Emerging Disease-Modifying Therapies in Cystic Fibrosis

Author’s Note:
REPORT FROM NACFC 2017

Editor’s Note: Dr. Clancy attended this year’s NACFC and has provided this report.

Many of the emerging disease-modifying therapy presentations at the most recent NACFC (North American Cystic Fibrosis Conference) — held November 2017 in Indianapolis — focused on addressing the F505del CFTR defect. This mutation, heterozygous in the large majority of persons with CF, has proved particularly difficult to correct, with defects in folding, opening, and stability at the cell membrane.

Taylor-Cousar and et al reported the results (since published in NEJM)¹ of a large phase 3 study of tezacaftor/ivacaftor in patients > 12 years and homozygous for F508del. After 24 weeks, tezacaftor/ivacaftor increased FEV₁ percent predicted by 4% over placebo, and lowered the rate of pulmonary exacerbation by 35%. The incidence of adverse events was similar in both the treatment and placebo groups, with serious adverse events less frequent with tezacaftor/ivacaftor.

Rowe et al reported the results (also published in NEJM)² of a phase 3 study of tezacaftor/ivacaftor vs ivacaftor alone vs placebo in CF patients with one copy of F508del and a second mutation predicted to have some residual function. Improvement in the absolute FEV₁ percent predicted was 6.8% for tezacaftor/ivacaftor and 4.7% for ivacaftor alone (compared with placebo), with adverse events similar across the intervention groups. In addition, scores on the respiratory domain of the Cystic Fibrosis Questionnaire-Revised were also significantly increased in the tezacaftor/ivacaftor and ivacaftor groups compared with placebo.

Clinical trials continue on “next generation correctors” — CFTR modulators added to tezacaftor/ivacaftor. Early evidence has shown efficacy in both F508del/F508del and F508del/minimal CFTR function genotypes.

Addressing F508del from another direction were reports on the phase 1 open label, proof of concept studies of QR-010, a first-in-class RNA-based oligonucleotide designed to target the mRNA in patients with the F508del mutation. This inhaled therapy seeks, in essence, to introduce a short stabilized RNA template that instructs F508DEL CFTR airway cells to produce normal CFTR. Results in patients homozygous for F508del showed early evidence of QR-010 tolerance and potentially restored CFTR activity.

References:

In this Issue...
Cystic fibrosis (CF) is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Drugs that restore CFTR function are termed CFTR modulators, and currently approved CFTR modulators include the potentiator ivacaftor and the combination F508del corrector lumacaftor + ivacaftor. Prior randomized, placebo controlled trials have demonstrated benefits of these therapies in patients with gating and conductance mutations (ivacaftor) and patients with two copies of the common F508del mutation (lumacaftor combined with ivacaftor).

In this issue, Dr. John P. Clancy from the Cincinnati Children’s Hospital Medical Center examines recent research regarding CFTR modulation, including:

- evidence for long term benefit
- lower limit of measureable benefit
- relationships with changes in lung function and sweat chloride
- potential side effects associated with currently available CFTR modulators
- new and novel mechanisms of action

**LEARNING OBJECTIVES**

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

- Summarize the potential side effects associated with CFTR modulators.
- Explain the relationship between changes in sweat chloride and changes in lung function during CFTR modulator treatment.
- Discuss the benefits observed in young patients with the F508del/F508del genotype treated with lumacaftor/ivacaftor.

**GUEST AUTHOR OF THE MONTH**

**Commentary & Reviews**

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**Guest Faculty Disclosure**

Dr. John Clancy has disclosed that he has served on clinical trial contracts for Bayer, Concert, ProQR, and Vertex; clinical trial grant review contracts for Gilead; clinical advisory board contracts for Nivalis; and an unbranded educational talk for Genzyme.

**Unlabeled/Unapproved uses**

Dr. John P. Clancy has indicated that there will be no references to the unlabeled/unapproved use of any drugs or products.

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Ivacaftor/Lumacaftor in Patients Aged 6-11 Years with Two F508del CFTR Mutations

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COMMENTARY

The data in the articles summarized in this issue teach us quite a bit about the clinical use of CFTR modulators, including long term effects in different groups, activity in younger patients, limitations to modulator use based on genotype, relationships between sweat chloride and a clinically relevant biomarker used regularly in care (lung function), and a novel mechanism that may contribute to CF lung disease and the rapid benefits observed with CFTR modulation.

Two of the studies address questions of long-term experience with CFTR modulation, including the impact of chronic ivacaftor treatment in patients with the G551D mutation (Sawacki et al), and the impact of chronic lumacaftor/ivacaftor treatment in patients with two copies of the F508del mutation (Konstan et al). Important similarities and differences in these two articles impact their interpretation and clinical application. First, both examined data from open label extension studies that followed definitive placebo-controlled trials of ivacaftor (in patients with G551D mutations) and lumacaftor/ivacaftor (in patients with F508del/F508del mutations), respectively. They also compared data from each study with historical controls from the US Cystic Fibrosis Patient Registry (CFFPR), attempting to match each modulator-treated subject with several CFFPR subjects controlled for age, sex, chronic therapies, etc. It is important to note that this type of analysis can potentially introduce bias, as the data from the subjects within the open label extension modulator trials were part of a research dataset.

Participation in research may influence patient motivations or select for subjects more capable of adhering to therapies. With this in mind, important observations were similar across the two groups, despite different levels of acute modulator efficacy. Specifically, both ivacaftor treatment in patients with G551D and lumacaftor/ivacaftor treatment in patients with F508del/F508del reduced the decline in lung function over time compared with their respective control groups. What was remarkable was the similarity in this effect, which ranged from 40%-50% across both drugs and both study populations. These results provide data supporting the notion that CFTR modulators can indeed modify CF lung disease.

The term "CF disease modification" has recently been highlighted in connection with the development of CFTR modulators. This term (when applied to new therapies) implies that the trajectory of CF disease has been fundamentally changed. While disease modification is most directly demonstrated when describing the impact of therapies on loss of lung function over time (change in the rate of FEV1 decline), it can also be demonstrated by other effects such as reduced mortality. This type of analysis is beneficial when discussing the use of CFTR modulators with patients. Although acute effects on lung function and weight may be modest (particularly for patients with F508del/F508del starting lumacaftor/ivacaftor), data is emerging that the long-term benefits of lung function stability are significant. This ultimately may have a much greater impact on outcomes and survival and therefore is an important consideration with modulator therapy.

Results from the manuscript by Rowe et al demonstrated some of the limitations in extending CFTR modulators into new populations. Specifically, CF patients with one copy of F508del CFTR and moderate lung disease were treated for two months with lumacaftor/ivacaftor and compared with placebo. No benefits were observed as measured by FEV1 percent predicted, but there was clear evidence of drug bioactivity (11 mMol/L reduction in sweat chloride) and improvements in pulmonary symptoms. The results do raise the question of whether there would be some clinical benefits (e.g., perhaps such as those described above) if F508del CFTR heterozygous subjects received prolonged lumacaftor/ivacaftor therapy. The study also highlights the need for sensitive disease biomarkers that would predict disease modification.

Some of these novel biomarkers were evaluated in the article by Milla et al, which
summarized results of an open label study of lumacaftor/ivacaftor in young children (aged 6-11 years) with CF and preserved lung function. It was reassuring to find that the drug was well tolerated in this younger population, particularly since respiratory symptoms are not infrequently reported on initiation of therapy in older patients. Despite the study's open label nature, the impact of treatment on sweat chloride and the lung clearance index were remarkable and provide support for the use of CFTR modulators in young patients without easily detected lung disease.

The investigations summarized by Fidler et al examined relationships between changes in sweat chloride concentrations and FEV_1 across several CFTR modulator trials. The results of this comprehensive review indicated that negative changes in sweat chloride were associated with positive changes in lung function (FEV_1 percent predicted) in aggregate but could not predict individual patient responses. This is an important consideration for clinical application, as relying on changes in patient sweat chloride concentration is not clearly beneficial in determining responsiveness to modulator treatment.

Finally, the studies reported by Adam and et al examined smooth muscle and small airway distensibility following initiation of ivacaftor therapy. These studies build on prior investigations of CFTR activity and smooth muscle function in newborn piglets with CF (ie, Fidler et al, reviewed herein). The studies ask whether some of the ivacaftor benefits observed in patients with the G551D CFTR mutation may reflect effects on smooth muscle function. The results provide evidence that some of the acute changes (within 48 hours of starting ivacaftor) are due to smooth muscle dilation rather than reflecting only the restoration of mucociliary clearance. These studies identify a novel mechanism contributing to airflow obstruction in CF, which may be beneficial to advancing new therapies and to improving patient management.

CFTR modulators are typically well tolerated, but regular monitoring of lung function tests for patients treated with either ivacaftor or lumacaftor/ivacaftor, and for cataracts (for children treated with ivacaftor or lumacaftor/ivacaftor) is recommended. These drugs can have interactions with other CF therapies (eg, rifampin and antifungals), which should be considered during cotherapy and may require adjustment in dosing. Finally, treatment with lumacaftor/ivacaftor can produce chest tightness in some patients with CF, which can usually be managed with inhaled bronchodilators and/or slow dose escalation. These symptoms usually resolve within one to two weeks of starting treatment.

Overall, the results of these studies provide several key points relevant to CF care. First, in addition to the short term benefits measured in clinical trials, CFTR modulators appear to affect the long term trajectory of lung decline. This is seen with both highly active CFTR modulators (eg, ivacaftor treatment of patients with CF with the common gating mutation G551D), and modestly active CFTR modulation (eg, lumacaftor/ivacaftor in patients with CF with two copies of the F508del CFTR mutation).

Second, patients with one copy of F508del CFTR mutation and a second mutation that has minimal function do not receive clear benefits from lumacaftor/ivacaftor treatment, despite some improvements in sweat chloride and symptoms. This highlights the need for more effective therapies for this population, and the need for more sensitive, clinically relevant biomarkers of restored CFTR activity.

Third, the lung clearance index (LCI) may serve as a more sensitive biomarker of lung function improvement than FEV_1 percent predicted, as young patients with two copies of F508del CFTR and normal baseline lung function demonstrate improvements in LCI (and sweat chloride), despite no improvements in FEV_1.

Finally, a novel mechanism of action of CFTR modulators may include relaxing bronchial tone, helping to reduce airway obstruction.

Clinical trials in patients with CF possessing at least one G551D mutation and treated with ivacaftor have demonstrated clear pulmonary and nutritional benefits,\(^1\) raising the question whether prolonged ivacaftor treatment might produce sustained improvements in both lung function and nutritional parameters compared with controls.

In the current study, the investigators compared the impact of prolonged ivacaftor therapy on pulmonary function and nutritional status in patients with CF caused by the G551D mutation compared with CF patients homozygous for the F508del mutation. The research team designed a propensity scoring process to match patients ≥ 6 years of age and a G551D \(CFTR\) mutation treated with ivacaftor in clinical trials for up to 144 weeks. They compared those scores with data from F508del homozygous patients in the U.S. Cystic Fibrosis Foundation Patient Registry. The matching was based on a variety of variables that included age, sex, weight for age, height for age, body mass index for age, FEV\(_1\) percent predicted, and conventional chronic therapies commonly used to treat CF (including dornase alfa, inhaled antibiotics, and inhaled and oral corticosteroids). The study team showed that the ivacaftor-treated subjects had a rapid increase in FEV\(_1\) of 8.29 percentage points above controls. Importantly, this difference increased one and two years after initiating the drug, and the loss of lung function for the ivacaftor-treated group was reduced to -0.91% per year, while the F508del/F508del group demonstrated a loss in lung function of -1.72% per year.

Treatment with ivacaftor also led to improvements in body mass index and weight-for-age \(z\) scores for the ivacaftor-treated patients with G551D over the three-year period of observation. These findings provided support for the notion that ivacaftor is a disease-modifying therapy for the treatment of cystic fibrosis.

References:

Lumacaftor/Ivacaftor in F508del Homozygous Patients — Long Term Benefit


Two randomized, blinded, placebo-controlled trials have demonstrated safety and efficacy of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis ≥ 12 years of age and homozygous for the F508del-CFTR mutation.1 In the current trial, the study team aimed to assess the long-term safety and efficacy of lumacaftor/ivacaftor treatment in this group of patients during open-label extension.

This PROGRESS study was a phase 3, parallel-group, 96-week evaluation of patients who completed the placebo-controlled portion of the study (TRAFFIC or TRANSPORT) across 191 study sites in 15 countries. Patients who had previously received active treatment in TRANSPORT or TRAFFIC remained on the same dose in the subsequent trial, while patients who had received placebo were randomly assigned (1:1) to receive either lumacaftor (400 mg every 12 hours)/ivacaftor (250 mg every 12 hours) or lumacaftor (600 mg once daily)/ivacaftor (250 mg every 12 hours). The primary outcome focused on demonstrating the safety of prolonged combined therapy. The estimated annual rate of decline in FEV1 percent predicted in the lumacaftor/ivacaftor-treated patients was compared with that of a matched cohort from the U.S. Cystic Fibrosis Foundation Patient Registry. Some 1030 patients from the TRANSPORT and TRAFFIC studies enrolled in this active treatment study: 340 patients continued treatment with lumacaftor 400 mg/ivacaftor 250 mg every 12 hours, and 176 patients who had received placebo during the placebo-controlled studies initiated treatment with lumacaftor 600 mg daily/ivacaftor 250 mg every 12 hours.

During the active treatment study, the most common adverse events included infective pulmonary exacerbations, cough, increased sputum, and hemoptysis. Modest increases in blood pressure were also observed during the extension study.

For patients continuing treatment, the mean change from baseline in FEV1 percent predicted was 0.5% (95% CI -0.4 to 1.5) at extension week 72 and 0.5% (-0.7 to 1.6) at extension week 96. In this group, the change in BMI was 0.69 (0.56 to 0.81) at extension week 72 and 0.96 (0.81 to 1.11) at extension week 96. The yearly rate of pulmonary exacerbations in patients who continued treatment through 96 weeks (0.65, 0.56 to 0.75) was lower than that observed in the control arm from the placebo-controlled trials. Yearly decline in FEV1 percent predicted was reduced by 42% in lumacaftor/ivacaftor-treated patients compared with matched controls (-1.33% per year, -1.80 to -0.85 vs -2.29, -2.56 to -2.03). Similar benefits were observed in the patients treated with lumacaftor 600 mg once daily/ivacaftor 250 mg every 12 hr.

The long-term safety of lumacaftor/ivacaftor combination therapy was similar to that observed during the randomized, placebo-controlled trials. These findings provided support for the notion that lumacaftor/ivacaftor is a disease-modifying therapy for the treatment of cystic fibrosis in patients homozygous for the F508del CFTR mutation.

References:

Pulmonary Benefit of Ivacaftor/Lumacaftor in Adults Heterozygous for a F508del CFTR Mutation


Short term (28 days or less) treatment of patients with one copy of the F508del mutation with lumacaftor/ivacaftor did not improve lung function.¹ This study was designed to evaluate a lumacaftor/ivacaftor dosing regimen based on large studies and a longer treatment duration in a cohort of patients with one copy of F508del.

One hundred twenty-six patients were enrolled and 119 completed the study. Lumacaftor/ivacaftor was generally well tolerated, but an increased incidence of chest tightness and dyspnea was observed more frequently with the active drug compared with placebo (27.4% vs 14.3%, and 14.5% vs 6.3%, respectively). The baseline FEV₁ percent predicted was 62.9 (14.3) in the lumacaftor/ivacaftor group and 60.1 (14.0) in the placebo controls. The absolute change in FEV₁ percent predicted (least squares mean [SE]) at day 56 of treatment was -0.6% (0.8) in the lumacaftor/ivacaftor cohort and -1.2% (0.8) in the placebo controls (P = .60). Respiratory symptom scores improved by 5.7 points (mean) compared with a decrease of -0.8 in the placebo controls (P < .01). Body mass index (BMI) did not change in either group, but sweat chloride concentrations increased significantly from baseline in the lumacaftor/ivacaftor group. Sweat chloride in lumacaftor/ivacaftor-treated subjects dropped -11.8 mMol (1.3) (least-squared means, SE) by day 56, while there was no change in the placebo arm [-0.8 mMol (1.2); (P < .0001)].

However, despite significant changes in sweat chloride and pulmonary symptoms, lumacaftor/ivacaftor treatment failed to produce measurable benefits in lung function or BMI in adult CF patients heterozygous for the F508del CFTR mutation and moderate lung disease.

References:

Prior studies have demonstrated that the combination of lumacaftor/ivacaftor improves lung function and other clinical outcome measures in patients > 12 years of age with two copies of the F508del mutation. This open-label phase 3 trial was designed to evaluate the safety, tolerability, pharmacodynamics, and efficacy of lumacaftor/ivacaftor treatment in pediatric patients with CF aged 6-11 years with two copies of the F508del mutation.

Fifty-eight patients were treated with 200 mg lumacaftor/250 mg ivacaftor orally every 12 hours for 24 weeks. All patients continued their baseline CF therapies. Lumacaftor/ivacaftor treatment was generally well tolerated, and the safety profile was similar to that reported in the larger TRANSPORT and TRAFFIC trials conducted in older CF patients. Four pediatric patients discontinued the study drug, with two due to drug-related adverse events (elevated liver transaminases, n = 1; rash, n = 1). No pulmonary function safety concerns were observed.

There were no significant changes in FEV₁ percent predicted over the study (change from baseline at week 24, +2.5 percentage points; 95% CI, -0.2 to 5.2; P = .067). However, at week 24, significant reductions from baseline were observed for sweat chloride concentration (-24.8 mMol; 95% CI, -29.1 to -20.5; P < .0001) and lung clearance index (-0.88; 95% CI, -1.40 to -0.37; P <.002). Significant improvements also occurred in BMI z score (+0.15; 95% CI, 0.08 to 0.22; P < .0001) and respiratory symptoms as reported by the Cystic Fibrosis Questionnaire-Revised respiratory domain score (+5.4; 95% CI, 1.4 to 9.4; P < .01).

The results of this study provide evidence that lumacaftor/ivacaftor treatment is well tolerated in younger CF patients, with no new safety concerns observed. While a control group was not included, the study provided evidence for drug bioactivity (changes in sweat chloride) and potential clinical benefits (improvements in BMI, LCI, and respiratory symptoms).

References:

Ivacaftor is a well described CFTR potentiator that improves the gating function of CFTR. It has been extensively evaluated in CF patients with various CF-causing mutations and has demonstrated its greatest clinical impact in CF patients with gating mutations. Previous reports have examined whether relationships exist between changes in sweat chloride values and changes in lung function as measured by FEV1 percent predicted in patients receiving ivacaftor treatment.1,2 To date, no statistical correlation has been demonstrated between these parameters.

The primary goal of the post hoc analysis in this manuscript was to expand on prior studies and explore correlations between changes in sweat chloride concentrations and FEV1 percent predicted, using data from multiple study cohorts with different CF-causing mutations treated with ivacaftor. During examination of individual studies, changes in sweat chloride levels and improvements in FEV1 percent predicted failed to correlate for individual patients. However, when the data from all studies were evaluated together, clear and statistically significant correlations between changes in sweat chloride concentrations and FEV1 percent predicted were observed (P < .0001).

This data analysis indicates that changes in sweat chloride concentrations produced by potentiation of CFTR with ivacaftor predict lung function changes on a population level, but do not clearly predict treatment benefits in individual patients.

References:

Acute Benefits of CFTR Modulation


It is well established that airflow obstruction is a frequent manifestation of CF lung disease, but the causative factors remain incompletely defined. In addition to mucus plugging, airway hyperresponsiveness is a common occurrence in CF, but its relative contribution to airflow obstruction is unclear. Recent studies have provided evidence that CFTR is expressed and functional in airway smooth muscle (ASM), with increased ASM tone observed in newborn CF pigs. These observations suggest that CFTR dysfunction produces a primary defect in ASM function (ie, prior to the development of infection and inflammation).

In the current study, the research team tested the hypothesis that restoring CFTR activity via potentiation with ivacaftor would decrease smooth muscle tone in people with CF caused by the G551D mutation. Twelve adults with the G551D mutation were enrolled prior to initiating ivacaftor treatment. Patients were studied before and soon after starting ivacaftor (48 hours), with the goal of minimizing the secondary consequences of CFTR restoration. Smooth muscle function was assessed via spirometry, airway distensibility, and vascular tone testing.

As anticipated, ivacaftor rapidly improved CFTR function and reduced sweat chloride concentration. Airflow obstruction and air trapping also rapidly improved. While small airways increased their distensibility, these changes were not seen in the larger airways. Smooth muscle function outside of the lung was measured via vascular pulse wave velocity (PWV) and augmentation index. Both of these smooth muscle parameters decreased following the initiation of ivacaftor. On comparison of changes in the lung and the vascular smooth muscle, the change in distensibility of < 4.5 mm airways demonstrated a correlation with changes in PWV.

The results of this small study provide evidence that CFTR potentiation rapidly improved two markers of smooth muscle tone and suggest that ASM dysfunction may contribute to airflow obstruction in CF.

References:


KEY TAKEAWAYS

- Treatment with ivacaftor (of patients with the G551D CFTR mutation), and lumacaftor/ivacaftor (of patients with two copies of F508del CFTR mutation) modifies CF lung disease by reducing the loss of lung function decline compared with CFFPR controls.
- Lumacaftor/ivacaftor treatment of patients with one copy of F508del CFTR is not sufficient to improve lung function as measured by FEV1 percent predicted.
- Lumacaftor/ivacaftor treatment of children age 6-11 years with normal baseline lung function improves lung function as measured by the lung clearance index and reduces sweat chloride. LCI may be a more sensitive pulmonary biomarker of CFTR modulation than FEV1 percent predicted in young patients with mild lung disease.
- Sweat chloride is a powerful biomarker of CFTR modulation that correlates with improvement in FEV1 percent predicted. This is observed across several studies with
patients with different genotypes and CFTR modulator treatments, but these effects are not observed on an individual patient basis.

- Reduced airway smooth muscle tone may contribute to the acute pulmonary benefits observed with ivacaftor treatment of CF patients with gating mutations.
This activity was developed in collaboration with DKBmed.