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Recent advances in the management of cystic fibrosis

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ABSTRACT

Cystic fibrosis is a disease that still causes a reduced life expectancy. The treatment burden remains high for affected individuals with often a combination of multiple oral and inhaled medications, as well as physiotherapy, required on a daily basis. In this article, we look at an overview of the pathogenesis, how this might lead to treatment options and look at some of the available new therapies, all in the aim of increasing life expectancy and reducing treatment burden.

BACKGROUND

Cystic fibrosis (CF) affects over 8000 people in the UK and an estimated 100 000 globally. Prognosis has improved greatly over the last few decades, but patients still have a reduced life expectancy and a huge treatment burden. This review focuses on treatment developments for CF lung disease over the last 3–4 years. We start with a brief overview of disease pathogenesis (which can be read in more detail in¹) and highlight areas at which new drugs are being targeted.

CF PATHOGENESIS

CF is caused by a defect in the CF transmembrane conductance regulator (CFTR) gene, on the long arm of chromosome 7, which leads to absence of normal CFTR protein, a cAMP-activated ion channel. The almost 2000 mutations identified can be grouped into six classes depending on their effect on protein expression/function. Class I mutations are 'nonsense' mutations containing premature stop codons preventing the protein from being synthesised. Class II mutations are the most commonly identified and include Phe508del, at least one copy of which is found in around 70% of all patients with CF.² The protein folds incorrectly, therefore cannot traffic to the apical cell membrane, but undergoes degradation within the lysosomes. In class III mutations, the protein is correctly positioned on the cell surface but fails to open in response to intracellular signals. In class IV mutations, channel opening is normal but conductance is reduced due to pore abnormalities. In class V mutations, there is a splicing abnormality leading to a reduced amount of CFTR protein on the cell surface and class VI mutations lead to protein with a shortened half-life.

Absence of normally functioning CFTR leads to decreased chloride secretion and (due to loss of the normal inhibitory relationship with the epithelial sodium channel (ENaC)) increased sodium absorption across the epithelial surface. The net result of this is depletion of the airway surface liquid (ASL) and impaired mucociliary clearance (MCC).

Infection and inflammation start early and become chronic; accumulation of DNA and actin released from incoming neutrophils further increases mucus viscosity and impairs clearance. Proteases and other inflammatory cell products, while possibly being responsible for limiting the infection to the airways, lead to airway wall inflammation, remodeling and, ultimately, irreversible bronchiectasis. Despite currently available treatments, around 90% of patients will die of respiratory failure unless they receive a lung transplant.

TREATMENT STRATEGIES

New treatment strategies target multiple steps in this cascade, including (a) gene therapy, (b) CFTR protein modulation, (c) rehydration of the airway surface and/or mucolytics, (d) anti-inflammatories and (e) anti-infective agents.

CFTR gene therapy

Since the discovery of the *CFTR* gene, numerous attempts have been made to reverse the basic defect by gene transfer. In vitro experiments demonstrated successful restoration of ion transport with either modified viral vectors or synthetic gene transfer techniques, but achieving similar success in the clinic has been challenging. The majority of clinical trials have been single-dose, proof-of-concept design, often administering the gene therapy to the nasal epithelium for ease of access. Several of these trials have reported success based on transgene expression (mRNA) and electrophysiology (nasal potential difference (PD)), but the results have been variable and expression of short duration. Attempts to dose repeatedly have confirmed that currently used viral vectors lead to immune responses that limit efficacy upon subsequent administration. There are few groups now still working in this field. The UK CF Gene Therapy Consortium (<http://www.cfgenetherapy.org.uk/>) is currently conducting a large, phase IIb, repeated dose, randomised, placebo-controlled trial of cationic liposome-mediated *CFTR* gene therapy. Nebulised doses are being administered at monthly intervals for 1 year, with a primary outcome of change in FEV₁. Secondary outcomes include lung clearance index, CT scans, validated quality-of-life questionnaires and sputum/serum inflammatory markers. A subgroup will undergo nasal dosing and nasal PD measurements or will have similar electrophysiological measurements made bronchoscopically. In parallel to this clinical programme, the Consortium is developing a second wave product, a pseudotyped lentivirus, which unlike most viral vectors appears to be repeatedly administrable. The advantages of this approach are high levels of



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transfection and the potential for long duration of expression, which may allow infrequent dosing. Clearly this approach requires detailed preclinical toxicity testing and optimisation before clinical trials commence, so is some way off.

CFTR modulators

Ribosomal read-through drugs

Ataluren (PTC124) has been developed as an orally bioavailable drug that allows the ribosome to 'read through' the premature stop mutation, but without the toxicity profile of the aminoglycoside agents that were first discovered to possess this property. Several phase II trials were conducted, which seemed to provide proof of concept based largely on nasal electrophysiological changes (PD). A large, multicentre phase III trial has recently been completed; unfortunately, for the group as a whole, neither primary (FEV₁) nor secondary outcomes differed significantly between treatment and placebo groups. However, an interesting post hoc subgroup analysis has identified a potential interaction with inhaled tobramycin. Patients who were not taking this concomitantly appeared to demonstrate an Ataluren treatment effect. Further trials are being planned at present to examine this more closely.

Potentiators

Class III mutations lead to protein that is correctly situated within the cell and amenable to 'potentiation' by drugs that increase open probability. The most well-studied CFTR potentiator is Ivacaftor (VX-770), now available to patients with the Gly551Asp (G551D) mutation as Kalydeco. Two phase III double-blind, placebo-controlled trials have been completed in G551D patients, 12+ years and 6–11 year olds. Both studies demonstrated significant and clinically important increases in FEV₁ (of around 10% absolute percentage points), significant weight gain and a decrease in sweat chloride. The larger of the two trials in older patients also showed a reduction in exacerbation rate and an increase (above the defined minimal clinically important difference) in the validated quality-of-life questionnaire, the CFQR.^{3 4} The drug was well tolerated with the number of adverse events being similar in both treatment and placebo groups. Ivacaftor is more recently being tested in patients with other class III mutations and in the class IV mutation, R117H.

Correctors

Class II mutations may pose significant challenges as highlighted by the recent recognition that at least two separate misfolding steps may need to be corrected in Phe508del CFTR. However, these are by far the commonest mutations in patients with CF worldwide so this approach is receiving substantial attention; several so-called 'corrector' drugs are under investigation and more are at the preclinical stage. Lumacaftor (VX-809) has been administered as a single agent to adult patients with CF, homozygous for Phe508del in a phase II study. The primary aim was to evaluate safety and tolerability of the drug with secondary endpoints of CFTR function (sweat chloride and nPD) and spirometry.² There was a small but statistically significant decrease in sweat chloride values at the higher doses of drug, but no changes were seen in the other outcomes. Currently, lumacaftor is undergoing investigation in combination with the potentiator, ivacaftor, which may hold more promise. A large phase III programme of over 1000 patients has recently completed recruitment and results are eagerly awaited. In parallel, a second corrector, VX-661, is in phase II trials alongside ivacaftor and other molecules developed by Vertex and a number of other

Pharma companies are at the preclinical or safety stages of development.

Airway surface rehydration

Increasing the volume of ASL and therefore improving MCC is the method by which osmotic agents work, the most commonly used of which is hypertonic saline (most usually 7%). This has previously been shown to reduce exacerbation rates,⁵ although the impact on lung function was less clear. It has recently been proposed as a useful early agent for young children and babies. The first efficacy trial in children aged 4 months to 5 years old was performed over a 48-week period with a primary endpoint of exacerbation rates.⁶ A subgroup of the children aged 4–16 months at enrolment also had infant lung function performed. The overall results showed no change in exacerbation rates between treatment and placebo groups, but there was a significant improvement in FEV_{0.5} in the infant subgroup, as well as a significant decrease in lung clearance index (LCI).⁷ This may reflect the difficulty in detecting functional change in this group of patients with minimal lung disease. Of note 7% saline was tolerated as well as placebo with no increased rates of adverse events.

Mannitol, administered as a dry powder, has been more recently assessed in a phase III trial (double-blinded, placebo-controlled).⁸ The patients were 6 years and over with an FEV₁ between 30 and 90% predicted, and followed for 26 weeks initially then for a further 26-week open-label phase. There was a significant increase in FEV₁ (absolute volume) during the first 26-week period that was maintained to 52 weeks. This was independent of whether the patient was also using dornase alfa as a regular treatment. There was an increased rate of adverse events relating to the drug in the mannitol group, mainly cough, pharyngolaryngeal pain and haemoptysis, with a small number of patients withdrawing from study secondary to these events. Of note the placebo used in this trial was a subtherapeutic dose of mannitol (50 mg twice daily). Previous trials of mannitol had used non-respirable doses of mannitol. There is a further double-blinded crossover study ongoing within Europe and Canada looking specifically at the use of mannitol in 6–18 year olds. Mannitol is already used in routine practice in adults worldwide and children in Australasia.

Denufisol tetrasodium is an investigational compound that acts on P2Y₂ receptors on the epithelial cell surface within the airway. It has been shown to activate an alternative chloride channel, inhibit sodium absorption and increase ciliary beat frequency. All of these actions would be predicted to result in improved MCC and therefore increase lung function and decrease exacerbation rates. An initial 48-week placebo-controlled double-blind trial in patients aged 5 years and over with an FEV₁ >75% predicted showed a small but significant increase in FEV₁ over the first 24-week period, which extended into the 24-week open-label phase. This increase, however, was less than half of what had been predicted by the research group.⁹ A second trial enrolling the same patient population was unfortunately negative,¹⁰ and further development of this agent seems unlikely.

Mucolytics

Dornase alfa (Pulmozyme), a recombinant human deoxyribonuclease (DNase), cleaves the extracellular DNA found within the airway, reducing mucus viscosity and improving MCC and has been part of standard care since early trials confirmed efficacy. A recent study looked at the effect of dornase alfa on 6–18 year olds with CF and mild lung disease defined by an FEV₁ ≥80%. LCI, generally thought to be more sensitive than FEV₁,

improved after 4 weeks of dornase alfa treatment when compared with placebo.¹¹ There is increasing awareness that this drug may have a role as an anti-inflammatory agent¹² and should possibly be used earlier in disease to prevent inflammation-related airways damage.

Anti-inflammatory agents

Due to the importance of inflammation within the CF airway, this has long been a therapeutic target. Ibuprofen has been shown to slow the progression of lung disease in children,¹³ but concerns over side effects have limited its widespread uptake. A recent pilot study looking at novel biomarkers of kidney injury suggests that ibuprofen can be used safely within a selected patient group (>6 years, $FEV_1 \geq 60\%$) although still recommended to be temporarily ceased when the patient is also receiving intravenous aminoglycosides.¹⁴ Another drug, azithromycin, is thought to work at least in part as an anti-inflammatory agent and has proven efficacy in patients with and without chronic Pa infection. A current study is looking at the efficacy of azithromycin in infants with CF, specifically its effect on the development of bronchiectasis (COMBAT-CF, ClinicalTrials.gov identifier: NCT01270074). Glutathione is a major antioxidant, levels of which are decreased in CF lungs. A recent trial of inhaled glutathione in children over 8 years and adults reported no improvement in lung function or exacerbation rates.¹⁵ Another promising family of drugs is the phosphodiesterase type 5 (PDE5) inhibitors. In addition to possible effects on misfolded CFTR protein, there is evidence of attenuated inflammation in CF mice.¹⁶ There is a registered clinical trial looking at sildenafil as an anti-inflammatory in those over 12 years with CF in a single US centre (NCT00659529). SB-656933 is a CXCR2 antagonist that aims to inhibit the recruitment and activation of neutrophils into the lung. A double-blind, placebo-controlled study in 146 CF adults has shown generally good tolerability of the drug¹⁷ and trends towards decreasing sputum inflammatory markers over the 28-day study period, but an increase in blood inflammatory markers. Further evaluation of this drug and potential effects is ongoing. The recent murine study demonstrating reduced inflammation but increased pseudomonal counts and bacteraemia following treatment with the leukotriene antagonist BIIL284 (24183915) not only provides a possible explanation of the adverse events leading to early cessation of a clinical trial of this agent, but also highlights the caution that must be employed when considering anti-inflammatories for the treatment of CF, a disease characterised by a high burden of bacterial infection.

Anti-infective treatments

There are no newly identified antibiotics, but there have been many trials investigating alternative delivery methods. The advantages of inhaled drugs are increased airway concentrations in ventilated regions of the lung and minimisation of systemic side effects.¹⁸ The most common pathogen in older children and adults is *Pseudomonas aeruginosa* (PA); chronic infection is associated with increased rates of decline in lung function, morbidity and mortality.

Tobramycin, used for several years as a nebulised solution tobramycin inhaled solution (TIS), can now be delivered more quickly as a dry powder tobramycin inhalation powder (TIP), via a Podhaler. It was found to be comparable in terms of lung function changes and PA sputum density changes to the nebulised solution.¹⁹ It can be used by children aged 6 years and older but was associated with higher rates of cough and

dysphonia than TIS. Similarly, a new dry powder formulation of colomycin (Colobreathe) administered via a Turbospin device has been developed for patients at least 6 years old. In a phase III randomised open-label trial, there were no differences in lung function, colistin resistance or adverse events over a 24-week period, confirming non-inferiority to TIS and patients preferred the dry powder.

Aztreonam is available in a nebulised form, azreone for inhalation solution (AZLI). An 18-month open-label placebo-controlled study (28 day on/off cycles) compared twice and three times daily doses.²⁰ There was a greater improvement in lung function on three times daily, but in all patients the lung function had fallen back to baseline by the end of the 'off' period. There was a decrease in bacterial density sustained over the total duration of the study and a sustained weight gain. Another study examined the same primary and secondary outcomes in patients with $FEV_1 > 75\%$ predicted. Over 50% of participants were aged 6–18 years.²¹ Results were similar but somewhat less pronounced, likely due to the milder disease. A comparison study, over 3×28 -day treatment courses, between TIS and AZLI in patients 6 years and over with an $FEV_1 < 75\%$ has shown AZLI to be superior in terms of increased lung function and decreased exacerbation rates.²²

Nebulised liposomal amikacin results in a prolonged airway half-life and activation of the drug at sites of infection, due to liposome breakdown by *Pseudomonas rhamnolipid*. In phase II trials, once-daily dosing was safe and well tolerated, led to significant increase in FEV_1 and quality of life and a decrease in PA sputum density; in an open-label study, these benefits were sustained over six cycles.²³ A novel preparation of levofloxacin with magnesium chloride (MP-376, Aeroquin) for nebulisation has been studied in a double-blinded, placebo-controlled, phase II trial in subjects 16 years and older.²⁴ At the higher doses tested, there was a reduced sputum PA density at day 28, an increase in FEV_1 and a reduced need for other antipseudomonal antibiotics. The drug was tolerated well with the main complaint relating to an alteration of taste. By day 56, both the sputum PA density and lung function had returned to baseline levels. A unique antibiotic combination of inhaled fosfomycin/tobramycin (FTI) is being evaluated. Fosfomycin has activity against gram-positive, gram-negative and anaerobic bacteria. In a double-blind, placebo-controlled adult study, it was administered twice daily for 28 days following a 28-day run-in course of AZLI. Patients receiving active drug maintained the improvements in lung function from the run-in phase, which did not occur in the placebo group.²⁵ There was a significant decrease in sputum PA density, and the drug combination appeared safe.

The global increase in resistance to conventional antibiotics has led to alternative strategies being investigated. One such approach that is currently in the clinical pipeline is the avian antibody against PA (PsAer-IgY), purified from immunised hens' eggs. In a phase III double-blinded, placebo-controlled study (ClinicalTrials.gov identifier: NCT01455675), patients aged 5 years and over who have had one previous PA infection eradicated gargle the solution. The primary endpoint is time to reinfection with PA; data collection should be complete by the end of 2014.

FUTURE CHALLENGES

There is a large amount of work underway investigating treatment options at the molecular level and further downstream. For patients with CF aged 6 years and over, there are several new treatment options available for use and more on the horizon. But what about younger children? The problem in

infants and young children with CF is the lack of sensitive and reliable clinical markers to track changes of disease in intervention trials.²⁶ There are now a number of trials examining LCI as a more sensitive marker of lung disease, but this is a challenging test to perform in the preschool child and potentially needs sedation in the infant. Chest CT scans are being used as an endpoint for the first time in COMBAT-CF but require a cooperative child or general anaesthetic to ensure comparable images for use in clinical trials and involve ionising radiation. This age group is particularly important when examining the further use of the small molecule drugs and gene therapy as these could minimise the need for the end-organ treatment options within the next generation of patients with CF. Paediatricians working in CF need to address this deficiency and work together to design pragmatic and feasible clinical trials for young children, acceptable both to families and regulatory agencies.

Competing interests JCD has been principal investigator on a number of trials for Vertex, PTC, Pharmaxis, Novartis and Forest, all of which produce drugs that were discussed above. She has also served on Advisory Boards for several of these companies and have undertaken educational activities for their staff. All fees/honoraria have been paid to Imperial College or the Royal Brompton Hospital. She does not hold any shares of relevance.

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