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eCysticFibrosis Review VOLUME 5, ISSUE 9

The Effects of CFTR-modifying therapies

In this Issue...

While therapies treating the downstream consequences of cystic fibrosis (CF), such as antibiotics and therapies that improve mucus clearance, have had a significant impact on outcomes for people with CF, it has now become clear that the basic defect in CF - the absence or dysfunction of CFTR — can be modified by small-molecule correctors and potentiators. This advance changes the paradigm of CF treatment, with clinical trials demonstrating significant improvements in lung function and reductions in pulmonary exacerbations following treatments which restore CFTR function.

In this issue, we review key research into the effects of CFTR modifiers in patients with CF due to G551D, R117H, and other class III CFTR gating mutations, as well as the use of ivacaftor and lumacaftor in combination to treat the class II F508del CFTR mutation.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Explain the relevance of specific mutations in people with CF to new therapies currently available or likely to be approved in the near future.
- Identify which patients are suitable for disease-modifying therapies based on mutation class.
- Explain the risk and benefits of CFTR modification therapy

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Michael P. Boyle, MD, FCCP, discloses that he has served on scientific advisory boards for Gilead Sciences, Inc, Genentech, Vertex Pharmaceuticals Incorporated, and Savara. He has also served as Principal Investigator for Vertex Pharmaceuticals.

No other planners have indicated that they have any financial interests or relationships with a commercial entity.
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**IMPORTANT CME/CE INFORMATION**

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Guest Faculty Disclosures

Dr. Stuart Elborn has disclosed that he has served as a consultant for Boehringer Ingelheim and Vertex. He has received research support from Vertex, Gilead, and Novartis.

Unlabeled/Unapproved Uses

Dr. Stuart Elborn has disclosed that he will discuss off-label or unapproved uses of lumacaftor, ivacaftor, and ataluren.

Planning Committee Disclosures

COMMENTARY

Over the past four years the treatment for people with cystic fibrosis (CF) has been undergoing radical change. Until 2012 all therapies recommended for the management of cystic fibrosis treated the downstream consequences of CFTR dysfunction. Antibiotics, treatments that improve mucociliary clearance and antiinflammatory therapies have been used effectively in CF, improving lung function by around 5%, reducing the frequency of pulmonary exacerbations, and improving symptom scores measured by the CFQ-R respiratory domain. The focus now has turned to developing therapies that can correct the basic defect in CF by correcting defective CFTR protein function.
Understanding how these developing therapies function begins with increased knowledge of both the biology of CFTR production, from gene to cell membrane, as well as the targeting of pathways to correct the impact on CFTR gene mutations. Investigations into these mutations have identified six overall classes of defective CFTR:

- **Class I** mutations result in no manufacture or reduced manufacture of CFTR protein because of a defect in the translation process. The best examples are mutations with a stop codon, such as G542X, which interrupts the transcription of CFTR protein.

- **Class II** mutations have a defect in processing the completed protein. Proteins with class II mutations fail to move from the protein assembly part of the cell (Golgi apparatus) to the cell surface and are recycled within the cell by a series of processes within the proteasome. An example of this mutation is F508del, the world's most common CFTR mutation. Class II mutations usually remain defective in function, even if their degradation by the proteasome can be prevented.

- **Class III** mutations are less severe mutations of the CFTR protein. The full protein is assembled and subsequently modified within the cell and delivered to the cell membrane. However, the mutation results in no function of the protein at the cell membrane, where it should conduct chloride and bicarbonate ions. This is rather like closing a gate, and these mutations are often referred to as "gating mutations."

- **Class IV** mutations are similar to class III mutations, with the complete protein being assembled and delivered intact to the cell membrane. However, in class IV mutations, while the gate is not as tightly closed, the channel through which chloride and bicarbonate are transported remains restricted, leading to reduced function of CFTR. An example of this mutation is R117H, which is associated with a less severe phenotype of CF, often with pancreatic sufficiency, less lung function impairment, and a lower prevalence of chronic *Pseudomonas aeruginosa* infection.

- **Class V** mutations are also fully assembled and present in the cell membrane, but there is a less-than-normal amount of CFTR on the cell surface. These CFTR mutations often lead to abnormal mRNA splicing.

- **Class VI** mutations result in the protein being less stable, so it falls out of the membrane back into the cell where it is recycled back up again. This reduces the amount of CFTR available and is associated with less severe phenotypic CF.

The identification of the biological processes within the cells of people with CF who have different mutations is an excellent example of a precision-medicine approach to new therapies. Specific drugs or combinations of drugs are required to address these different processes. For class I CFTR mutations, drugs that overcome the stop codon mutations by allowing read-through in the transcription process have been developed and have shown positive effects in the laboratory. A clinical trial has been undertaken with ataluren, a drug derived from an aminoglycoside. This study demonstrated no overall effect on lung function or pulmonary exacerbations. However, in a subset of participants who were not taking an inhaled aminoglycoside (mostly tobramycin) a benefit compared to that with placebo was found. Further studies are now underway to determine whether this may be an effective treatment in this group of patients.

For class II CFTR mutations, such as F508del, lumacaftor helps overcome the processing defect and ivacaftor acts on the gating defect of the mutated CFTR protein. Two large clinical trials have demonstrated improved lung function and decreased exacerbations with this drug combination. It is possible that for this particular defect, two correctors will be necessary to overcome the complex pathways in processing CFTR from the Golgi to the cell membrane. Several drug development programs are now exploring this approach, as well as seeking to identify more efficient corrector agents.

The treatment of class III mutations such as G551D remains the proof of principle for this CFTR modification approach. The majority of class III mutations were corrected by ivacaftor in the laboratory, and this has translated to impressive clinical responses in lung function, exacerbations, and symptoms. The data described in this issue suggest that these effects are sustained and complemented by other important effects, which may in the longer term result in significant modification of disease progression.
The situation for class IV mutations (also described within this issue) is a little more complex. Longer-term studies are required to clarify exactly when and how to use ivacaftor effectively in this patient group. For a large number of other class IV, as well as class V and class VI mutations associated with some residual function in the abnormal CFTR, further research and possibly individual patient studies (sometimes called N = 1 studies) will be required to determine benefit from treatment. Some novel assays, such as using rectal or nasal biopsy specimens in Ussing chambers, can check whether a patient's cells are responsive to corrector and potentiator therapy. This approach may be a helpful way to proceed when considering using these drugs in the less common CFTR mutations associated with residual function.

Other approaches to correcting CFTR function are also being explored. Gene therapy using a liposomal vector has been studied in a proof-of-concept trial in the United Kingdom, with results just published which demonstrate a stabilization of lung function. A major advantage of gene therapy is its potential to work independently of the specific mutation and so may be applicable to all people with CF. Other novel vectors that are more efficient than liposomes are being developed for gene therapy approaches, as well as other molecular approaches using very innovative therapies that allow gene editing at the level of the DNA or RNA.

Cystic fibrosis researchers have been pioneers in translating an understanding of the biology of mutated CFTR all the way through to therapies that are now being used in the clinic and have the potential to change the natural history of the disease. Early intervention with ivacaftor before the development of bronchiectasis in the lung could result in the postponement of disease progression and allow children with the G551D CFTR mutation to develop normal lungs. Over the next ten years we will see a number of further innovative therapies introduced to correct the CFTR dysfunction and will be further challenged to understand the best drug or combinations of drugs for patients with specific mutations, as well as when is optimal in the disease progression to start therapy.

Reference

**IVACAFTOR THERAPY AND A G551D CFTR MUTATION**


The G551D CFTR mutation occurs in around 4% of people with CF and in combination with a second severe mutation results in a severe CF phenotype and sweat chloride concentration of around 100 mmol/L. This mutation results in a protein that does not transport chloride or bicarbonate ions when stimulated, thereby altering the surface liquid in the airways, which impairs mucociliary clearance and innate immune function. The protein is present in the correct place in the cell membrane but is mostly closed. This is called a "gating defect" or class III mutation. It is associated with a severe phenotype similar to people with class I (stop codon with no protein produced such as G542X) and class II (processing defect such as F508del) CFTR mutations.

Ivacaftor has now been used by many patients with at least one G551D CFTR mutation for over two years as an open label extension of the randomized, placebo-controlled trials STRIVE\(^1\) (adults) and ENVISION \(^2\) (children). In the 219 patients enrolled, the benefits of improved spirometry, weight gain, and reduced exacerbations were maintained. No new adverse effects were demonstrated. This is very reassuring data and suggests there is no tachyphylaxis of the key beneficial effects of ivacaftor and no additional concerns about adverse effects. Careful pharmacovigilance must be maintained, as there is still limited patient–year experience with this drug.

A further three mechanistic studies report very interesting data on the effect of ivacaftor in people with CF starting the drug for clinical indications. The studies were designed to explore the specific impact of treatment on malabsorption, infection, and inflammation.

Two reports (Rowe et al and Heltshe et al) are from the G551D Observation-AL (GOAL) study, which included 153 subjects studied over the first six months following initiation of ivacaftor therapy. The improvement in spirometry, BMI, sweat chloride, and exacerbations was confirmed by comparing to baseline measurements prior to treatment. Additionally, significant improvements in mucociliary clearance, gastrointestinal pH and airway infections were also demonstrated.

Thirty percent of those who were culture positive for \textit{P. aeruginosa} prior to ivacaftor treatment were negative the year following treatment. Additionally, the majority (88%) of those uninfected with \textit{P. aeruginosa} remained uninfected in the year after ivacaftor use began, as compared with the prior year. Ivacaftor also significantly reduced the occurrence of mucoid \textit{P. aeruginosa} and Aspergillus in sputum culture but showed no measurable effect on \textit{Staphylococcus aureus} or other common CF pathogens.

In the study by Pohl et al, intriguing effects on neutrophil function were demonstrated. In previous studies defective CFTR function has been shown to impair neutrophil cytosolic ion homeostasis, leading to reduced degranulation. In this study, ivacaftor treatment corrected neutrophil degranulation and normalized bacterial killing.

These studies point to important pulmonary and systemic effects of ivacaftor in patients with a G551D CFTR mutation and suggest a range mechanisms to explain its therapeutic benefit. These studies also suggest that treatment may slow down disease progression and, if used before bronchiectasis develops, may prevent chronic infection.

References
IVACAFTOR IN OTHER CLASS III (GATING) MUTATIONS


Ivacaftor has been shown to increase chloride transport in cell lines in other class III gating mutations at a level similar to that of G551D. However, these mutations are rare, occurring in around 1% of people with CF. This makes it impossible to study each mutation in an individual clinical trial. To overcome this problem, all potentially responsive gating mutations were included in a combined, randomized, placebo-controlled, crossover study of 39 people with CF older than six years with at least one gating mutation other than G551D. The 150 mg dose of ivacaftor was the same as used in the STRIVE and ENVISION trials.

In the KONNECTION study, De Boeck et al randomized patients to receive either ivacaftor or placebo for eight weeks. After a four- to eight-week washout phase, each patient was crossed over to the other treatment for an additional eight weeks. An open-label extension of ivacaftor treatment continued for a further 16 weeks to assess the durability of any treatment effects. Nine different gating mutations were studied with two to eight patients in each mutation subgroup.

Eight weeks of ivacaftor resulted in significant improvements in percent predicted FEV₁, BMI, and CFQ-R scores and significantly reduced sweat chloride concentrations. These effects were maintained through 24 weeks, and the effect size was similar to that in the STRIVE and ENVISION studies. The study was too small to detect an effect on pulmonary exacerbations.

The four patients with one particular mutation, G970R, had little change in sweat chloride concentration (-6 mmol/L compared to -56 mmol/L in the overall group), as well as little change in CRQ-R respiratory symptoms or FEV₁. While this mutation responds well in the cell lines tested in the laboratory, it not clear why there was a limited clinical response. The Food and Drug Administration (FDA) approved Ivacaftor for the other eight mutations studied:

<table>
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<tr>
<th>G551S</th>
<th>G178R</th>
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<th>G1349D</th>
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<tr>
<td>S549N</td>
<td>S549R</td>
<td>S1251N</td>
<td>S1255</td>
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The European Medicines Agency (EMA) is currently considering ivacaftor for these extended indications. This study is important, as it facilitated approval of ivacaftor in rare mutations and is a good example of how precision medicine can be advanced in rare diseases.

IVACAFTOR IN PATIENTS WITH THE R117H MUTATION


Ivacaftor has also been studied in individuals who have the class IV mutation R117H. This is a complex mutation that shows in vitro properties of impaired gating and conductance and is associated with residual function of CFTR. In laboratory studies using cell lines with this mutation, ivacaftor was shown to improve chloride transport and has now been studied in a randomized, placebo-controlled trial.

The R117H CFTR mutation is associated with a variable disease phenotype. It often presents in adults who may have had few symptoms in childhood. The phenotype of individuals with
this mutation significantly depends on a second genetic variation in intron 8 (c1210-12[T]), with variations in the number of thymidines just before exon-9 affecting the splicing of DNA. Individuals with seven or nine thymidines splice efficiently and make enough mutant protein with sufficient overall function to result in a normal phenotype. In contrast, in people with five thymidines (5T) splicing is inefficient and, as a consequence, less mutant protein produced due to an increased rate of exon skipping. In individuals with R117H/5T and a second severe mutation, there is still variability in phenotype. Approximately 50% of people with this genotype are pancreatic-sufficient and have a wide range of impairment of FEV₁ but in general have a slower rate of decline in FEV₁, a lower prevalence of Pseudomonas aeruginosa infection, and a lower incidence of CF-related diabetes than the general CF population.

The KONDUXT study included 69 patients with CF who had one R117H CFTR mutation and a second mostly severe mutation on the second chromosome. Around 75% had F508del as a second mutation: 70% had R117H/5T, with the remainder having R117H/7T. Sweat chloride concentrations at randomization were 70 mmol/L, which is lower than is observed in individuals with CF due to G551D or other gating mutations (around 100 mmol/L). The baseline FEV₁ was 73% predicted (higher than the baseline lung function in STRIVE/ENVISION or KONNECTION). The trial was conducted over 24 weeks as a placebo-controlled double blind randomized trial and recruited subjects over 6 years of age. Sixty-five patients continued in an open-labeled extension: no significant difference was demonstrated in FEV₁ compared to placebo, although significant reductions in sweat chloride of around 24 mmol/L and an improvement in the CFQ-R respiratory domain of 8 points were achieved. While no significant impact was seen on exacerbations, insufficient numbers of patients were included in the study to assess this properly.

There are a number of possible reasons for the variability and response in this study. First, in patients with very little impairment in FEV₁ there may be little benefit from potentiator therapy action directly on FEV₁. However, it may be that in such patients ivacaftor could prevent the development of lung damage. The magnitude of the reduction in sweat chloride concentrations suggests the drug was having an effect on CFTR function at the sweat gland. A further complication with the 5T configuration on intron 8 is that there may have been insufficient CFTR at the cell membrane to have a large effect on mucociliary clearance following treatment with ivacaftor. Splicing in this situation is variable and cannot be predicted.

The FDA has approved the use of ivacaftor in patients over 6 years who have at least one R117H CFTR mutation and the EMA is currently considering the indication in Europe.

**DRUG PROTEIN INTERACTIONS BRING NEW CHALLENGES**


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The combination of ivacaftor and lumacaftor has been studied in two important laboratory studies which have used an ex vivo airway epithelial cell model to investigate interactions between lumacaftor and ivacaftor with the CFTR protein. In the first of these studies, Cholon et al demonstrated that ivacaftor reversed lumacaftor-mediated CFTR correction by causing destabilization of the F508del-CFTR mutated protein cell membrane. This was paralleled with a reduction of CFTR function. In the second study Veit et al also showed that ivacaftor and other potentiators reduce the correction efficacy of VX809 and the investigational corrector VX661. They also confirm that ivacaftor diminished the folding efficiency and metabolic stability of F508del-CFTR within the cell. These findings were only apparent when cells were exposed over 48 hours and were not present in shorter-term experiments.

These studies may in part explain why the clinical investigations have shown only very small improvements in sweat chloride and modest improvements in FEV₁ with the lumacaftor/ivacaftor combination. The in vitro data of combination therapy suggests that a greater clinical improvement would have been expected, but it is possible that the interaction of the two drugs reduces the effectiveness of potentiation of corrected F508del-CFTR. These interactions need to be explored further, as it is important that this phenomenon be considered in the development of further corrector/potentiator combinations.

**CORRECTOR/POTENTIATOR COMBINATION IN 508DEL**


The majority of people with CF worldwide are homozygous (50%) or heterozygous for a class II mutation. F508del is the most common class II mutation, and with a second class I, II, or III mutation is usually associated with a severe phenotype, making the restoration of CFTR function in these individuals a high priority. F508del-CFTR folds abnormally and is not processed through the cell to the membrane, where it is required for a normal function. The vast majority (> 95%) of F508del-CFTR is degraded in the proteasome and the amino acids recycled. The small amount of protein that does make it to the cell membrane is dysfunctional, with gating defects similar to those found in G551D. F508del-CFTR responds to ivacaftor but current clinical studies found in no significant clinical benefit, presumably because of insufficient CFTR at the cell membrane. Lumacaftor (VX809) was developed as a drug that would interact with mutant F508del-CFTR and overcome the intracellular processing steps to deliver the mutant CFTR protein to the cell membrane. This was achieved in the laboratory and the corrected CFTR could then be potentiated by ivacaftor.

In the phase II clinical trials patients with 160 F508del homozygous and 28 compound heterozygous were studied. This study was designed to determine the right dose of both ivacaftor and lumacaftor and elucidate the clinical outcomes in patients with homozygous and heterozygous F508del CFTR mutations. The first cohort of patients received lumacaftor for 14 days, followed by ivacaftor (150 mg or 250 mg) twice daily or placebo. Further cohorts received 200 mg, 400 mg, or 600 mg of lumacaftor daily with ivacaftor, again at 250 mg twice daily. Lumacaftor used alone had little effect, but a dose-dependent though modest reduction in sweat chloride was demonstrated for combination therapy. Similarly, there was an indication of improved FEV₁ for patients on the combination therapy.
Heterozygous patients showed no effect. These data were sufficiently strong to proceed to two large phase III studies, TRAFFIC and TRANSPORT. These studies enrolled 1,108 patients. Patients were randomly assigned to one of three treatment groups lumacaftor 600 mg daily and ivacaftor 250 mg twice daily; lumacaftor 400 mg twice daily and ivacaftor 250 mg twice daily; or placebo.

All the subjects studied were over 12 years of age and had an FEV1 of 40 - 90% predicted. The primary endpoint was FEV1 at week 24, with key secondary endpoints being BMI, CFQ-R respiratory domain, time to first exacerbation, and number exacerbations throughout the 28 week study. The two studies were run in parallel and analyzed independently; the results were combined to perform a prespecified, pooled analysis of the identical study arms. The outcomes were improvement in FEV1 of around 5% (P < .001); a significant reduction in pulmonary exacerbations with a rate ratio of 0.65 P < .05; and total number of exacerbations requiring hospitalization and those requiring antibiotics were also reduced. In the pooled analysis there was significant improvement in BMI of 0.26 kg/m2 (P < .001), as well as significant improvements in CFQ-R respiratory domain. However, the changes in the CFQ-R were less than the minimal clinically important difference, which is a validated treatment change known to be associated with meaningful symptoms improvement.

The major side effects reported more commonly in the treatment group compared to placebo was mild to moderate dyspnea and chest tightness described in about 10% of those receiving the active drug compared to 5% in patients receiving placebo. These symptoms were also seen in the phase II study in patients receiving lumacaftor only and in patients on the combination. In general these symptoms did not persist, although five patients discontinued therapy because of them. Some minor changes in transaminases were also described but no other concerning side effects were reported.

The results of this study are very encouraging as they demonstrate clinical benefit in FEV1 and reduced exacerbations in patients homozygous for the F508del CFTR mutation. The reduction in pulmonary exacerbations is an important clinical effect, as exacerbations are associated with decline in lung function and reduced survival. The modest improvement in FEV1, compared to that achieved by ivacaftor in gating mutations, is a little disappointing. However this is similar to the improvements seen with trials of both inhaled mucolytic and antibiotic therapies, both of which at this level of absolute improvement in FEV1 are associated with a reduction in further decline in FEV1. The additional benefit of combination therapy in this group of patients on already receiving optimal antibiotic therapy and mucoactive treatment is also important. Combination therapy appears safe, though patients and clinical teams need to be aware of the potential for chest tightness associated with bronchoconstriction, particularly during the first few weeks of treatment. This probably can be overcome with the use of the inhaled beta-2 adrenergic receptor agonists that many people with CF are already prescribed, and regular use of beta-2 adrenergic receptor agonists is recommended with lumacaftor/ivacaftor therapy.

Overall, these studies demonstrate that CFTR function in patients with CF caused by two F508del CFTR mutations can be modulated by a combination of corrector and potentiator combination therapy. More efficient correctors are currently being developed as single and potentially double agents to be used in combination with ivacaftor or other potentiators, some of which are in clinical trials. Modulating the function of CFTR is clearly possible, and the drive now is to identify the best combination of drugs to achieve this in all patients.
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LAUNCH DATE
This program launched on November 12, 2014 and is published monthly; activities expire two years from the date of publication.

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Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, Windows Media Player 9.0 or later, 128 MB of RAM, 800 x 600 pixels, Sound card and speakers, Adobe Acrobat Reader.

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STATEMENT OF NEED
Based on a review of the current literature, including national and regional measures, detailed conversations with expert educators at Johns Hopkins, and a survey of potential program participants, this program will address the following core patient care gaps:

Disease-Modifying Therapies
- Clinicians need guidance in understanding how new findings describing CFTR-modifying therapies may improve their treatment of patients with cystic fibrosis.
- Incomplete clinician awareness of genotype/phenotype correlations in non-pulmonary targets of CFTR-modifying therapies may limit their ability to provide optimal patient care.

Nutrition
- Clinicians lack effective guidance to increase caloric intake in patients who are nutritionally compromised.
- Clinicians do not fully understand how to manage the complexities of pancreatic enzyme replacement therapy to achieve optimal results in their patients.

Pseudomonas Aeruginosa
- Clinicians have unanswered questions about P. aeruginosa eradication in asymptomatic patients with positive cultures.
- New data and new choices for selecting initial inhaled anti-pseudomonal agents have created confusion.
- Conflicting data about pulmonary exacerbations has led to incorrect clinical assumptions and inappropriate treatment regimens.

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