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Medications to Enhance CFTR Activity

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Abstract

Since the basic defect in cystic fibrosis (CF) involves a defective cell surface protein controlling chloride channel transport across cell membranes, medications which are developed to enhance the cystic fibrosis transmembrane conductance regulator (CFTR) protein should result in improvement in patients with CF. The presence of over 2000 genetic mutations have made these efforts difficult. However, a classification scheme of these mutations has allowed three basic approaches: to bypass missense mutations by having the cellular translation machinery read through the premature stop codon, to enhance the “gating” function of the CFTR protein on the cell surface, and to correct a defective CFTR protein “trafficking” through the cytoplasm to be inserted properly in the cell membrane. This chapter will review clinical trials using drugs which are designed to enhance CFTR protein activity.

Keywords: Cystic fibrosis, CFTR, CFTR modulators, CFTR potentiators, CFTR correctors, VC-770, ivacaftor, VX-809, lumacaftor, VX-661, PTC124, ataluren

1. Introduction

The identification of the genetic defect in CF allowed the classification of CFTR mutations into six types of mutations. The over 2000 mutations which has been described can be placed in one of these classes: Class I mutations, which may be the result of the genetic mutation resulting in a stop codon or a shift in the reading frame in the messenger RNA which eventually results in a downstream stop codon, do not produce a complete CFTR protein. Class ii mutations result in an altered CFTR protein which is degraded in the endoplasmic reticulum and/or Golgi systems within the cell. Some proteins may be able to make it to the cell surface and have

variable levels of function (or Class III, IV, or VI effects). Class III mutations result in amino acid substitutions which affect how the CFTR protein is regulated on the cell surface, usually decreasing the channel opening. Class IV mutations result in amino acid substitutions which affect how the CFTR protein functions in its conduction of chloride ions. Class V mutations result in decreased production of normal functioning CFTR protein. Therefore, there is a reduced amount of normal CFTR protein on the cell surface. Finally, class VI mutations are those which affect the stability of CFTR.

Awareness of the types of genetic mutations affecting the normal functioning of the CFTR protein has resulted in searches for treatments directed at various CFTR dysfunctions. This chapter will review recent attempts to develop treatments specific for the various classes of mutations.

2. Premature termination codons

In approximately 10% of patients with CF, the responsible mutation results in a nonsense mutation that terminates the CFTR protein production due to a premature stop codon in the CFTR messenger ribonucleic acid (mRNA). The resultant truncated protein cannot properly transport chloride ion across the membrane. PTC Therapeutics, Inc. had discovered a small molecule drug ataluren (PTC124[®]) which enables the mRNA containing the premature stop codon to be read through the ribosome. The molecule is a 1,2,4-oxadiazole with a molecular weight of 284 Daltons. Using cell culture as well as a mouse model of CF, investigators determined that oral administration of ataluren was effective as long plasma concentrations in the range of 2 to 10 mcg/mL will result in functional CFTR activity. [1, 2] There was no evidence of nonspecific read through of normal stop codons. It did not appear to be teratogenic in rats and rabbits. However, there did appear to be inhibition of cytochrome P450 (CYP2C9) at therapeutic concentrations of ataluren. Therefore, monitoring blood levels of medications which are primarily metabolized by this enzyme (such as warfarin or phenytoin) may be needed clinically.

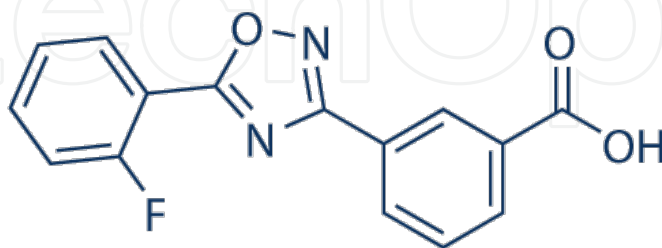


Figure 1. Structural formula of ataluren

Phase 1 studies indicate that serum ataluren levels of 2 to 10 mcg/mL can be achieved with a three times per day (TID) dosing schedule. Since administration with meals can result in prolonged levels in the blood, dosing after a meal appears to be desired.

Phase 2a studies have been conducted in 30 children and 47 adult patients in the United States, Israel, and Europe. [3, 4, 5] Using transepithelial potential difference (TEPD), which assesses transepithelial chloride conductance, as the primary outcome measure, these studies found statistically significant improvements. Pulmonary function testing also showed positive trends with decreased sputum volume and thickness, easier elimination of sputum, decreased coughing, and increased quality of life. There were no serious adverse drug effects. Phase 2a extension study looked at a 3-month administration of ataluren and confirmed its effectiveness and safety. [6] Optimal responses appear to be with doses of 10-, 10-, 20-mg/kg on the TID schedule and were seen with numerous different missense mutations.

The encouraging results of these preliminary studies prompted PTC Therapeutics to conduct a Phase 3, randomized, double-blind, placebo-controlled study to look at the effects of 48 weeks of therapy on pulmonary function and clinical symptoms in CF patients with the appropriate mutation. Over 400 patients were enrolled and showed positive trends favoring ataluren over placebo with an increase in percent of predicted for forced expiratory volume in 1 second (FEV1) and decreased pulmonary exacerbation rate. [7] A subgroup of patients who were not receiving inhaled antibiotics (primarily tobramycin) showed an even greater improvement on ataluren. The study continued to show the drug was well tolerated and had a good safety profile. There were some cases of creatinine elevation which were associated with the combination of potential nephrotoxic antibiotics with ataluren. These results resulted in conducting another international, multicenter study in which patients will not be allowed to receive treatment with chronic inhaled aminoglycosides (such as tobramycin or TOBI) in early 2015. The aim is to randomize approximately 208 patients who will receive either ataluren or placebo for 48 weeks.

3. Potentiators

The presence of some CFTR on the cell surface in mutation classes III, IV, and VI suggests another approach may be to increase the “gating” function of these protein molecules. The most common gating mutation is G551D, a missense mutation that results in the replacement of a glycine for an aspartic acid at position 551 of the CFTR protein. The resulting CFTR protein is present at the cell surface but does not open and close properly, which is called defective channel gating. The effort to find an effective “potentiator” of the channel opening has resulted in the Federal Drug Administration (FDA) approval of the first medication which modulates the function of CFTR, ivacaftor (Kalydeco), in January 2012.

Ivacaftor (or VX-770) was developed by Vertex Pharmaceuticals, Inc., to potentiate the action of the mutated CFTR on the cell surface. It has a molecular weight of 392 and a molecular formula of $C_{24}H_{28}N_2O_3$. Studies with recombinant cell lines with G551D-CFTR indicated that VX-770 did result in increased total chloride transport by greater than 10%. [8] There was evidence to indicate that it acted directly on the mutated CFTR protein to keep the channel open. It apparently has similar activity on other mutant CFTR forms resulting from other CFTR gating mutations. However, since the G551D mutation affects about 5% of all CF patients and

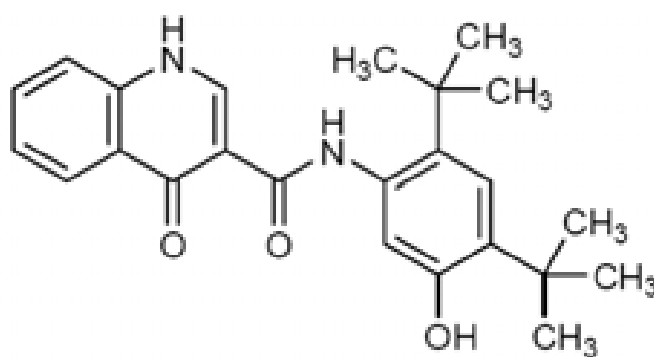


Figure 2. Structural formula of ivacaftor

is the most common gating mutation, initial studies focused on patients with this particular mutation.

Phase 1 studies indicated that ivacaftor is primarily metabolized in the liver and moderate hepatic impairment may reduce its elimination. Since *in vitro* studies indicated that ivacaftor is a substrate of CYP3A4/5 and therefore, strong (e.g., ketoconazole) and moderate (e.g., fluconazole) CYP3A inhibitors as well as strong CYP3A inducers (e.g., rifampin) will affect ivacaftor's metabolism. A detailed list of the numerous drug interactions is found in the package insert of ivacaftor (Kalydeco®) (see http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203188lbl.pdf).

An initial phase 2 study by Accurso found that the safety profile of ivacaftor in adult patients with at least one G551D mutation was excellent for a wide variety of daily doses (from 50 mg to 500 mg for 2 to 4 weeks). An improvement in FEV1 and drop in sweat chloride were also noted (although these were not primary end points of the study). [9] This prompted two randomized, placebo-controlled, double blind studies eventually resulting in FDA approval. Ivacaftor 150 mg twice daily for 48 weeks was studied in 167 patients 12 years or older with at least one G551D mutation. There was a 10.6% improvement in predicted FEV1 from baseline versus placebo. Additionally, a 55% reduction in pulmonary exacerbation was also observed. Sweat chloride levels dropped to a mean of 47.8 mmol/L compared with 100.0 mmol/L in the placebo group. There was improvement in quality of life measurements as well as a more significant increase in weight gain (4.1 kg increase) in those receiving ivacaftor. [10] An additional pediatric study of 52 patients 6 to 12 years of age showed a 12.5% improvement in FEV1 and a 2.8 kg increase in weight. A decrease in sweat chloride of 54 mmol/L was also seen. [11] In both studies, the incidence of adverse events was similar in both treated and placebo groups.

Similar results were observed in studies examining non-G551D gating mutations. [12] These 36 patients also showed significant improvements in FEV1, sweat chloride measurements, changes in BMI, and quality of life indices. Therefore, the FDA also approved ivacaftor for G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, G1349D, and S1255P mutations in February 2014. Finally, in December 2014, one additional mutation, R117H, was added by the FDA to the list of approved CF mutations for ivacaftor administration after 69 patients greater

than 6 years of age were studied showing similar efficacy and safety data. [13] However, their decrease in sweat chloride was only 24.0 mmol/L and BMI treatment differences were not significant.

Since its initial FDA approval in 2012, follow-up studies in 144 patients with the G551D mutation have confirmed the persistence of lung function improvement (9.4% increase in adults and 10.3% in children) for up to 144 weeks on ivacaftor. [14] Additionally, treated patients continued to have reduced hospitalizations and decreased *Pseudomonas aeruginosa* culture rates, which may be related to increased mucociliary clearance. [15] There was a reduced rate of decline in FEV1. The absolute increase in weight was 5.1 kg in adults and 14.8 kg in children after almost 3 years, indicating that there was an increased rate of weight gain and improved BMI. [16] Not all the nutritional improvement may be attributed to improved lung function since treated patients also showed a normalizing in small bowel pH which may have improved pancreatic enzyme function.[14]

Although the FDA approval was for patients greater than 6 years of age, Davies et al. found ivacaftor to be well-tolerated in 34 children between 6 months and 5 years of age at doses 50 to 75 mg twice a day. [17] They also showed a significant decrease in sweat chloride with a mean drop of 44 mmol/L, and many patients showed improvement in pancreatic function with increases in stool elastase. However, 14.7% showed a higher rate of elevated liver function test results indicating the need to especially monitor these younger patients.

4. Correctors

Most patients with CF have the F508del mutation in which the defective CFTR protein has defective folding and processing in the endoplasmic reticulum, resulting in minimal amounts of CFTR at the cell surface. After screening a large number of molecules, Vertex Pharmaceuticals found two in which the CFTR molecule appears to be “corrected” in its “trafficking” through the cytoplasmic to the cell membrane. Importantly, the F508del-CFTR corrected by VX-809 (subsequently named lumacaftor) appears to have biochemical and functional characteristics similar to normal CFTR such as biochemical susceptibility to proteolysis, time in the plasma membrane, and single-channel openness. [18]

Although there was a statistically significant reduction in sweat chloride values, no effect was seen in CFTR function in the nasal epithelium as measured by nasal potential difference (NPD) or in lung function as measured by FEV1. Therefore, although it appeared to be safe and was well tolerated at all doses, there did not appear to be any significant effect on CFTR function in upper and lower respiratory tracts. Indeed, a phase 2 study with 140 patients did not show any difference in lung function although there was a slight reduction in sweat chloride of 2.9 mmol/L which was barely significant ($p=0.04$).

VX-661 is another corrector with very similar structure to lumacaftor (see Figures 3 and 4). In a Phase 2 study of 128 adult patients with homozygous F508del mutation in whom four doses of VX-661 (10, 30, 100, and 150 mg) dosed once daily were given either alone or with ivacaftor

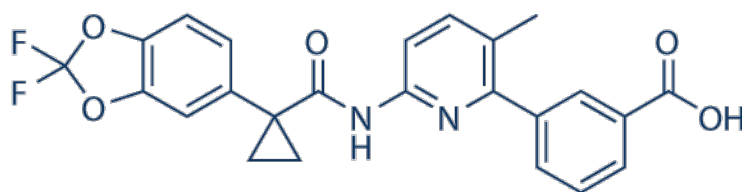


Figure 3. Structural formula of lumacaftor (VX-809)

tor150 mg twice a day for 28 days. Interim results found decreases in sweat chloride with both treatments. However, significant increases in FEV1 were found in both doses 100 mg and 150 mg of VX-661 with ivacaftor at 9% and 7.5% over baseline, respectively. [19]

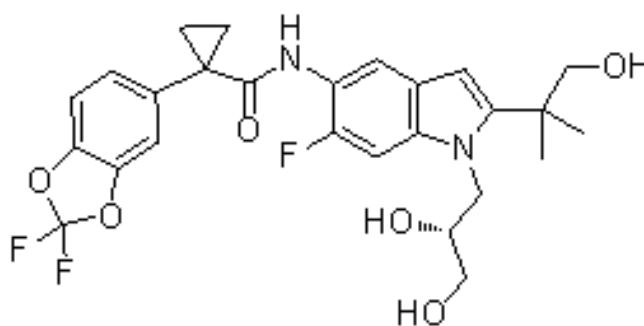


Figure 4. Please Add Caption

[20] There were significant improvements in the mean absolute change in percent predicted of FEV1 and BMI after 24 weeks. Because there appeared to be no difference in two doses studied, the submission to the FDA selected lumacaftor 400 mg BID plus ivacaftor 250 mg BID. An open label roll-over study is still in progress and expected to continue for another 24 weeks.

Patients receiving just VX-661 monotherapy in the Phase 2 study also did not show any improvement, further supporting the strategy of combining a corrector and potentiator in treating patients with F508del mutation. In 2015, Vertex is starting a series of large-scale Phase 3 studies examining the efficacy of the combined therapy with VC-661 and ivacaftor in patients with one or two copies of the F508del mutation.

5. Conclusions

The capability of molecules to enhance CFTR protein activity offers potential new treatment options for patients with CF. Long-term follow-up studies on ivacaftor, the first CFTR modulator to obtain FDA approval, look very promising. However, the drawback with these targeted therapies is the wide range of CFTR dysfunction seen in CF. Expanding the use of ivacaftor to nine other gating mutations only benefit about 10% of the total CF patient population.

Combination therapy appears to offer the optimal opportunity for many more patients with CF to benefit from modulating CFTR protein. The preliminary studies on ivacaftor with lumacaftor for patients with homozygous F508del mutation look promising and may benefit another 50% of patients. Whether the combination of VC-661 and ivacaftor is more effective remains to be seen for these patients and those with one F508del and a gating mutation, which represents another 30% of patients.

Although Vertex has been the first to develop chemicals which correct trafficking of F508del-CFTR and restoring its activity, other companies such as Novartis are also actively testing other molecules, such as picolinamide-based compounds. [21] It is hoped that with increased competition from other companies, the high cost of these medications can be lessened.

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