JOHNS HOPKINS MEDICINE eLITERATURE REVIEW

eCysticFibrosis Review

Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

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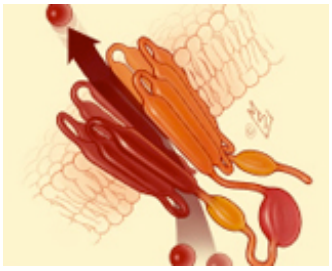

Editor's Note: Look out for the next issue where we will feature Dr. Lori Stark, of the University of Cincinnati College of Medicine. Dr. Stark will discuss behavioral treatment to improve dietary adherence and weight gain in children with cystic fibrosis.

eCysticFibrosis Review VOLUME 4, ISSUE 7

New Therapies in Cystic Fibrosis Directed Toward the Basic Defect

In this Issue...

New therapies directed toward the underlying cause of cystic fibrosis (CF) – targeting repair of its causative protein, the cystic fibrosis transmembrane conductance regulator (CFTR) – are coming to fruition. The first drug that targets the basic CF defect in a small subset of individuals with CF was recently approved, and a number of successful clinical trials have recently been conducted. These therapies promise to change the face of CF care in the future and are important to understand in the context of current CF therapies.

In this issue, we review new developments surrounding *CFTR* modulators, including the basis of the approval of ivacaftor (formerly VX-770) for people with CF age 6 years and above with the G551D *CFTR* mutation; the current status of therapies intended to repair *CFTR* mutations caused by premature termination codons; and progress toward developing agents that target the most common *CFTR* mutation, F508del.

LEARNING OBJECTIVES

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

- Summarize several clinical approaches to modulate CFTR function in a variety of mutation groups
- Describe the clinical effects of modulation of CFTR function
- Recognize the current limitations of CFTR modulator therapy given the state of present knowledge

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IMPORTANT CME/CE INFORMATION ▼ Program Begins Below

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Length of Activity
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October 29, 2013

Expiration Date
October 28, 2015

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LAUNCH DATE

This program launched on February 28, 2013 and is published monthly; activities expire two years from the date of publication.

HARDWARE & SOFTWARE REQUIREMENTS

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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 may be unfamiliar with recently introduced disease-modifying therapies and how they are altering the therapeutic landscape for patients with cystic fibrosis.
- Clinicians may be uncertain how to integrate genotyping into therapeutic decisions and how to communicate with patients and families about the relationship between genotype and therapy

Nutrition

- Many clinicians lack strategies to persuade patients to adhere to CF nutritional requirements, resulting in low body weight and nutritional failure in patients with cystic fibrosis.
- Many clinicians remain uncertain how to optimize pancreatic function in patients with cystic fibrosis.

Treating CF Patients with Inhaled Antibiotics

- Clinicians lack knowledge about the use of existing and emerging inhaled ABX to treat chronic pulmonary infections.

Michael P. Boyle, MD, FCCP discloses that he has served as a consultant for Vertex, Novartis, Genentech, Savara, Pharmaxis, and Gilead Sciences, Inc. He has also received grant/research support from Vertex.

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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- Clinicians need more information to make informed decisions about the use of inhaled ABX in combination.
- Clinicians lack information about best practices for scheduling ABX therapy to suppress chronic airway infections.
- Common clinician assumptions about treating pulmonary exacerbations lack supporting evidence.
- CF clinicians are not aware of and/or are not actively advocating inhaled ABX patient-adherence strategies.

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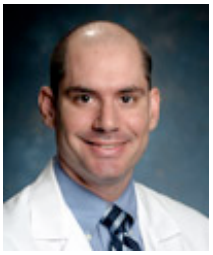

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The author has indicated that he has received grants/research support from Novartis, PTC Therapeutics, N30 Pharmaceuticals, and Vertex. In addition, he has served as a consultant for Novartis.

Unlabeled/Unapproved Uses

The author has indicated that he will refer to unlabeled/unapproved uses of ivacaftor, lumacaftor, ataluren, N6022, and aminoglycosides.

Planning Committee Disclosures

COMMENTARY

Two decades after the discovery that mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) lead to cystic fibrosis (CF), new therapies that address the underlying protein defect are coming to fruition and mark a considerable advance in protein-based therapeutics. Successful clinical studies have helped place people with CF into subgroups based on *CFTR* mutations and are beginning to usher in a new era of personalized CF therapeutics.

Ivacaftor is a potentiator of CFTR channel gating that augments anion transport activity by enhancing protein gating. The agent is particularly effective in augmenting the function of Class 3 *CFTR* mutations, which are minimally active because of defective channel gating. The most common among these is the G551D mutation, which is found in ~ 4% of people with CF. In phase 3 studies among people aged 12 years and above with at least one

G551D *CFTR* mutation, ivacaftor treatment caused marked improvements in clinical outcomes, as measured by improved pulmonary function, frequency of pulmonary exacerbations, weight gain, and quality of life. Further, CFTR activity, measured by sweat chloride, also dramatically improved, with mean levels falling below the accepted diagnostic threshold of 60 mEq/L. Similar results were observed in children. Improved lung function, reduced exacerbation frequency, and weight gain were all observed compared to placebo. Predefined stratifications revealed similar changes in spirometry among typical subgroups, such as minimal compared to moderate pulmonary dysfunction at enrollment, gender, and age. The improvement in spirometry was rapid: within two weeks, 90% of the maximal improvement was observed, suggesting that the mechanism may be clearance of inspissated mucus from plugged airways, rather than reversal of long-standing structural lung disease. These results firmly establish CFTR as a viable therapeutic target in CF and provide confidence that CFTR modulators directed toward other more common *CFTR* mutations might also result in meaningful improvements in the clinic.

The degree of improvement in spirometry among participants of the phase 3 trials of ivacaftor in individuals with at least one G551D *CFTR* mutation compares favorably to that of commonly used therapies for chronic CF care, including inhaled recombinant human DNase,[1] inhaled tobramycin,[2] azithromycin,[3] and hypertonic saline.[4] In both clinical studies, ivacaftor appeared safe and well-tolerated. Moreover, serious adverse events were less common among those treated with ivacaftor, including the incidence of hemoptysis, and theoretical mechanistic-based toxicities related to nonspecific CFTR activation such as secretory diarrhea were not observed. Since the FDA approved the drug, there has been a rapid use of ivacaftor among people with the G551D genotype living in the U.S. and strong interest in understanding whether others might benefit from CFTR modulator treatment.

A number of studies are now ongoing to better define others who could respond to ivacaftor treatment, including evaluation of patients with other Class 3 gating mutations, as well as those with partially active CFTR forms in which the protein is known to be at the cell surface, such as R117H. Younger populations (age 2-5 years) with G551D *CFTR* mutations are also being tested, and tests of the effects of *CFTR* modulation among individuals with little pulmonary dysfunction at baseline will begin soon.

Among people homozygous for the F508del *CFTR* mutation, ivacaftor had little effect as observed in a four-month study, resulting in a trivial reduction in sweat chloride and no measureable benefit in lung function[5]. Further, ivacaftor did not improve outcome with longer administration to an unbiased subset of responders homozygous for F508del. The implications of this study are clear: ivacaftor as a monotherapy is not appropriate for everyone with CF and should be employed only as a treatment for those with a mutation shown to be responsive.

To develop an approach for people with F508del *CFTR* mutations, in which ~ 50% of individuals are homozygous and ~ 90% have at least one copy, investigational CFTR correctors such as lumacaftor (VX-809), VX-661, and N6022 (N30 Pharmaceuticals) are under evaluation. Some of the agents are being evaluated in combination with ivacaftor. Among these, the evaluation of lumacaftor is farthest along in clinical trials. As a monotherapy, lumacaftor provides only a modest change in CFTR activity by sweat chloride testing, and altered CFTR function was not detected by nasal potential difference testing. Likewise, clinical efficacy was not observed, suggesting for this agent, potentiation of CFTR must accompany correction of F508del misprocessing to confer clinical benefit. An improvement in lung function was observed in interim results released from a phase 2 trial of lumacaftor and ivacaftor in combination. Based on these results, a phase 3 trial of lumacaftor and ivacaftor in combination will be evaluated in patients homozygous for F508del, and further testing of those with one copy of F508del is under consideration.

An approach using small molecules to interrupt premature translation termination caused by abnormal stop codons within CFTR has also been under investigation.[5,6] Ataluren (PTC124) had shown some promise in early phase testing,[7] but phase 3 placebo-controlled testing did not detect clinically meaningful changes in lung function, exacerbation frequency, or other markers of biologic activity.[8] However, subgroup analysis did show some effect in patients who were not receiving inhaled tobramycin, which has been shown to block the activity of ataluren in vitro.

Newer approaches to enhance efficacy of therapy for these mutations are also under investigation. For example, new aminoglycosides synthetically derived to enhance translational read-through, rather than antimicrobial activity,[9] have been shown to improve the therapeutic index of these agents,[10] providing proof of concept that this strategy can be successful. Efforts in a number of laboratories are also under way to identify more efficacious agents that may be broadly active against *CFTR* mutations and may be applied in combination with other agonists, such as CFTR potentiators, to further enhance their activity.

In summary, CFTR modulators represent a major advance in CF therapeutics, opening a new era of mutation-specific therapy and a personalized approach to the disease. A number of unanswered questions about the long-term effects of these agents and the ability to correct the most challenging *CFTR* alleles remain. However, if efforts are successful in treating a wider variety of CFTR forms, modulator therapy may be available for a greater number of people with CF in the coming years, altering the face of CF therapeutics.

Commentary References

1. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med.*1994;331:637-642.
2. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group.*N Engl J Med.* 1999;340:23-30.
3. Saiman L, Marshall BC, Mayer-Hamblett N, et al. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: A randomized controlled trial.*JAMA.* 2003;290:1749-1756.
4. Elkins MR, Robinson M, Rose BR, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis.*N Engl J Med.*2006;354:229-40.
5. Kerem E, Hirawat S, Armoni S, et al. Effectiveness of PTC124 treatment of cystic fibrosis caused by nonsense mutations: a prospective phase II trial. *Lancet.*2008;372(9640):719-27
6. Wilschanski M, Yahav Y, Yaacov Y, et al. Gentamicin-induced correction of *CFTR* function in patients with cystic fibrosis and *CFTR* stop mutations. *N Engl J Med.*2003;349(15):1433-1441.
7. Sermet-Gaudelus I, Boeck KD, Casimir GJ, et al. Ataluren (PTC124) induces cystic fibrosis transmembrane conductance regulator protein expression and activity in children with nonsense mutation cystic fibrosis.*Am J Respir Crit Care Med.* 2010;182:1262-1272.
8. Rowe S, Sermet-Gaudelus I, Konstan M, et al. Results of the phase 3 study of ataluren in nonsense mutation cystic fibrosis (NMCF). *Pediatr Pulmonol.* 2012;47(S35):190.
9. Kandasamy J, Atia-Glikin D, Shulman E, et al. Increased selectivity toward cytoplasmic versus mitochondrial ribosome confers improved efficiency of synthetic aminoglycosides in fixing damaged genes: a strategy for treatment of genetic diseases caused by nonsense mutations.*J Med Chem.*2012;55(23):10630-43
10. Rowe SM, Sloane P, Tang LP, et all. Suppression of *CFTR* premature termination codons and rescue of *CFTR* protein and function by the synthetic aminoglycoside NB54.*J Mol Med (Berl).* 2011;89(11):1149-1161.

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IVACAFTOR FOR THE TREATMENT OF PATIENTS WITH THE G551D *CFTR* MUTATION

Ramsey BW, Davies J, McElvaney NG, et al. A *CFTR* potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*. 2011;365:1663-1672.

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Davies JC, Wainwright CE, Canny GJ, et al; on behalf of the VX08-770-103 (ENVISION) Study Group. Efficacy and Safety of Ivacaftor in Patients Aged 6 to 11 Years with Cystic Fibrosis with a G551D Mutation. *Am J Respir Crit Care Med* . 2013 Apr 3.

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After successful phase 2 testing of ivacaftor (formerly VX-770) in people with cystic fibrosis (CF) who have at least one copy of the G551D *CFTR* mutation, two long-term phase 3 studies were conducted to definitively evaluate the efficacy of this CFTR modulator in a specific group of patients with a mutation highly responsive to drug treatment. The principal study (Ramsey et al) was a randomized, double-blind, placebo-controlled trial that evaluated patients 12 years and older who had CF with the G551D *CFTR* mutation. Randomization was 1:1, and the duration of treatment was 48 weeks. The primary end point was the mean change in the percentage of predicted forced expiratory volume in one second (FEV_1) from baseline through week 24. Secondary endpoints included FEV_1 change through 48 weeks, frequency of pulmonary exacerbations, quality of life, body weight, and sweat chloride as indicators of CFTR activity. The second study (Davies et al) was similarly designed but involved patients aged 6-12 and included patients with FEV_1 percent predicted up to 105% at baseline.

Results of the studies were dramatic, demonstrating a significant treatment benefit compared to placebo for all endpoints evaluated. In patients 12 years and older, FEV_1 increased by 10.6 percentage points in the ivacaftor group compared to the placebo group ($P < 0.001$) at week 24. The benefit to lung function was readily detected at week 2 and sustained for the duration of the trial. Over the study, those receiving ivacaftor were 55% less likely to have a pulmonary exacerbation ($P < 0.001$). The Cystic Fibrosis Questionnaire - Revised (CFQ-R) achieved a highly significant improvement in the respiratory domain that exceeded the known minimally clinically important difference for the survey. Patients who received ivacaftor experienced significant weight gain compared to placebo (2.7 kg, $P < 0.001$). Compared to placebo, sweat chloride improved by 48 mEq/L ($P < 0.001$), and the mean value in subjects treated with ivacaftor was slightly below the accepted diagnostic threshold for CF (60 mEq/L). Ivacaftor was well tolerated, and those taking ivacaftor had a lower incidence of serious adverse events compared to those treated with placebo. In the second study, efficacy was also observed, with a 12.5% increase in FEV_1 observed at 24 weeks compared to placebo ($P < 0.0001$). An increase in weight gain was also observed, and sweat chloride improved to a degree similar to that seen in the older population.

The study by Ramsey et al provided the basis for the Food and Drug Administration approval of ivacaftor for treating people with CF caused by at least one G551D *CFTR* mutation. The magnitude of sweat chloride improvement suggested CFTR activity was partially restored, approaching ~ 30% of normal function based on genotype-phenotype correlations in the disease. All measures of clinical benefit improved in those treated with ivacaftor, and the magnitude of those differences compared favorably to those of other approved therapies for CF. The effects of ivacaftor on lung function were surprisingly rapid, indicating that benefit of CFTR modulation on respiratory health can be observed quickly and implying the mechanism is likely due to augmentation of mucociliary clearance and reversal of mucus plugging. The benefit on body weight was unexpected and has raised questions about the role of CFTR in mediating absorption, even in the context of pancreatic enzyme replacement therapy.

The effect in younger patients with CF was very similar, providing confidence in the initial results and confirming that ivacaftor exhibits similar efficacy in patients with a broad range of pulmonary dysfunction at baseline. The study was not of sufficient size or duration to establish whether progression of lung disease is altered by ivacaftor, and this will remain an important question to address with additional observation. The magnitude of clinical benefit has provided a major impetus for additional studies to determine whether ivacaftor can also be efficacious in patients with CF who have other *CFTR* mutations, and it provides a crucial proof of concept that CFTR is a valid target in the disease.

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SAFETY AND EFFECTS OF IVACAFTOR IN INDIVIDUALS HOMOZYGOUS FOR F508DEL-*CFTR* MUTATIONS

Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in Subjects with Cystic Fibrosis who are Homozygous for the F508del-*CFTR* Mutation. *Chest.* 2012 Sep;142(3):718-24.

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This two-part study included a 16-week trial designed to establish the safety of ivacaftor in patients with CF who are homozygous for F508del *CFTR* and to test whether CFTR potentiation could be effective in a population with little surface CFTR expression. The second part of the study continued ivacaftor through 40 weeks in patients demonstrating a significant improvement in either sweat chloride or spirometry to provide further observation of a subpopulation thought to be responsive to ivacaftor therapy. Randomization of this study was 4:1 in favor of ivacaftor treatment.

Although there was a statistically significant reduction in sweat chloride compared to the placebo group, the effect was small (3 mEq/L), and there was no significant improvement in the primary outcome — the change in FEV_1 percent predicted from baseline through week 16, compared to placebo (1.7%, P = 0.15). In addition, the second part of the study included 38 patients based on therapeutic response; prolonged observation demonstrated that those selected because of a presumed therapeutic response during the first part of the study did not demonstrate sustained clinical benefit. There were no significant safety abnormalities in the ivacaftor-treated group compared to the placebo group. There was no difference in secondary outcome measures, including pulmonary exacerbations, use of antibiotics, body weight, or quality of life as measured by the CFQ-R.

In this trial ivacaftor was tested in people with CF who had two F508del-*CFTR* mutations and served to determine whether any residual surface-localized F508del CFTR that may be present could be a therapeutic target, thus providing guidance for using ivacaftor in this population. This four-month, placebo-controlled trial revealed no statistically significant change in FEV_1 after ivacaftor treatment in this population. Although sweat chloride did improve by a small amount in the ivacaftor treatment group (3 mEq/L reduction compared to placebo), this is considered a trivial change and was clearly subtherapeutic in nature. Follow-up evaluation of an unbiased selection of responders identified during the placebo-controlled study revealed that any benefit in spirometry was not sustained, leading to the conclusion that the antecedent improvement in lung function was unlikely to be related to drug efficacy. Further, patients eligible to continue to the extension study were not more common in those assigned ivacaftor than those assigned to placebo, suggesting eligibility determined by predefined thresholds of sweat chloride and lung function was related to variation rather than to efficacy. These findings provide a strong basis for the conclusion that ivacaftor therapy is not efficacious among patients homozygous for F508del without cotherapy with agents that augment expression of the channel to the cell surface. However, the study demonstrated that ivacaftor was safe in an additional cohort of individuals.

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THE CFTR CORRECTOR LUMACAFTOR FOR INDIVIDUALS HOMOZYGOUS FOR F508DEL *CFTR*

Clancy JP, Rowe SM, Accurso FJ, et al. Results of a phase IIa study of VX-809, an investigational CFTR corrector compound, in subjects with cystic fibrosis homozygous for the F508del-*CFTR* mutation. *Thorax*. 2012 Jan;67(1).

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Pharmacologic "correctors" of F508del-*CFTR* folding are sought to improve surface localization of the mutant channel in an attempt to restore its function. Lumacaftor (VX-809) is an investigational F508del corrector that demonstrated modest efficacy using in vitro models, achieving ~ 15% of normal CFTR function in a panel of primary human bronchial epithelial monolayers. This study was a phase 2, randomized, double-blind, placebo-controlled trial to test the safety, tolerability, and efficacy of various doses of oral administration of lumacaftor for 28 days in patients homozygous for F508del-*CFTR*.

Lumacaftor was generally well tolerated and had an adverse effect profile similar to placebo, although one patient in each active treatment arm did discontinue therapy because of respiratory adverse events. Subjects treated with lumacaftor demonstrated dose-dependent improvements in sweat chloride, although the maximum effect seen (8 mEq/L compared to placebo) was at the highest dose tested but below a threshold thought to be clinically meaningful. Other measures of CFTR activity (nasal potential difference) and expression (rectal biopsy Western blot) were not altered by the therapy, but the study was underpowered to detect a significant change because these outcome measures were only used in a subset of patients. There was no statistically significant or clinically meaningful change in lung function measured by change in FEV_1.

This study suggested that lumacaftor has a reasonable safety profile after one month of administration and had an acceptable pharmacological profile. While modest efficacy was seen in the most sensitive CFTR biomarker tested, this was not associated with changes in spirometry, indicating greater efficacy is needed to confer clinical benefit.

Because the study demonstrated its greatest efficacy at the highest dose tested, without exceeding the therapeutic index established in animals, higher-dose administration appeared warranted and was later conducted in ongoing clinical studies examining lumacaftor in combination with ivacaftor. Overall, this study indicated further testing warranted with lumacaftor in combination with ivacaftor, since the latter agent might address residual defects in channel gating that might limit the efficacy of lumacaftor alone. Studies of this sort are presently enrolling subjects.

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ATALUREN FOR THE TREATMENT OF NONSENSE MUTATIONS

Wilschanski M, Miller LL, Shoseyov D, et al. Chronic ataluren (PTC124) treatment of nonsense mutation cystic fibrosis. *Eur Respir J*. 2011;38:59-69.

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Sermet-Gaudelus I, Boeck KD, Casimir GJ, et al. Ataluren (PTC124) induces cystic fibrosis transmembrane conductance regulator protein expression and activity in children with nonsense mutation cystic fibrosis. *Am J Respir Crit Care Med*. 2010 Nov 15;182(10):1262-72.

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These two studies evaluated the effects of ataluren (PTC124) in people with CF caused by premature termination codons in open-label study designs involving patients with at least one premature termination codon. The former study enrolled pediatric subjects with CF aged 6 and above, and the latter study included adults in a follow-up three-month trial involving participants in a previous phase 2 study. The objectives were to evaluate the safety, pharmacokinetics, and efficacy of ataluren as a suppressor of premature termination codons as determined by markers of CFTR activity and expression.

The pediatric study included 30 patients age 6-18 years in a two-week, open-label, crossover design that tested low-dose and high-dose treatments. Ataluren was associated with improved CFTR function as measured by a 4.6 and 3.9 mV improvements in nasal potential difference following the end of the second treatment interval, for the low- and high-dose treatment periods, respectively (each $P < 0.05$). There was also a significant increase in the proportion of nasal cells exhibiting CFTR expression based on immunohistochemical staining.

The adult study included 19 patients age 19-57 years. They were assigned to either low-dose or high-dose ataluren therapy depending on the effects observed in previous phase 2 testing in each person. Combining both dose groups, the mean change in nasal potential difference was -5.4 mV at the three-month time point ($P < 0.05$), and these changes were time-dependent. In both studies, ataluren was well tolerated with few mild adverse events, and pharmacokinetic goals were achieved.

In these studies, bioelectric improvements in CFTR activity were measured by nasal potential difference (NPD) in patients receiving two different doses of open-label ataluren therapy. These changes were not dose-dependent, and in both studies the effects were time-dependent, including the unexpected observation of serial improvements during the washout period among children. This provided promising information substantiating the approach; however, subsequent phase 3 studies that included placebo-controlled assessments of NPD did not confirm these findings and emphasized the importance of placebo control in studies that rely on this endpoint[1]. In addition, while the primary endpoint did not demonstrate a therapeutic effect, a predefined cohort of patients who did not use inhaled antibiotics exhibited improved lung function in the ataluren treatment group compared to placebo, suggesting the need for additional studies to further define treatment response and the role of concomitant tobramycin, which antagonizes the effect of ataluren in the laboratory, toward altering treatment effects.

1. Rowe S, Sermet-Gaudelus I., Konstan M, et all. Results of the phase 3 study of ataluren in nonsense mutation cystic fibrosis (NMCF). *Pediatr Pulmonol*. 2012;47(S35):190.

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SWEAT CHLORIDE AS A TOOL FOR PREDICTING EFFICACY OF *CFTR* MODULATORS

Durmowicz AG, Witzmann KA, Rosebraugh CJ, Chowdhury BA. *Chest*. 2013:Jan;143(1):14-18. Change in sweat chloride as a clinical end point in cystic fibrosis clinical trials: the ivacaftor experience.

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Seliger VI, Rodman D, Van Goor F, Schmelz A, Mueller P. The predictive potential of the sweat chloride test in cystic fibrosis patients with the G551D mutation. *J Cyst Fibros*. 2013:Apr 26.

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Biomarkers of response to CFTR modulators are needed, particularly as these treatments are brought to a wider variety of people with rare *CFTR* mutations. Sweat chloride was used as the primary biomarker of ivacaftor activity in phase 3 testing of ivacaftor among patients with CF who have the G551D mutation (see Review 1, above). Two retrospective analyses were conducted to evaluate the correlation between sweat chloride and improvement in lung function and its predictive value for determining who is likely to exhibit a therapeutic response.

Although ivacaftor induced statistically significant and clinically meaningful improvements in lung function measured by FEV_1 percent predicted and sweat chloride among patients randomized to receive ivacaftor, there was no correlation between the absolute change in sweat chloride and the absolute change in FEV_1 percent predicted. This was attributed to the multiplicity of factors that alter changes in lung function seen within the context of clinical trials, such as heterogeneous CFTR expression among tissues, genetic modifiers, and environmental factors. In a second analysis, an evaluation of the sweat chloride response cross-referenced to the relative change in FEV_1 percent predicted revealed that patients fell into two clusters, principally because of treatment group assignment (ie, ivacaftor vs placebo). This allowed calculation of a positive predictive value of 86.3% for a change in sweat chloride of 20 mEq/L, or an absolute sweat chloride of 80 mEq/L at week 2, to predict a ≥ 5% improvement in baseline FEV_1 percent predicted at week 16 in a pooled analysis; in contrast, the negative predictive value was 65.5%. Use of these predictive values in other settings should be done with caution, since the prevalence of patients likely to respond to ivacaftor may be very different in a CF patient population without G551D *CFTR*.

Data continue to emerge on how measures of CFTR function such as sweat chloride can be used to predict clinical response. While there appears to be a poor correlation between change in sweat chloride and change in individuals' lung function, it stands to reason that because of the importance of CFTR activity in the pathogenesis of the disease, significant improvements in sweat chloride cannot be ignored. At present, analysis is limited, because the response of sweat chloride to ivacaftor treatment among patients with G551D is dramatic and approaches a binary function. Further, improvements in FEV_1 depend on a number of factors, such as degree of mucus obstruction at the start of the study and underlying structural damage that may not be reversible, as well as many other genetic and environmental factors that may impact clinical response. While a change in sweat chloride of 20 mEq/L or an improvement to 80 mEq/L resulted in a relatively high positive predictive value, this was derived from a retrospective analysis of a randomized controlled trial — we do not yet know whether this can be applied to a broader array of patients with a greater variety of alleles, in whom response to CFTR therapeutics may be more variable. This may be particularly problematic for agents such as CFTR correctors or translational read-through agents, in which the group response to sweat chloride and lung function has been even more variable. Continued long-term data from trials evaluating CFTR modulators that exhibit a range of efficacy will ultimately be needed to fully understand the landscape of personalized approaches to CFTR therapeutics.

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