-resolution computed tomography and bronchoalveolar lavage studies demonstrating that significant abnormalities can be present in CF patients despite normal results for routine lung function tests. This suggests the need not to rely on these test results alone but to be aggressive in the treatment approach in patients with normal lung function.

CFTR gene mutations lead to a defective or absent CFTR protein, and the most logical way of treating CF would therefore be to replace the *CFTR* gene to restore normal protein production. There are multiple hurdles that have to be overcome to make gene therapy successful.[13] The first major goal of gene therapy is to bring enough of the gene product into the primary target cells, the respiratory epithelial cells. Both viral vectors and non-viral vectors have been used to accomplish this. The second goal is to achieve gene expression, so that a normal CFTR protein is formed. This expression should ideally be sustained over the lifespan of the respiratory epithelial cell. However, respiratory epithelial cells regenerate, and therefore gene therapy will be unlikely to work as a one-time, one-dose strategy.

One approach of *CFTR* gene therapy that has shown some promise is based on an adeno-associated viral vector system. Two clinical studies have been completed to date in CF patients. Although the initial study was primarily designed to assess safety (treatment being found to be safe), treated patients showed improvement in FEV_1 after 30 days of treatment compared with the placebo group.[14] This was paralleled by a decrease in concentration of interleukin-8, a proinflammatory cytokine, in sputum samples.[14] Subsequently, a larger trial powered to demonstrated efficacy has been performed.[15] The study confirmed safety of the vector system, but no effect on lung function was observed. Further improvements in the vector system will probably be necessary before this virally mediated gene therapy approach will come back into clinical trials. In reality, despite considerable effort and financial investment, CF gene therapy is some years away from clinical practice.

Another strategy is to increase the expression or improve the function of the mutated CFTR protein with pharmacological agents. It is important to understand that CFTR pharmacotherapy will not be applicable to all patients, but will rather be mutation specific.[16] *CFTR* mutations have distinct functional consequences for the production of the CFTR protein and are therefore subdivided into different classes. In general, five classes of mutation are differentiated based on their functional relevance: CFTR is not synthesised (I), is inadequately processed (II), is not regulated (III), shows abnormal conductance (IV) or has partially defective production or processing (V).

Class I mutations are considered to be stop mutations, which lead to decreased or absent protein production. The mRNA contains false stop signals earlier in the mRNA, so-called premature termination codons (PTCs), which lead to a truncated and non-functional protein.[17] Substances have been developed that allow read-through of these PTCs, thereby resulting in a full-length, potentially functional normal protein. Gentamicin was used in the initial studies and was shown to improve CFTR expression in CF patients treated with topical application to the nasal epithelium.[18] A derivative without antibiotic function, named PTC124, that can be administered orally has subsequently been developed.[19] However, response rates for both gentamicin and PTC124 have been variable between patients.[20] In vitro studies have shown that the amount of transcript produced may predict the clinical response, patients with higher transcript levels showing a higher response rate.[21,22] Studies with PTC124 are currently under way to further evaluate its clinical effect in both adult and paediatric CF patients.

Since only 5–10% of the CF population carries stop mutations, PTC read-through therapy, even if demonstrated to be efficacious, would not be a viable option for most CF patients. The most common mutation, DF508, is a class II mutation, in which misfolded CFTR is degraded in the endoplasmic reticulum prior to reaching the cell membrane.[23] Since this misfolded CFTR has a chloride-conducting function, compounds that affect intracellular trafficking could potentially provide clinical benefit. High-throughput screening for drugs that can either improve CFTR trafficking (correctors) or improve CFTR function (potentiators) has been performed and yielded candidate compounds, some of which have passed the preclinical stages. Interestingly, VX-770, a novel compound, has been shown to have CFTR-potentiator properties as it increases cyclic-AMP-dependent chloride secretion in cell cultures expressing wild-type, G551D-, R117H- or F508del-CFTR.[24] This compound is currently being studied in CF patients carrying the G551D mutation to evaluate both safety and efficacy on chloride secretion.

Chloride transport in epithelial cells is not limited to CFTR. An alternative chloride channel that can be activated either directly or via activation of the P_2Y_2 receptor with ATP or one of its derivatives is present in respiratory epithelial cells. It is established that CFTR knockout mice do not develop lung disease, and this could be explained by upregulation of this alternative chloride channel.[25] Using drugs that activate this channel could therefore be one way to circumvent the CFTR defect.

The agent that is most advanced in clinical development is the P_2Y_2 receptor agonist denufosol. A recently published