

New and Evolving Therapies for Cystic Fibrosis Patients

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Cystic fibrosis (CF) is a common autosomal recessive inherited disorder affecting 1 in 2,500 births and ~75,000 people in North America, Europe, and Australia. The purpose of this review is to discuss the most recent advances in therapies for CF patients. The CF drug development pipeline provides information regarding the phase of each new therapy and those that are already in use by patients. The ultimate goal of therapy will be to deliver tailored individualized therapies to those who need it the most. This review will focus on new research on CF transmembrane conductance regulator protein modulator agents and the effort of gene therapy.

THE EMERGING TREATMENTS for cystic fibrosis (CF) have been cresting in the past decade and have been a topic of much discussion. There has been a shift in management with attention focused on the underlying genetic defect rather than controlling the symptomatology. Current treatment can be divided into categories based on the pathophysiology of the primary mutation. There are more than 2,000 mutations that fit into 1 of 5 classes of the CF protein defect. The challenge has been to correct the underlying CF transmembrane conductance regulator (CFTR) protein dysfunction, which is the foundation of the CF phenotype.¹ On the other hand, CF gene therapy offers the potential of a cure; however, symptomatic treatments and multiorgan management continue to be the backbone in the management of CF.

CFTR mutation class-specific treatments can be subdivided into potentiators, correctors, and agents that promote ribosomal read through of nonsense mutation.² The first available treatment approved by the U.S. Food and Drug Administration (FDA) is ivacaftor (Kalydeco[®]) a CFTR modulator. Ivacaftor offers an effective and well-tolerated treatment for clinical management of CF patients with the G551D mutation.³ It is an oral CFTR potentiator that increases the CFTR transport of chloride ions already on the epithelial surface. Two phase III randomized, double-blind, placebo- controlled trials were done: STRIVE performed in adolescents and adults and ENVISION in children 6–11 years old.^{4,5} The study designs for both trials were similar and both demonstrated ~10% absolute improvement in FEV1 sustained for 48 weeks.³ Efficacy outcomes in children were consistent with those in older population despite milder disease suggesting that the disease might be reversible or even preventable.³ At the end of the 48-week

period, STRIVE patients were offered entry into an open-label study (PERSIST) for long-term impact over 96 weeks, which is still ongoing. Preliminary analysis demonstrates sustained improvement of FEV1 beyond 12 weeks and in those who switched from placebo to ivacaftor.⁶

The STRIVE and ENVISION adverse events were pooled and the most common were found to be headache, upper respiratory tract infections, nasal congestion, rash, and dizziness.³ However, these events were not significantly different compared with placebo and none led to study medication discontinuation.³ The only adverse event that led to discontinuation of ivacaftor was an increase in hepatic enzymes, but all subjects were able to resume taking the study drug and complete the trial. Overall, the studies had dramatic improvement in self-reported respiratory symptoms, nutritional status, and reduced pulmonary exacerbations by greater than 50% compared with baseline.³

The CFTR corrector, lumacaftor, improves CFTR expression at the cell surface by affecting the folding and processing of CFTR. Studies have shown that lumacaftor monotherapy has limited efficacy; however, CFTR function might be improved with CFTR potentiator and corrector synergy.⁷ Currently, there are 2 phase III trials underway by Vertex, TRAFFIC and TRANSPORT, in patients ages 12 and older who have 2 homozygous F508del mutations, to evaluate the combination therapy.² Another potential CFTR corrector of protein misfolding is VX-661. Ongoing phase II trials with VX-661 monotherapy and in combination with ivacaftor would look at the improvement in FEV1 as the primary outcome compared with placebo.²

Ataluren is an oral drug that permits ribosomes to continue producing functional CFTR proteins in the presence of

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premature stop codons. Nonsense mutations account for only 5%–10% of all CFTR mutations worldwide, however, for CF patients in Israel, it accounts for greater than 60%.^{2,8} The phase II trials looked at chloride transport in nasal epithelium by potential differences (NPD), which was statistically significant.⁹ The same dosing regimens were studied in CF patients 6–18 years of age and also demonstrated significant changes in NPD. A multinational phase III trial was completed in CF patients greater than 6 years of age. Neither the primary endpoint of change in FEV1 nor the secondary endpoint of pulmonary exacerbation reached significance.⁷ Another study is planned to evaluate the use of ataluren as a treatment option in class I mutations, which have no functional CFTR proteins.²

On February 2014, Vertex announced the approval of ivacaftor use for 8 additional CF mutations by the FDA.¹⁰ According to the press release, ivacaftor can now be used in CF patients greater than 6 years of age with the following mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D. Data from the phase III trial will be used to support regulatory submissions in Canada, Europe, and Australia. In the United States, Europe, and Australia, there are ~400 people with CF who have these additional mutations, along with 2,000 people with the G551D mutation.

As opposed to correcting the CFTR protein or potentiating its transport, gene therapy works to establish a normal copy of the CFTR gene. The most difficult aspect is finding a suitable vector for gene therapy. Initial studies using viral vectors to carry a healthy CFTR plasmid were challenged with overcoming the body's host defenses.¹¹ The vector must be able to enter the airways of a CF patient, cross the epithelium, and be transported into the cell nucleus for transcription of the gene. The new emergence has been the nonviral gene vector, which was first reported by Alton and colleagues administration of lipid-DNA complex to the lungs of CF patients.¹² The UK Cystic Fibrosis Gene Therapy Consortium has developed 2 Wave programs, Wave 1 based around liposomal gene transfers and Wave 2 focused on a novel virus such as lentivirus.¹³ The current update about Wave 1 is the recruitment of all patients from CF centers across the United Kingdom, approximately half have received all 12 doses of the gene therapy or placebo at monthly intervals with completion in June 2014. Analysis will follow and findings to be expected to be presented in October 2014 at the North American CF conference.¹¹ For the Wave 2 program, the final form of the virus has been chosen and quantities are being produced for first clinical trials since preliminary safety studies were uneventful.¹¹

With all the new therapies in development, the main challenge that is arising is maintaining adherence to the complicated medical regimens. A CF patient spends hours a day inhaling mucolytics, inhaling antibiotics, doing airway clearance, and taking nutritional enzymes and supplements.¹ According to recent studies, adherence to these complicated regimens is in only ~50%, but can range from 31% to 79% depending on the patient's age. For instance, studies have demonstrated that children with CF adhere more to their nebulized medications on evenings versus mornings, weekdays versus weekends, and during the school year versus while on vacation.^{14,15} The level of adherence does affect pulmonary health outcomes and frequency of hospitalizations due to more frequent pulmonary exacerbations requiring intravenous antibiotics and lower baseline lung function.¹⁶

The commonly identified barriers are the complexity of the treatment regimen, poor health/fatigue, lack of perceived benefit, competing social and work demands, stigma/embarrassment, frequency of interaction with the healthcare team, financial barriers, amount of family/significant other support, and depression/anxiety.¹ It is clear that the people with CF face a wide variety of challenges and potentially several barriers concurrently, therefore, an individualized approach should be utilized to reduce these barriers. It will be helpful in the future to incorporate electronic monitors into daily clinical practice, since they better capture adherence data in an unobtrusive manner; however, the electronic monitors can be costly and are not yet widely approved.

The rapidly evolving therapies are a step in the right direction when it comes to the management of CF. In the past, pulmonary therapies have always targeted the viscous mucus of chronic airway infection of CF lung disease. This resulted in improved outcomes with better survival, but never addressed the underlying basis of the disease or halted the progression. Recent studies have demonstrated that correction of the underlying channel defect of CFTR is possible and results in significant clinical benefit for individuals with CF. The newest research has even started to address the correction of many different types of underlying CF mutations. The next step is gathering a better understanding of the very earliest changes that occur in the infant lung, to deliver tailored individualized therapy to those who need it the most. Subsequently, when the new therapies are finally approved for use in the newly diagnosed baby with CF, the lung disease may become a thing of the past.

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