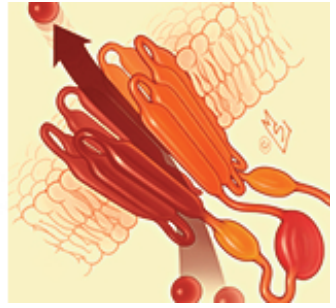




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eCysticFibrosis Review
Podcast Issue

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VOLUME 6 — ISSUE 2: TRANSCRIPT

Featured Cases: The Current State of CFTR Modification

Our guest author is Noah Lechtzin, MD from the Johns Hopkins University in Baltimore, Maryland.

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

- Explain the long-term benefits of ivacaftor therapy in people with G551D *CFTR* mutations.
- Describe the effects of ivacaftor therapy in people with non-G551D *CFTR* mutations.
- Evaluate the impact of the combination of ivacaftor plus lumacaftor in people with two F508del *CFTR* mutations.
- Describe the current research into therapeutic options for people with CFTR class I also known as nonsense or missense mutations.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to the current state of CFTR-modifying therapies in the format of case-study scenarios for the clinical practice. This program is a follow up to Volume 6, Issue 1 *eCysticFibrosis Review Newsletter* — [The Current State of CFTR Modification](#).

MEET THE AUTHOR



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Guest Faculty Disclosure

Dr. Noah Lechtzin has reported that he has served as principal investigator for Vertex Pharmaceuticals Incorporated. In addition, he has served as a consultant for Hill Rom.

Unlabeled/Unapproved Uses

Dr. Lechtzin has disclosed that his discussion today will refer to certain off-label or unapproved uses of lumacaftor, ivacaftor, and ataluren.

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MR. BOB BUSKER: Welcome to this eCysticFibrosis Review podcast.

Today's program is a follow-up to our newsletter topic on the current state of CFTR modifiers. Our guest today is eCysticFibrosis Review Program Director Dr. Noah Lechtzin, director of the Adult Cystic Fibrosis Program and associate professor of medicine at the Johns Hopkins University in Baltimore, Maryland.

eCysticFibrosis Review is presented jointly by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from Chiesi USA, Inc., Vertex Pharmaceuticals Incorporated, and Gilead Sciences.

Learning objectives for this audio program are, that after participating in this activity, the participant will demonstrate the ability to:

- Explain the long-term benefits of ivacaftor therapy in people with G551D *CFTR* mutations.
- Describe the effects of ivacaftor therapy in people with non-G551D *CFTR* mutations.
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Dr. Lechtzin has reported that he has served as principal investigator for Vertex Pharmaceuticals Incorporated. In addition, he has served as a consultant for Hill Rom.

Dr. Lechtzin has disclosed that his discussion today will refer to certain off-label or unapproved uses of lumacaftor, ivacaftor, and ataluren.

I'm Bob Busker, managing editor of eCysticFibrosis Review. Dr. Lechtzin, welcome to this eCysticFibrosis Review podcast.

DR. NOAH LECHTZIN: Thank you very much. It's a pleasure to be here today.

MR. BUSKER: The recent newsletter by Dr. Peter Mogayzel reviewed studies describing the current

research into CFTR modifier therapies — and how they increase the clinician's ability to go beyond treating the symptoms of cystic fibrosis and actually correct the underlying cause of the disease. Our focus today is on how some of that new information can be applied in the clinic. So please start us out with a patient description.

DR. LECHTZIN: I'd like to tell you about a patient of mine, TM, a 27 year old gentleman with cystic fibrosis whose genotype is F508del/G551D. He's pancreatic insufficient, has chronic sinus disease, and has chronic pulmonary infections with both *Pseudomonas aeruginosa* and methicillin resistant staph. Throughout adolescence and into early adulthood his daily therapy has included airway clearance high frequency chest wall oscillation vest twice a day, dornase alfa nebulizer daily, azithromycin three days a week, and aerosolized tobramycin twice a day on alternating months. His lung function was approximately 90% predicted when he attended college; however, in his senior year of college he started to run into problems. His FEV₁ fell to 66 % predicted and he began to have more cough, sputum production, dyspnea, weight loss, and fatigue. We added hypertonic saline and aztreonam nebulizer treatments, and he was also treated with courses of both oral antibiotics and IV antibiotics but did not improve dramatically.

MR. BUSKER: An airway clearance regimen, chronic macrolide therapy, inhaled antipseudomonal antibiotics — it sounds like you tried just about everything with this patient, without a lot of success.

DR. LECHTZIN: Yes, he was having progressive loss of lung function and worsening symptoms in spite of very aggressive care. He was becoming frustrated, as was the CF team. And until fairly recently, there wouldn't have been other options.

Fortunately, he has the G551D mutation, which is a gating mutation, and this is the first group of patients for whom ivacaftor was approved. This has been a breakthrough therapy and is the first therapy that addresses the underlying problem in cystic fibrosis; that is, a defective chloride channel. Based on a randomized clinical trial, published by Ramsey, et al in the New England Journal in 2011, we would expect to see an improvement in FEV₁ of over 10%

at 24 weeks, a decrease in exacerbations by up to 55%, an increase in weight by approximately 2-1/2 kg, and an improvement in respiratory symptoms.

MR. BUSKER: Would these effects sustain over time? What does the evidence show?

DR. LECHTZIN: That's a great question. As I said, the introduction of ivacaftor was a real breakthrough, but the initial clinical trial only followed people up to 24 weeks. Based on results of more recent publications such as the PERSIST study, which was published by McKone and colleagues in 2014, the beneficial effects of ivacaftor were maintained up to 144 weeks after starting treatment. In that study, FEV₁ improved by approximately 10%, weight improved by approximately 14.8 kg and 4.1 kg in adults and children, respectively, and this was maintained up to 144 weeks.

This was one of the studies reviewed in the newsletter.

MR. BUSKER: The patient you presented us: what did you do for him and how did he respond?

DR. LECHTZIN: This is one of our early "feel good" stories with ivacaftor. We initiated ivacaftor in this patient, and his lung function increased from 65 % predicted. His weight increased by 13 kg, his respiratory symptoms improved, and he has gone several years without a pulmonary exacerbation requiring IV antibiotics. Furthermore, he's gone on to graduate from college, is now working full time, and is also exercising regularly. He's happy and we're happy.

MR. BUSKER: Just to clarify, doctor: the only change in his treatment was the addition of ivacaftor. There were no changes in his airway clearance regimen or antimicrobial medications. Is that correct?

DR. LECHTZIN: That's correct. The only change we made to his regimen was adding ivacaftor.

MR. BUSKER: Thank you for that case and discussion, Dr. Lechtzin. Please bring us another patient scenario.

DR. LECHTZIN: This patient is CS, who has cystic fibrosis, genotype F508del/R117H, and has a lifelong history of sinopulmonary infections. His cystic fibrosis wasn't diagnosed until he was in his 60s. This

occurred after his sister was found to have cystic fibrosis. His sweat chloride was 76 and his usual FEV₁ has been approximately 75 % predicted.

In general, he required treatment with antibiotics for increased pulmonary symptoms several times per year, and his usual therapies included azithromycin, dornase nebulizer, bronchodilators, and airway clearance with the Acapella PEP device.

MR. BUSKER: F508del and R117H CFTR mutations — would this patient be an appropriate candidate for CFTR modulator therapy?

DR. LECHTZIN: Yes. Ivacaftor was not initially approved for patients with the R117H mutation. The CONDUCT study published by Moss, et al in 2015 showed a significant benefit in patients with this mutation. The effect on lung function wasn't significant in children ages 6 to 11, but in patients 18 and older, there was a 5% increase in FEV₁, which was significant in patients with the R117H mutation.

There were also improvements in the respiratory subscale of CFQR and lower sweat chloride. This patient had the R117H mutation, which made him a candidate for CFTR therapy, but it's also worth considering another study recently published by De Boeck, et al, which evaluated the effect of ivacaftor in non-G551D gating mutations. That study showed that ivacaftor resulted in improvements in FEV₁ of approximately 10% at the eight-week follow-up. In that study, BMI also improved by 0.7 kg/m² after eight weeks of treatment.

MR. BUSKER: In these patients who are candidates for ivacaftor therapy, are there any drug-drug interactions that clinicians should worry about?

DR. LECHTZIN: Yes. Clinicians prescribing ivacaftor need to realize that it's metabolized in the liver by the cytochrome P3A system, and drugs that inhibit CYP3A such as azole antifungals require decreases in doses of ivacaftor. For strong inhibitors such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin, the dose should be decreased to 150 mg twice per week. Moderate CYP3A inhibitors such as fluconazole and erythromycin, the dose should be decreased to 150 mg per day.

On the other side, reducers of CYP3A such as rifampin, phenobarbital, and phenytoin are not recommended in conjunction with ivacaftor. Therefore, if a patient requires these drugs, ivacaftor should be held. It's worth noting that many of these medications such as the azole antifungals and rifampin are commonly used in cystic fibrosis.

MR. BUSKER: Did you start this patient on ivacaftor, and what were the results?

DR. LECHTZIN: Yes, we chose to start him on ivacaftor, given his frequent symptoms and impaired lung function. He's tolerated ivacaftor quite well without any difficulties; he's had no adverse events, and his lung function is now consistently around 90 % predicted, whereas it had been around 75 % predicted before starting ivacaftor.

MR. BUSKER: We'll return with Dr. Noah Lechtzin from Johns Hopkins, in just a moment.

MR. BUSKER: Hello. I'm Bob Busker, managing editor of eCysticFibrosis Review.

eCysticFibrosis Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to pulmonologists, gastroenterologists, infectious disease specialists, pediatricians, respiratory therapists, dietitians, nutritionists, nurses, and physical therapists.

Bimonthly podcasts are also available as downloadable transcripts, providing case-based scenarios to help bring that new clinical information into practice in the clinic.

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MR. BUSKER: Welcome back to this eCysticFibrosis Review podcast. I'm Bob Busker, managing editor of the program. We've been talking with eCysticFibrosis Review program director Dr. Noah Lechtzin from the Johns Hopkins University about how recent research into CFTR modification can be applied in the clinic to improve patient outcomes. So please bring us another patient.

DR. LECHTZIN: The third patient is MM. He is a 21 year old man with cystic fibrosis, genotype F508del/F508del whose CF was diagnosed as an infant due to failure to thrive. He had recurrent pulmonary infections and sinus infections as a child and required sinus surgeries throughout childhood. His course was complicated by malnutrition and required a gastrostomy tube as an adolescent. He transitioned to our adult CF program at age 19. At that point his FEV1 was 75% predicted, and he weighed 157 pounds, which translates to a BMI of 20. He was attending college full time but required hospitalization for intravenous antibiotics about once a year. His therapies included airway clearance with high frequency oscillating vest, inhaled tobramycin, dornase alfa nebs, hypertonic saline nebs, azithromycin, and pancreatic enzymes.

MR. BUSKER: Homozygous genotype F508del. Is this a patient who would benefit from ivacaftor therapy?

DR. LECHTZIN: No. In this case ivacaftor alone would not be indicated. Ivacaftor has been shown not to benefit patients who are homozygous for the F508del mutation, and it's not approved for this group. However, ivacaftor when combined with lumacaftor was approved in July 2015 for patients homozygous for F508del.

This was based on the results from two phase 3 randomized clinical trials. These two separate randomized trials both showed an improvement in FEV1 of approximately 3%, and importantly showed an approximately 30% reduction in pulmonary exacerbations.

MR. BUSKER: What about tolerability? Is the ivacaftor/lumacaftor combination well tolerated?

DR. LECHTZIN: Yes. In the two phase 3 clinical trials, the rate of serious adverse events was 29% in the placebo group compared to 20% in the ivacaftor/lumacaftor group. Approximately 4%

of patients stopped therapy in the ivacaftor/lumacaftor group compared to 1.6% in the placebo group. The most common nonserious adverse events in the ivacaftor/lumacaftor arm were respiratory and commonly included some shortness of breath and chest tightness.

MR. BUSKER: And your patient's response to the ivacaftor/lumacaftor combination therapy?

DR. LECHTZIN: He has tolerated it quite well. His FEV₁ is now consistently around 83% and his body mass index has improved to 22.

MR. BUSKER: Thank you for that case and discussion, doctor. We've got time for one more case, please.

DR. LECHTZIN: I'd be glad to tell you about another case. ZO is a 47 year old woman with cystic fibrosis. Her genotype is F508del/W1282X, and she has a baseline FEV₁ of 65%. Her symptoms include chronic cough, sputum, and dyspnea, in spite of aggressive care, which includes high frequency oscillating vest, dornase alfa nebs, hypertonic saline, azithromycin, and tobramycin nebs. She exercises regularly and struggles to maintain her weight. In general, her weight is 92 pounds and her BMI is 17.5. She has had exacerbations requiring intravenous antibiotics at least once a year, and she has been quite frustrated that in spite of her best efforts she continues to have problems and decline.

MR. BUSKER: I think every clinician and every patient can completely understand her frustration. So is this patient a candidate for ivacaftor or ivacaftor plus lumacaftor therapy?

DR. LECHTZIN: No. Because she has what's called a class I mutation, W1282X, she isn't a candidate for ivacaftor or the combination of ivacaftor and lumacaftor. In this type of mutation, a stop has been inserted into the DNA coding region, and therefore, no CFTR protein is made so there is no target for drugs like ivacaftor and lumacaftor to act on.

MR. BUSKER: What can you tell us about the current research being done to help patients with these class I mutations?

DR. LECHTZIN: Studies of small molecules may address these types of mutations. One such drug under investigation is ataluren, which is designed

to allow ribosomes to read through premature stop codon in class 1 mutations. A study published by Kerem and colleagues is a phase 3 trial of 138 patients enrolled at 36 sites in 11 countries and enrolled patients age 6 and older who had FEV₁ between 40 and 90 percent predicted. They were treated with ataluren by mouth three times per day or placebo.

The FEV₁ did not differ significantly between the two treatment groups at the end of the trial. In addition, the frequency of pulmonary exacerbations did not differ. However, a post hoc analysis of a subgroup of patients who didn't use chronic inhaled tobramycin showed a significant difference between FEV₁ in the ataluren group compared to placebo. In this subgroup there was a 5.5% difference in relative percent predicted FEV₁, and there were fewer exacerbations in the ataluren-treated group. At this time, ataluren is still considered investigational and is not currently approved.

MR. BUSKER: That subgroup analysis found that patients with class I CFTR mutations not on inhaled tobramycin did receive some benefit from ataluren therapy. Did the investigators come to any conclusions — or did they speculate — about why there was that 5.5% improvement in FEV₁?

DR. LECHTZIN: One explanation for the findings in this trial is that tobramycin, which is an inhaled antibiotic, binds to bacterial ribosomes, which interferes with the ataluren at a cellular level. This seems to be a plausible explanation for the results and has led to the initiation of a second phase 3 trial studying ataluren in patients who are not receiving inhaled tobramycin.

MR. BUSKER: Thank you for today's discussion, Dr. Lechtzin. I'd like to ask you to shift gears for us now, and look to the future. Overview for us, if you would, some of the new cystic fibrosis therapies that are currently in development.

DR. LECHTZIN: Current potentiators and correctors have been very exciting and are extremely helpful for some of our patients with cystic fibrosis, but many patients still are not benefiting from these therapies. It is an exciting time for drug development in clinical trials for CF, and more drugs are moving into phase 2 and phase 3 clinical trials in the next year than ever before.

We need treatments for patients with class I, otherwise known as nonsense or missense mutations such as W1282X, and we also need treatments for patients with only one copy of F508del. Furthermore, we need more potent therapy for patients with F508del and therapy with fewer drug interactions. Currently drugs are under investigation that also target other mechanisms. One such mechanism is known as ENaC, or the epithelium sodium channel. This is a sodium channel that is regulated in part by CFTR. There is currently an ongoing trial of an inhaled agent that inhibits ENaC, and others are under development.

Gene therapy generated lots of excitement in the 1990s, after the CFTR gene was discovered, and there was hope that a cure for cystic fibrosis was just around the corner. Unfortunately, early trials of gene therapy were largely unsuccessful. Nevertheless, studies of gene therapy are still underway and it shouldn't be written off as a potential area for treating cystic fibrosis. One benefit to gene therapy is that it would not be genotype specific.

MR. BUSKER: Thank you for sharing your thoughts, doctor. Let's wrap things up by reviewing our discussion today in light of our learning objectives. So to begin: the long-term benefits of ivacaftor therapy in people with G551D CFTR mutations.

DR. LECHTZIN: In case 1 I reviewed some of the recent data on sustained effects of ivacaftor. Two recent studies showed ivacaftor has sustained benefits beyond the 12 month initial clinical trials. In the PERSIST trial, which included almost 200 patients, FEV₁ was maintained by 9% to 10% above baseline for more than two years, and weight and BMI were also maintained.

Another study using the CF registry showed that when compared to matched patients who were homozygous for F508del, patients with G551D who were on ivacaftor had a 10% difference in FEV₁ decline that was sustained over three years. They also had improvements in weight that were maintained over that time period.

MR. BUSKER: And our second learning objective: the effects of ivacaftor therapy in people with non-G551D CFTR mutations.

DR. LECHTZIN: In case 2 I discussed the use of ivacaftor in a patient with the R117H mutation and reviewed the recent literature on the effects of ivacaftor in this population. Ivacaftor resulted in an approximately 5% improvement in FEV₁ for patients 18 and older. There was also improvement in respiratory symptoms as measured by the CFQR and reduced sweat chloride. In patients with other non-G551D nongating mutations, a short-term study of eight weeks showed a 10% improvement in FEV₁ and a 0.7 improvement in BMI.

MR. BUSKER: And our third learning objective: the impact of the combination of ivacaftor plus lumacaftor in people with two F508del CFTR mutations;

DR. LECHTZIN: Case 3 describes a patient who started lumacaftor/ivacaftor and presents the results of recent clinical trials of ivacaftor and lumacaftor for patients with two copies of F508del CFTR mutations. Lumacaftor and ivacaftor combined is effective for this population. In clinical trials the combination resulted in greater than a 30% reduction in acute exacerbations and a 3% to 4% improvement in lung function. Additionally, the combination of lumacaftor and ivacaftor was well tolerated and had fewer serious adverse events than in the placebo arm.

MR. BUSKER: And finally: the current research into therapeutic options for people with CFTR class I, also known as nonsense or missense mutations.

DR. LECHTZIN: These patients have a severe mutation in which no CFTR is made and potentiators and correctors don't have a role. However, there are small molecules that allow CFTR to be made in the cell nucleus which are currently under investigation and are beginning to show some promise.

MR. BUSKER: Dr. Noah Lechtzin from the Johns Hopkins University — thank you for participating in this eCystic Fibrosis Review Podcast.

DR. LECHTZIN: You're very welcome. It's been my pleasure speaking to you today.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.ecysticfibrosisreview.org/test.

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