Development of Cystic Fibrosis Transmembrane Regulator Therapies

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Do you know someone with cystic fibrosis? I did not, until a lovely young college student in her twenties asked for assistance researching the latest advances in cystic fibrosis (CF) treatments. She confided her interest to me in new drug development. The average life expectancy for someone with CF is under 40 years of age. Thus began our journey into a review of conventional CF therapies and new drug entities in the investigational pipeline. Working alongside my newfound friend has propelled my desire to educate my own pharmacy students, as well as fellow clinicians, researchers and the general public, on advances in CF care. Recent innovations in drug development hold promise in targeting the underlying cause of CF. We believe my friend now has hope for a long, bright future.

Scientists described complications from CF in the 1930’s. Researchers discovered the genetic code for the disease in 1989. Today the goal is to target the underlying cause of CF to prevent complications from occurring. Disease manifestations are due to a mutation of the cystic fibrosis transmembrane regulator (CFTR) gene located on the seventh chromosome. Types of mutations vary between patients and are generally classified into one of five different groups. All mutations result in functional impairment of the CFTR protein which serves as a chloride channel on epithelial cells. The primary effects from these mutations are seen in the pancreas and the respiratory system. The limited excretion of digestive enzymes from the pancreas often results in poor growth, weight loss, and greasy stools. The recurrent cycles of lung inflammation and infection lead to pulmonary fibrosis and account for much of the disease pathogenesis and shortened survival. Gastrointestinal, reproductive (in males), and hepatic dysfunction are also recognized.

Standard treatments are currently aimed at symptomatic relief. These therapies improve quality of life and extend life expectancy but have not changed the overall course of the disease [1]. The complex nature of CF requires that patients use multiple pharmacotherapies to manage their disease, often resulting in poor adherence.

In January of 2012 the FDA approved ivacaftor (marketed as Kalydeco® by Vertex Pharmaceuticals) as a treatment for some patients with CF. Ivacator, the first of the CFTR modulators, targets one of the underlying causes of CF mutation and leads the way toward finding a cure for CF. Ivacator potentiates the CFTR gene by improving the time that chloride channels in epithelial cells remain open. This drug is currently available for patients six years of age and older who have at least one Class III G551D mutation. This particular mutation occurs in 4-5% of patients, equating to approximately 1,500 of the 30,000 patients in the US with CF [2]. Ivacator is currently being tested in patients with other types of CF mutations [3].

In a 48-week randomized, double-blind placebo-controlled trial with 161 patients, Ramsey (2011) detected increases in lung function (10.1% absolute change in FEV1 vs. -0.4% for placebo), increases in body weight (3.1 kg vs. 0.4 kg for placebo), a decrease in sweat chloride (~48.7 mEq/L vs. -0.6 mEq/L for placebo) and a decrease in pulmonary exacerbations (28 vs. 44 for placebo). She also found a median change from baseline in the CF Questionnaire-Revised tool which determines changes in health-related quality of life (5.9 points to –2.7 points for placebo). A significant change is defined as one of 4 points or more [1]. Ivacator is currently being investigated for use in patients with other types of mutations [4].

Ivacaftor has simple twice daily dosing and should be taken with a fat-containing meal to increase absorption. Side effects are minimal and the drug is well tolerated which should have a positive effect on adherence. Clinicians should be aware of the potential for drug interactions with ivacaftor. Moderate- strong 3A4 inhibitors can increase ivacaftor drug levels by several folds. Caution should be used with other medications as well, such as benzodiazepines and warfarin. Rifampin and St. John’s Wort should be avoided [5]. Unfortunately, ivacaftor is extremely expensive, with therapy costing well over a quarter of a million dollars annually. Vertex Pharmaceuticals has a cost-free drug program for individuals who meet income and insurance qualifications.

Other CFTR modulators in the investigational stages include ataluren, which targets Class I CFTR mutations, known as “nonsense mutations”. This mutation affects about 10% of the CF population. It results in an inappropriate stop codon in the mRNA which disrupts chloride channels. Ataluren induces ribosomes to read through the stop codons, increasing CFTR function in patients with CF. Phase 2 trials demonstrated encouraging changes in chloride transport. In a Phase 3 multi-center clinic trial conducted by PTC Therapeutics, ataluren showed a statistically significant improvement from baseline in %-predicted FEV1 at 48 weeks as compared to placebo [6-9].

VX-809, another CFTR modulator in the investigational pipeline, is intended to correct the Class F508del CFTR mutation which is present in 90% of patients with CF [10-11]. In Class II mutations little or no CFTR protein reaches the membrane and therefore chloride is not transported effectively through the channel. VX-809 increases the cell surface density of the CFTR protein, improving chloride transport. Moderately promising results were demonstrated in a clinical trial conducted by Vertex Pharmaceuticals with 89 patients [10]. No significant positive changes were noted in pulmonary exacerbations, but significant decreases in sweat chloride values and an adequate safety profile was noted for VX-809. Additional research is needed to determine its effectiveness in lung function and long-term clinical benefits.

Combinations of CFTR modulators are currently being investigated. Clinical trials have shown that the combination of some modulators may significantly decrease sweat chloride levels compared to placebo.

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but ideal dosing regimens have not yet been clearly identified. Vertex Pharmaceuticals is currently testing an investigational drug called VX-661 in patients with the common Class II Delta F508 CFTR mutation and in combination with ivacaftor [12].

Hope is alive and well for those suffering with life threatening CF. Drug development of the CFTR modulators, such as ivacaftor, ataluren, VX-809, and VX-661 will likely revolutionize treatment plans for patients with CF. Practitioners should be vigilant in monitoring continued research and availability of these drugs. It will be fascinating to watch how the incorporation of these new therapies affects the lives of those living with cystic fibrosis.

References


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