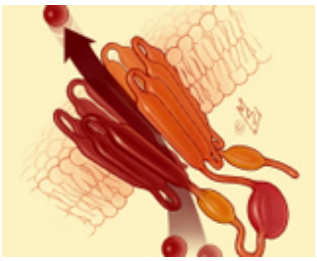
JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eCysticFibrosis Review
Jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Vol 5: Supported by education grants from AbbVie, Gilead Sciences, Inc., and Vertex Pharmaceuticals Incorporated



eCysticFibrosis Review VOLUME 5, ISSUE 11

Benefits of CFTR Modification Beyond FEV_1 Improvement

In this Issue...

Patients with cystic fibrosis who have specific mutations in their cystic fibrosis transmembrane conductance regulator (CFTR), notably a single copy of the G551D mutation, now have an available Food and Drug Administration approved agent to treat their disease. The initial phase 3 clinical trials demonstrated clinically meaningful and significant improvements in lung function and weight with a reduction in the sweat chloride biomarker.
In this issue, we review recent publications describing:

• Improvement in lung function and nutritional status with CFTR modulation of the G551D mutation;
• Improved mucocilliary clearance and alkalization of the duodenum associated with CFTR modulation of the G551D mutation;
• The reduction in respiratory cultures of *Pseudomonas aeruginosa* associated with CFTR modulation of the G551D mutation;
• Evidence of a defect in antimicrobial host defense and mucous cleavage from the pulmonary submucosal gland orifices in the CF pig model; and
• Improvements not specifically related to FEV_1 achieved with CFTR modulation.

LEARNING OBJECTIVES

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

- Summarize the newer advances in our understanding of the pathophysiology of cystic fibrosis and how CFTR modulation may impact this process.
- Describe the effects of CFTR modulation on nutritional status.
- Evaluate the observational data supporting the impact of CFTR modulation on chronic infection in cystic fibrosis.

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Dr. Christopher Goss reports that he has research grant funding from Vertex Pharmaceuticals Inc. In addition he has received honorarium from Gilead Sciences and L. Hoffman – La Roche Ltd.

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COMMENTARY

The advent of cystic fibrosis transmembrane conductance regulator (CFTR) modifiers as approved therapies for patients with cystic fibrosis (CF) have revolutionized the field of CF therapeutics. Ivacaftor is the first agent approved in CF that modifies mutated CFTR. This agent is termed a CFTR potentiator because it activated mutant CFTR on the surface of epithelial cells. The primary endpoint of the phase 3 clinical trial noted in the paper by Ramsey et al. found a significant improvement in lung function as measured by the forced expiratory volume in one second (FEV_1) that was larger than the treatment effect noted in other Food and Drug Administration approved therapies for CF. The treatment effect was both clinically and statistically significant. The study also demonstrated a significant improvement in sweat chloride, an important marker of CFTR function. All the patients in the clinical trial had a sweat chloride at the end of treatment that was no longer in the diagnostic range for CF (≥ 60 mmol/liter). The study by Rowe et al. confirmed the findings of the clinical trial in the real world setting in an observational study of individuals with CF with at least one G551D *CFTR* mutation. This observational study replicated the effect on lung function and sweat chloride observed by Ramsey et al. Often therapies have shown reduced effectiveness in the broader community when compared to the idealized setting of a phase 3 randomized controlled trial; however, this does not appear to be the case for ivacaftor.

Although FEV_1 has been a key endpoint in clinical trials for CF, this novel therapy had other effects not initially anticipated. One of the most marked impacts was the dramatic improvement in nutritional status over the duration of the phase 3 clinical trial as measured with by body mass index (BMI). The improvement in weight was an astounding 2.7 kg compared to placebo. Rowe et al. also replicated the finding of improved weight in the observational trial for those people with CF with a G551D *CFTR* mutation started on ivacaftor. The magnitude of the treatment effect was also comparable to the trial by Ramsey et al. The work of Rowe et al. work went further by trying to unravel the mechanism by which weight gain occurred. They clearly demonstrated that duodenal pH was markedly increased toward a more normal alkaline pH in those people treated with ivacaftor. Alkalizing the duodenum may enhance the efficacy of pancreatic enzymes thus reducing the fat malabsorption seen in pancreatic insufficient patients with CF who are adherent with enzyme therapy. Improvement in weight was an important non-pulmonary outcome due to modifier therapy. Observational data in CF have clearly demonstrated the association between nutritional status and lung health; those with improved nutritional status as children have both improved lung function and survival later in life.[1] The long-term implication of the effect of modulation on BMI is unclear, but clinical evidence to date suggests this effect will likely confer important clinical benefit.[2]

Additional data from the paper by Rowe et al. suggest that ivacaftor could impact the rate of culturing *Pseudomonas aeruginosa*, a key pathogen in CF. This work was further supported by an additional analysis by Heltshe et al. of the same study population augmented with data from the US CF Foundation Patient Registry. These data support a potential effect on host immunity through CFTR potentiation in patients with the G551D *CFTR* mutation that leads to eradication of a serious pathogen in CF. Eradication of chronic *P. aeruginosa* infection in CF has currently been deemed not possible with standard antimicrobial treatments.

These observational data are supported with very exciting experiments done in the CF pig model. Pezzulo et al. demonstrated that CFTR dysfunction in the CF pig model leads to acidification of the airway surface liquid, and that correction of the pH normalizes the bacterial killing defect in the animal. The effect, seen in the observational trial by Rowe et al. and Heltshe et al, if supported by further careful prospective studies, could have dramatic ramifications for all future therapies for CF that can demonstrate CFTR modulation.

The report described herein by Hoegger et al. further expands the potential implications of CFTR modulation in CF beyond merely improving FEV_1. He and his colleagues demonstrated that the CF pig trachea has a defect in detachment of mucous strands from the orifice of submucosal glands. This phenotype was replicated in non-CF pigs by acidifying the mucosa and blocking chloride uptake at the basolateral membrane. The goal of this investigation was to explain the conflicting results noted in studies of mucociliary clearance in CF. This work not only adds refinement to our understanding of mucous stasis in CF but may also explain the results noted in the mucociliary studies after initiation of ivacaftor in the paper by Rowe et al. Mucous stasis along with a defect in airway surface lining fluid alkalization could explain the initial pathophysiology of CF lung disease, and help elucidate

why CF children are infected at such an early age with *Staphylococcus aureus*, *Haemophilus influenza* and *P. aeruginosa*, all known pathogens in CF. These data also support the potential premise that CFTR modulation could prevent structural lung damage in CF.[3]

Two recent case reports also point to the intriguing potential effects of CFTR modification in CF. One report noted first stabilization of bronchiectasis in a patient treated with ivacaftor for a two year period but also found a marked reduction in airway wall thickness (noted on paired high resolution computed tomography of the lung).[4] An additional case report noted the reversal of CF-related diabetes in a patient with CF treated with ivacaftor, suggesting that CFTR modulation could potentially prevent progressive endocrine pancreas dysfunction.[5] This latter case report was supported by a small pilot study evaluating insulin secretion in patients with CF with the G551D *CFTR* mutation treated with ivacaftor.[6] While all of these findings are exciting and point to non-FEV_1 outcomes of CFTR modulation, further work is need to both validate these findings and assess durability of these effects.

Commentary References

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3. Stoltz DA, Meyerholz DK, Welsh MJ. Origins of cystic fibrosis lung disease. *N Engl J Med*. 2015 Apr 16;372(16):1574-5.
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6. Bellin MD, Laguna T, Leschyshyn J, et al. Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study. *Pediatr Diabetes*. 2013 Sep;14(6):417-21.

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EFFECTS OF IVACAFTOR IN CF PATIENTS WITH THE G551D MUTATION ON LUNG FUNCTION, SWEAT CHLORIDE, AND WEIGHT

Ramsey BW, Davies J, McElvaney NG, et al; VX08-770-102 Study Group. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. *N Engl J Med*. 2011 Nov 3;365(18):1663-72.

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This paper presents the results of a seminal double blind randomized placebo controlled clinical trial to assess the efficacy of the drug ivacaftor (VX-770), a novel cystic fibrosis transmembrane conductance regulator (*CFTR*) potentiator on patients with cystic fibrosis (CF) ages 12 years and older with at least one copy of the G551D-*CFTR* mutation. Patients were randomized to receive either 150 mg of ivacaftor or placebo every 12 hours for a total of 24 weeks. The primary endpoint of the trial was absolute change in forced expiratory volume in one second from baseline through week 48. The study demonstrated that ivacaftor provided an increase from baseline of 10.4% points in the percent of predicted forced expiratory volume in one second (FEV_1), as compared with a decrease of 0.2 percentage points in the placebo group ($P< 0.001$). The treatment effect in the ivacaftor group compared to placebo was 0.361 liters ($P< 0.001$), and ivacaftor was associated with a drop in sweat chloride of 47.9 mmol/liter compared to placebo ($P<0.001$). An important and unexpected finding in this phase 3 trial was the dramatic increase in weight: the treatment increase on weight was 2.7 kg in the ivacaftor arm compared the placebo arm ($P<0.001$). This magnitude of this effect was quite dramatic over the 48 weeks of receipt of ivacaftor and suggests direct impact on the gastrointestinal system of this CFTR potentiator.

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IVACAFTOR (POST APPROVAL) EFFECTS ON LUNG FUNCTION, SWEAT CHLORIDE AND WEIGHT

Rowe SM, Heltshe SL, Gonska T, et al; GOAL Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network. Clinical mechanism of the cystic fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis. *Am J Respir Crit Care Med*. 2014 Jul 15;190(2):175-84.

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This was an observational study over 6 months assessing the impact of ivacaftor after Food and Drug Administration approval for individuals with CF with the G551D-*CFTR* mutation. The 2012/2013 study enrolled subjects age 6 and older with at least one G551D *CFTR* mutation with no prior exposure to ivacaftor. The patients underwent a clinical assessment of lung function, sweat chloride measurement and nutritional status at baseline, and again at 1, 3, and 6 months after ivacaftor initiation. The study also involved a series of sub-studies to assess mucociliary clearance, beta-adrenergic sweat secretion rate, gastrointestinal pH using a pH pill, sputum inflammation as measured by inflammatory markers, and sputum microbiology. The study enrolled 153 subjects of which 151 were prescribed ivacaftor. Of the 151 patients treated with ivacaftor, 133 (88%) completed the 6 month follow-up. The mean age was 21.1 (SD = 11.4) years and 46.4% were female. Of the participants, 72.2% were compound heterozygous with G551D and F508del.

The results of the study mirrored the findings in the phase 3 randomized controlled trial (described above). Mean change in FEV_1 was 6.7% of predicted (95% CI, 4.9–8.5; $P < 0.001$) at 6 months, with this change detected very early (at one month). Body weight improved from baseline to 6 months, with a mean change of 2.5 kg (95% CI, 1.9–3.1). Thus, the study replicated those results from a randomized controlled trial despite very limited inclusion criteria and without the strict medication accounting that is commonly used in phase 3 randomized controlled trials.

Although replicated results from a placebo controlled randomized controlled trial are important, the findings in the sub-studies were the most informative as they potentially delineated the mechanism of action of the drug. Mucocilliary clearance in 21 subjects, measured by clearance of radiolabeled particles by gamma scintigraphy, improved significantly with clearance, increasing to twice the rate at baseline at one and three months of follow-up. Also, gastrointestinal pH in 11 patients was significantly higher at one month compared to baseline, indicating duodenal alkalization. This finding of potential duodenal alkalization likely improved nutrient absorption and pancreatic enzyme function, and may explain the significant weight gain noted in both this study and the phase 3 study. The authors also noted a reduction in episodes of isolation of *Pseudomonas aeruginosa* as well as in hospitalization rate.

The study was an observational study, thus the results must be interpreted with caution. However, this study was a carefully done prospective cohort study with carefully protocolized procedures and data collection.

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THE EFFECT OF IVACAFTOR ON INFECTION

Heltshe SL, Mayer-Hamblett N, Burns JL, et al; GOAL (the G551D Observation-AL) Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network. *Pseudomonas aeruginosa* in cystic fibrosis patients with G551D-*CFTR* treated with ivacaftor. *Clin Infect Dis*. 2015 Mar 1;60(5):703-12.

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Heltshe and colleagues employed data from the G551D Observation-AL [GOAL] study linked to the US CF Foundation Patient registry. Given findings in the initial GOAL study, the investigators wanted to further evaluate the intriguing finding that patients receiving ivacaftor

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had a reduced rate of isolation of *Pseudomonas aeruginosa* up to 6 months after treatment. Of the 151 patients in the study, 29% (26/89) who were culture positive for *P. aeruginosa* the year prior to ivacaftor use were culture negative the year following treatment; 88% (52/59) of those who became *P. aeruginosa* free remained uninfected. The odds ratio for being *P. aeruginosa* positive one year after initiating ivacaftor was reduced by 35% (odds ratio [OR], 0.65; P < .001). Interestingly, ivacaftor significantly reduced the OR of cultures growing mucoid *P. aeruginosa* (OR, 0.77; P = .013) and *Aspergillus* species (OR, 0.47; P = .039). The frequency of respiratory cultures and sputum culturing decreased in the post-ivacaftor period compared to the pre-ivacaftor period.

This finding could have suggested a bias leading to lower rates of *P. aeruginosa* discovery after ivacaftor. However, when the authors adjusted for the differences in both respiratory cultures and more specifically sputum cultures in the post-ivacaftor period compared to the pre-ivacaftor period, ivacaftor remained associated with a reduced OR of having *P. aeruginosa*, mucoid *P. aeruginosa* and *Aspergillus*. Further, when the authors performed sensitivity analyses (assuming that all clinical visit without a respiratory culture were positive for *P. aeruginosa*), the associations persisted. For a comparison period, the investigators evaluated the two year period prior to the initiation of ivacaftor and found no change in frequency of the above noted pathogens, suggesting the temporal initiation of ivacaftor was the causal factor associated with reduction in isolation of these common microbes. Next, the authors limited the analysis to just those subjects with ≥ 3 respiratory cultures per year and found similar results. Interestingly, *P. aeruginosa* status was not associated with change in clinical outcome unless modeled as a continuous variable based on the proportion of positive cultures.

This is a secondary data analysis therefore it could be subject to bias, the most important of which are sample bias and differential follow-up. While the authors' multiple analyses tried to address these biases as best as possible given the available data, formal prospective analyses would be necessary to confirm these microbiologic findings.

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AIRWAY SURFACE LIQUID PH MODULATES BACTERIAL KILLING

Pezzulo AA, Tang XX, Hoegger MJ, et al. Reduced airway surface pH impairs bacterial killing in the porcine cystic fibrosis lung. *Nature*. 2012 Jul 4;487(7405):109-13.

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Pezzulo and colleagues employed the CF pig model to test the hypothesis that changes in the airway surface liquid in CF impair antimicrobial killing and that alkalization of the airway surface lining fluid could restore the host immunity against known CF pathogens. The authors generated *CFTR* -/- pigs, and at 6–15 hrs after birth made a small tracheal incision and placed live bacteria-coated grids on the airway surface of the posterior trachea. They demonstrated that in non-CF pigs, less than 30 seconds was required to kill the bacteria on the *Staphylococcus aureus* impregnated grids. In CF litter mates, only half the bacteria were killed, demonstrating a host defect in antimicrobial killing. Because host defense at the tracheal surface is modulated by antimicrobial peptides in the submucosal glands, they stimulated gland production with methacholine and reported that the differences persisted. The authors also studied *P. aeruginosa* applied to the grids and noted that host defenses were still impaired in the CF pig compared to the wild type pig. Although potassium and sodium concentrations in the airway surface liquid did not differ between CF and wild type pigs, the pH of the airway surface liquid fluid was lower in CF compared to non-CF pigs. The authors then assessed whether antimicrobial killing was pH dependent by increasing the pH in the CF pig model. In non-CF pigs, increasing pCO2 (which will acidify the ASL) reduced bacterial killing, while adding NaHCO3 to the CF pigs airway increased pH and increased antimicrobial killing. This work links the role of abnormal CFTR and pH to host immunity in a CF pig model, and may suggest a mechanism for the chronic airways infections so frequently seen in CF.

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IMPAIRED MUCUS DETACHMENT FROM THE SUBMUCOSAL GLANDS — A KEY DEFECT LEADING TO CF RELATED LUNG DISEASE?

Hoegger MJ, Fischer AJ, McMenimen JD, et al. Impaired mucus detachment disrupts mucociliary transport in a piglet model of cystic fibrosis. *Science*. 2014 Aug 15;345(6198):818-22.

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Hoegger and colleagues used the porcine model to try to unravel the conflicting results noted to date regarding mucocilliary transport in CF. To do this, they evaluated in real time excised CF pig tracheas bathed in saline. They applied fluorescent nanospheres to the surface of the trachea and then stimulated the tracheas to enhance mucous secretions from the submucosal glands. The mucous strands emanating from the glands could be tracked by the adherent fluorescent nanospheres. They demonstrated that in the CF pig, the mucous strands emanating from the mucous glands failed to detach from the gland, while in the non-CF pig tracheas, they did detach. Altering the pH of the non-CF pig tracheas with HCO3—free saline or saline containing bumetanide (which inhibits basolateral membrane Cl- entry into the epithelium) each alone did not change the phenotype of the non-CF pig tracheas. However, when these two approaches were added together, the non-CF pig trachea appeared to act like the CF trachea, with mucous remaining tethered to the gland orifice. The authors thus demonstrated that in the non-CF pig trachea, both the bicarbonate defect and chloride defect were needed to generate a CF phenotype. The results suggest that tethering of the mucous to the mucous gland orifice combined with a host defense defect due to alkalization of the airway surface lining fluid could be the mechanism by which early CF lung disease begins.

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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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