Cystic fibrosis is caused by abnormalities in the cystic fibrosis transmembrane conductance regulator (CFTR), which resides at the surface of the epithelial cells. In addition to transporting chloride, CFTR regulates ion flow through the epithelial sodium channel (ENaC) channel, as well as the transport of bicarbonate and other ions. With the development of drugs that restore CFTR function, we have entered an era of precision medicine where therapies can now go beyond treating symptoms to actually correcting the underlying defect in cystic fibrosis.

In this issue, eCysticFibrosis Review Program Director Dr. Peter Mogayzel provides a snapshot of how far this new era has progressed.

**LEARNING OBJECTIVES**

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

- Describe the long-term benefits of ivacaftor therapy.
- Evaluate the effects of ivacaftor in people with non-G551D CFTR mutations.
- Explain the impact of lumacaftor/ivacaftor in people with cystic fibrosis due to two F508del CFTR mutations.

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- **THERAPY FOR NONSENSE CFTR MUTATIONS**
We have entered a new era of therapeutics, where drugs are now available to treat the underlying defect in cystic fibrosis (CF) — abnormal chloride transport caused by a defective cystic fibrosis transmembrane conductance regulator (CFTR) protein. Ivacaftor is a "potentiator" that activates CFTR located at the epithelial cell surface. Ivacaftor treatment leads to significant improvements in lung function and nutritional status in patients with CF who have at least one G551D CFTR mutation.

The significant results demonstrated in the STRIVE study in 2011 by Ramsey and colleagues\textsuperscript{1} led to the approval of ivacaftor for patients with CF caused by at least one G551D CFTR mutation. The studies by McKone and colleagues and Sawicki and colleagues (reviewed herein) demonstrate that ivacaftor has long-term benefit that has been demonstrated over three years. Importantly, not only does ivacaftor lead to an improvement in lung function with initial therapy, it also slows the rate of decline in lung function over time. This is in part because of the marked diminution in exacerbations that are known to lead to detrimental decline in lung function. Taken together, these studies indicate that over time ivacaftor should preserve lung function, thereby decreasing morbidity and improving survival. Further, because ivacaftor is unlikely to reverse bronchiectasis and other parenchymal damage, early initiation of the drug is likely to preserve lung function and thus should be thought of as a preventive therapy. Initial studies investigated ivacaftor in patients with mild to moderate lung disease. The study by Taylor-Cousar and colleagues demonstrated this therapy is also effective in those with severe lung disease and can be given safely to patients awaiting transplant or those with an FEV\textsubscript{1} less than 40% predicted.

Because ivacaftor is likely to be effective at stimulating any dysfunctional CFTR at the cell surface, studies have been undertaken to investigate whether it is effective in patients with CFTR gating mutations beyond G551D and conductance mutations such as R117H. The studies reviewed in this issue by De Boeck and colleagues and Moss and colleagues demonstrate that ivacaftor is indeed effective in potentiating CFTR in patients with these types of mutations. Other rare mutations may also amenable to ivacaftor therapy; however, studying the benefit of ivacaftor in these patients will be difficult. Novel study designs may be required to demonstrate efficacy in patients who have CF caused by rarely observed mutations.

The impressive improvement in lung function and nutritional status and decrease in pulmonary exacerbations observed in studies of ivacaftor has led to a rapid adoption of this drug in the CF population. A 2015 report by Sawicki and colleagues\textsuperscript{2} demonstrated that in the year following approval of ivacaftor, 81% of the 1,087 patients with at least one G551D CFTR mutation in the Cystic Fibrosis Foundation registry were taking this drug.

Although ivacaftor has significant impact on people with CF mutations that produce a protein that reaches the cell surface, ivacaftor is not effective in people with CF caused by F508del
CFTR mutations. Here the protein is manufactured but is degraded before it gets to the cell surface. Therefore, a two-drug therapy is required to improve chloride transport. Lumacaftor is a "corrector" that chaperones F508del-CFTR to the cell surface, where it can then be acted on by ivacaftor. The combination of lumacaftor and ivacaftor, as described by Wainwright and colleagues in the pooled results of the TRANSPORT and TRAFFIC studies, has demonstrated a modest but significant improvement in lung function after 24 weeks of therapy. More importantly, it is also associated with a dramatic reduction in pulmonary exacerbations requiring intravenous antibiotics or hospitalization. These findings led to the July 2015 approval of lumacaftor/ivacaftor for patients aged ≥ 12 years with cystic fibrosis caused by two F508del CFTR mutations.

The modest improvement in lung function in this patient group for lumacaftor/ivacaftor compared to ivacaftor therapy alone in those patients with G551D CFTR mutations suggests that a more robust therapy is possible. Therefore, a number of drugs are in development to find more effective corrector/potentiator combinations, such as VX661/ivacaftor. Additionally, add-on therapies are being developed that may act to stabilize CFTR at the cell surface or increase the production of CFTR protein, as well as therapies to enhance trafficking of F508del-CFTR to the cell surface. CFTR potentiator therapy may also be combined with therapies that affect other aspects of the pathology or the pathobiology of cystic fibrosis, such as blocking the hyperabsorption of sodium from the airway surface by the epithelium sodium channel (ENaC).

The current CFTR potentiators and correctors are not effective for people with CFTR mutations that do not lead to production of any protein. Ataluren is a drug being developed to allow a readthrough of premature stop codons in people with nonsense or class 1 mutations. Kerem and colleagues describe the results of a 48-week trial in which people not treated with tobramycin who received ataluren had a slower rate of decline in lung function compared to patients receiving placebo.

As we enter this new era of therapy, it is important to remember that CFTR modulators and other therapies that improve CFTR function are unlikely to reverse bronchiectasis and permanent damage in the lung. Therefore, we must aggressively use current symptomatic therapies to preserve lung function and allow the best results from the current and future modulator therapies. Additionally, beginning these therapies as early as possible will lead to restoration of chloride transport and prevent symptoms caused by CFTR defects.

Commentary References

LONG-TERM BENEFITS OF IVACAFTOR


Sawicki GS, McKone EF, Pasta DJ, et al. Sustained Benefit from Ivacaftor Demonstrated by Combining Clinical Trial and Cystic Fibrosis Patient Registry Data. Am J Respir Crit Care Med. 2015 Oct 1;192(7):836-842.
The initial phase 3 trial of ivacaftor (STRIVE) demonstrated significant improvement in lung function, weight gain, and a decrease in exacerbations over 48 weeks. Two further studies have been performed to show a long-term benefit beyond the first year of ivacaftor therapy.

The PERSIST trial, described by McKone and colleagues, followed people with cystic fibrosis (CF) caused by at least one G551D CFTR mutation who were enrolled in either the STRIVE or ENVISION trials with ivacaftor therapy of 150 mg every 12 hours. They followed 48 children aged 6 to 11 years, and 144 older patients (children aged ≥ 12 years and adults), for an additional two years after the initial phase 3 trial. Patients previously treated with ivacaftor showed sustained improvements in lung function as measured by FEV$_1$, weight and body mass index (BMI), and a decrease in pulmonary exacerbations for up to 144 weeks. The absolute improvement in FEV$_1$ was 9.4% to 10.3%. Patients initially treated with placebo in the prior study also had an improvement in absolute lung function as measured by FEV$_1$ at 96 weeks of 9.5% to 10.5%.

Sawicki and colleagues investigated the long-term benefit of ivacaftor by analyzing the US Cystic Fibrosis Foundation Patient Registry. They matched patients ≥ 6 years of age who had a G551D CFTR mutation and received ivacaftor in clinical trials for up to 144 weeks with patients homozygous for the F508del CFTR mutation. Patients were matched in a case-controlled fashion; variables used for matching included gender, age, year of CF diagnosis, sweat chloride value, and nutritional and infection status, as well as oral and inhaled chronic therapies.

The authors calculated that there was a slower rate of decline of lung function in patients with G551D CFTR mutations treated with ivacaftor compared to the F508del homozygous control group. The annual decline in lung function of the G551D cohort was -0.91% compared to -1.72% for the F508del homozygous patients, a 10.7% difference at the end of three years (P < .001). Further, for the cohort of G551D patients, treatment with ivacaftor was shown to improve body mass index and weight-for-age z scores. Taken together, these two studies demonstrate the long-term benefit of ivacaftor therapy in patients with at least one G551D CFTR mutation and suggest there is a slower rate of lung function loss over time. From a clinical viewpoint, early intervention with this therapy should greatly ameliorate the morbidity and mortality associated with CF.

**IVACAFTOR AND SEVERE LUNG DISEASE**


The initial STRIVE study of ivacaftor therapy was conducted in people with cystic fibrosis (CF) with an FEV$_1$ of > 40% predicted. This study by Taylor-Cousar and colleagues investigated the safety and effectiveness of ivacaftor in people with at least one G551D CFTR mutation and advanced lung disease through an expanded access program in the United States. Forty-four people aged 6 and over with an FEV$_1$ of ≤ 40% predicted or listed for lung transplantation received ivacaftor 150 mg every 12 hours. The primary endpoint was safety as determined by adverse events, with secondary endpoints including the assessment of lung function and weight.

The investigators report a reasonable safety profile for ivacaftor in this group of patients with severe lung disease, with 20 patients experiencing at least one pulmonary exacerbation during the 24 weeks of the study. There was an improvement in lung function, with the average absolute increase in percent predicted FEV$_1$ of 5.5. This increase was evident at two weeks after starting therapy, and the improvement in lung function continued over the 24 weeks of therapy. There was also an absolute increase in weight of 3.3 kg compared to baseline.
This study demonstrates that ivacaftor can lead to improvements in lung function and nutritional status in people with severe CF lung disease and is well tolerated in this group. These results suggest that ivacaftor 150 mg every 12 hours may be advantageous for people with CF from at least one G551D CFTR mutation who have significant lung disease.

THE MECHANISM OF IVACAFTOR EFFECTS IN PEOPLE WITH DUE TO A G551D CFTR MUTATION


The G551D observational study (GOAL) was designed to determine the mechanism by which improvements in lung function, weight, and other clinical features occurred in patients cystic fibrosis (CF) caused by at least one G551D CFTR mutation who received ivacaftor. Phase 3 trials demonstrated significant improvement in both lung function and nutritional status.

The study by Rowe and colleagues investigated several mechanisms that might be affected by ivacaftor therapy. They studied 151 individuals age ≥ 6 years who received ivacaftor 150 mg twice daily. Using data from the US Cystic Fibrosis Patient Registry, they analyzed clinical trends one year prior to ivacaftor initiation and one year following the onset of therapy. They found similar increases in lung function as measured by FEV1, body mass index, and decrease in exacerbations, as had been found in the previous phase 3 STRIVE study of ivacaftor therapy.

Twenty-three people participated in a mucociliary clearance substudy; the average age of these patients was 25.2 years. Average mucociliary clearance at 60 minutes was more than twice the baseline value in patients treated with ivacaftor for one month.

Additionally, Rowe and colleagues demonstrated a marked diminution in the number of patients who were infected with Pseudomonas aeruginosa after initiation of ivacaftor therapy. Airway cultures from 52% of patients grew P. aeruginosa prior to therapy, but only 34% of patients were infected six months following ivacaftor initiation. The rate of hospitalization declined from 27% in the six months prior to therapy to 8% in the six months following the initiation of therapy. Despite the changes in Pseudomonas aeruginosa infection, there were no significant changes in any sputum biomarkers of inflammation, including neutrophil elastase activity.

To investigate the mechanism of increased weight gain, 11 patients enrolled in a sub-study which measured pH of the gastrointestinal tract via a "pH pill." The average age of these patients was 32.2 years. There was a marked increase in pH of 1.46 (95% confidence interval 0.86–2.06), suggesting that bicarbonate secretion through CFTR was partially restored by ivacaftor therapy.

The study by Heltshe and colleagues performed a further analysis of the microbiology of the airway cultures obtained in the GOAL study, comparing the airway cultures in the two years before ivacaftor therapy with the year after beginning ivacaftor. The authors confirmed the decrease in P. aeruginosa infection and further characterized the airway microbiology as showing a decrease in mucoid P. aeruginosa infection, as well as a decrease in Aspergillus infection. This reduction in P. aeruginosa frequency, however, was not significantly associated with an improvement in lung function, BMI, hospitalization, or exacerbation rate alone. Of note, when looked at as a continuous variable, the proportion of positive cultures had a weak but
statistically significant association with lung function as measured by FEV$_1$. A 10% reduction in *P. aeruginosa* positivity corresponded with a 0.765% increase in FEV$_1$ percent predicted (95% confidence interval 0.4% – 1.5%, *P* = .030). Ivacaftor therapy had no impact on infection with *Staphylococcus aureus*, methicillin resistant *S. aureus*, *Stenotrophomas maltophilia*, or *Burkholderia cepacia*.

Taken together, these two studies of real-world treatment – demonstrating improved mucociliary clearance and decreased infection with *P. aeruginosa* – confirm ivacaftor's effect on the basic mechanisms underlying lung damage in CF and suggest that early therapy with this drug in the appropriate population may significantly ameliorate symptoms. Additionally, the improvement in gastrointestinal pH may be responsible in part for the improvement in nutrition.

**IVACAFTOR IN MUTATIONS BEYOND G551D**


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Initial studies of ivacaftor focused on people with cystic fibrosis (CF) from at least one G551D CFTR mutation; however, ivacaftor also has the potential to improve chloride transport in any defective CFTR that resides at the apical surface of epithelial cells. Therefore, studies were undertaken to investigate the effect of ivacaftor in people with other CFTR mutations.

De Boeck and colleagues evaluated 39 individuals with CF aged ≥ 6 years with non-G551D CFTR gating mutations in the two-part, double-blind crossover and open-label extension KONNECTION study. Patients received eight weeks of either ivacaftor 150 mg twice daily or placebo for eight weeks in a crossover fashion with a four- to eight-week washout period. This was followed by a 16-week open label period, so that some patients received 24 weeks of continuous therapy.

In a model-adjusted absolute mean, the difference in lung function measured by FEV$_1$ between ivacaftor and placebo groups was 10.7% (95% confidence interval 7.3-14.1). There were also improvements in body mass index (BMI), sweat chloride and quality of life as measured by the CFQ-R. During the open label period there was a 13.5% improvement in absolute FEV$_1$ (range -6.9 to 36.5), and a 1.3 kg/m$^2$ (range 0.16 to 2.9), improvement in body mass index. These results were similar to those obtained in individuals with CF due to at least one G551D CFTR mutation.

In the KONDUCT study, Moss and colleagues investigated the effect of ivacaftor 150 mg twice daily in patients with CF from at least one R117H CFTR mutation. This was a 24-week, placebo-controlled, double-blind study that enrolled 69 patients aged ≥ 6 years. The investigators found an improvement in absolute FEV$_1$ of 2.6% in those treated with ivacaftor compared to 0.5% in the placebo group.

An interesting phenomenon was seen in the washout from this study. Prior to patients enrolling in a 12-week open label study, there was a rapid loss of lung function back to baseline following discontinuing ivacaftor; however, lung function improvement was restored during the open label phase with a 5.5% improvement in FEV$_1$. 

Ivacaftor did not lead to improvement in lung function in children ages 6 to 11, and ivacaftor therapy seemed to have a more profound effect in adults and those with more severe lung function. This trial highlighted the difficulty of studying patients with normal or mildly impaired lung function, as well as a group of patients with significant phenotypic variability, which is the case for those patients with R117H CFTR mutations.

The results of these two studies led to an expansion of the initial Food and Drug Administration indication for ivacaftor to include gating CFTR mutations beyond G551D (G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D), as well as patients with CF due to R117H CFTR mutations. These data suggest that these drugs are effective in children age 6 and above and are likely to be beneficial in younger children as well, as was seen in studies of patients with cystic fibrosis CF with G551D CFTR mutations.

**IVACAFTOR TREATMENT IN F508DEL HOMOZYGOUS INDIVIDUALS**


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Approximately half of patients with cystic fibrosis (CF) have two F508 CFTR mutations; therefore, developing a therapy for this group has significant clinical importance. Since ivacaftor therapy alone does not benefit this group of patients, a combination therapy of ivacaftor with lumacaftor (a CFTR corrector that can chaperone defective F508del CFTR protein to the cell surface in combination with ivacaftor) was trialed in two distinct studies — TRAFFIC and TRANSPORT. This paper by Wainwright and colleagues reports on the pooled results.

Overall, 1,108 individuals with CF due to two F508del CFTR mutations participated. Subjects received either lumacaftor 600 mg once daily or 400 mg twice daily in combination with ivacaftor 250 mg twice daily, or placebo for 24 weeks. The baseline FEV1 for these patients aged 12 and older was 61% of predicted. Patients in both dosage cohorts showed a significant improvement in lung function as measured by FEV1, with mean improvement in absolute FEV1 ranging from 2.6 to 4.0%. There was also an improvement in nutritional status as measured by body mass index (BMI), and a marked diminution in the number of exacerbations, falling by 61% in the higher dosage group in the number of patients requiring hospitalization, and by 56% in the people requiring intravenous antibiotics.

While the patients receiving lumacaftor/ivacaftor had an increased incidence of adverse events, including chest tightness or other respiratory symptoms, they also experienced a significant decrease in serious adverse events (primarily pulmonary exacerbations). The dose of ivacaftor in this trial was higher than that typically given to patients receiving ivacaftor alone because of drug interactions, which lead to more rapid degradation of ivacaftor.

The results of this trial led to the approval of lumacaftor/ivacaftor by the Food and Drug Administration in July, 2015. The combination is indicated for children age 12 years and above and adults with CF from two F508del CFTR mutations.
Ataluren is an experimental drug designed to allow ribosomes to read through premature stop codons in class 1 (aka "nonsense") CFTR mutations. These are mutations that end in the letter X, where a stop has been abnormally inserted into the coding region. Kerem and colleagues describe a phase 3 trial of 238 patients with at least one stop codon CFTR mutation, enrolled at 36 sites in 11 countries. Children aged ≥ 6 years and adults with an FEV₁ between 40% and 90% predicted, received ataluren three times daily or a matching placebo for 48 weeks. The relative change in percent predicted FEV₁ did not differ significantly between the ataluren and placebo treated subjects at the end of the trial (-2.5% vs -5.5%, respectively). In addition, the frequency of pulmonary exacerbations did not differ between the treated and untreated individuals.

However, post hoc analysis of a subgroup of patients not using chronic inhaled tobramycin did show a difference in FEV₁ between the ataluren treated individuals and those receiving placebo. There was a 5.7% difference (95% confidence interval 1.5%-10.1% in relative percent predicted, P = .0082) and fewer exacerbations in the ataluren treated group (1.42 events) compared to 2.18 events in the placebo group (P = .0061). The safety profiles were generally similar for ataluren and placebo, except for the occurrence of increased creatinine concentration associated with acute kidney injury, which occurred in 15% of the people treated with ataluren compared to < 1% of the placebo group.

One explanation for the findings in this trial is that tobramycin, which is an inhaled antibiotic that binds to bacterial ribosomes, interferes with ataluren at a cellular level. This is a plausible explanation for the results and has led to the initiation of a second phase 3 trial studying ataluren in people who are not receiving inhaled tobramycin. This trial has recently completed enrollment and results should be available in the coming year. Ataluren therapy did not have an effect on sweat chloride or nasal potential difference measurements in the patients treated with ataluren or placebo.
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LAUNCH DATE

This program launched on December 30, 2015 and is published monthly; activities expire two years from the date of publication.

HARDWARE & SOFTWARE REQUIREMENTS

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 Monitor settings: High color at 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.

Incorporated. In addition, he has served as a consultant for Hill Rom.

Suzanne Sullivan has received honorarium from Vertex Pharmaceuticals Incorporated.

No other planners have indicated that they have any financial interests or relationships with a commercial entity.

Guest Author's Disclosures

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- 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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