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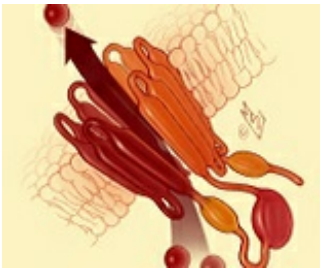

VOLUME 6 - ISSUE 12

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Future Landscape of CFTR Modulators

Our guest authors are Claire Wainwright, FRACP, MD and Tonia Douglas, FRACP, MD, respiratory physicians at the Lady Cilento Children's Hospital in Brisbane, Australia.

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

- Summarize the appropriate use of CFTR modulator therapies in clinical practice, including patient selection, clinical benefits and ongoing monitoring.
- Explain the potential barriers to the optimal use of CFTR modulators.
- Discuss the role of patient-physician collaboration and communication in the use of CFTR modulator therapies.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of the Future Landscape of CFTR Modulators. This program is a follow up to the Volume 6, Issue 11 *e*CysticFibrosis Review newsletter—CFTR Molulation: Today and Tomorrow.

Unlabeled/Unapproved Uses

Dr. Claire Wainwright and Dr. Tonia Douglas have indicated that there will be no off-label discussions of any drugs or products in this presentation.

MEET THE AUTHORS

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Guest Faculty Disclosure

Dr. Claire Wainwright has indicated that she has received honoraria from Novartis Pharmaceuticals, Vertex Pharmaceuticals, and Vertex Pharmaceuticals Australia, and has also served as a consultant/advisor for Vertex Pharmaceuticals.

Dr. Tonia Douglas has indicated that she has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of this presentation.

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Podcast Transcript

BOB BUSKER: Welcome to this *e*CysticFibrosis Review podcast.

I'm Bob Busker, Managing Editor of the program. Our discussion today is a follow-up to our newsletter topic, CFTR Modulation: Today and Tomorrow. We'll be talking in just a moment with that issue's authors. They're both from the University of Queensland in Brisbane, Australia, where Dr. Claire Wainwright is a Professor of Paediatrics and Child Health, and Dr. Tonia Douglas is a Senior Clinical Lecturer. Both authors are also Respiratory Physicians at the Lady Cilento Children's Hospital, also in Brisbane.

***e*CysticFibrosis Review is jointly presented 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, Inc.**

Learning objectives for this audio program include:

- **Summarize the appropriate use of CFTR modulator therapies in clinical practice, including patient selection, clinical benefits, and ongoing monitoring.**
- **Explain the potential barriers to the optimal use of CFTR modulators.**
- **Discuss the role of patient-physician collaboration and communication in the use of CFTR modulator therapies.**

By way of disclosures, Dr. Claire Wainwright has indicated that she has received honoraria from Novartis Pharmaceuticals, Vertex Pharmaceuticals, and Vertex Pharmaceuticals Australia and has also served as a consultant/advisor for Vertex Pharmaceuticals.

Dr. Tonia Douglas has indicated that she has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of this presentation.

Our faculty have also indicated that there will be no off-label discussions of any drugs or products in this today's presentation.Dr. Douglas, Dr. Wainwright, thank you both for joining us today.

DR. DOUGLAS: Thank you very much for asking me.

DR. WAINWRIGHT: You're very welcome. It's good to be here.

MR. BUSKER: Doctors, your newsletter issue gave us a pretty full picture of how the existing CFTR modulator

therapies came to be, as well as a preview of what's likely to come in the foreseeable future. What I'd like to do today is focus on how that information can be applied to actual clinical practice. So start us out, if you would please Dr. Douglas, with a patient scenario.

DR. DOUGLAS: We have a 15 year old patient with a G551D and a delta-F508 mutation, and she's attending her routine CF clinic with her mother. She's had moderately severe lung disease with bronchial wall thickening, mucus plugging, and bronchiectasis with air trapping on her CT scan images. She's also chronically infected with *Pseudomonas aeruginosa*. She's had four admissions to hospital over the last 12 months and has a decline in her lung function with a best FEV_1 of 68 percent predicted last year, down to 60 percent predicted this year.

On examination she was thin, with a BMI that had fallen from the 50th percentile to the 5th percentile. On physical examination, she was clogged and had a moist cough, and crackles were audible in the right lung base.

Going into her history, she started ivacaftor four years ago in 2012, and her lung disease appeared to be quite nicely stabilized until around this last six to 12 months. Her treatment regimen also includes albuterol and airway clearance with vest and a PEP device. She had alternate-month tobramycin solution for inhalation. She is using dornase alfa, pancreatic enzyme replacement, salt supplementation, and vitamin supplementation.
Her mother is concerned that ivacaftor is no longer working for her daughter and asked whether the lumacaftor and ivacaftor combination might address both the CFTR mutations and also provide a better outcome for her.

MR. BUSKER: Two initial questions: is ivacaftor actually failing in this patient? And might the mother's suggestion to switch to the lumacaftor/ivacaftor combination potentially be appropriate? Dr. Wainwright, your thoughts?

DR. WAINWRIGHT: I don't think there is any evidence at all that combination therapy with lumacaftor and ivacaftor would provide any benefit for this patient; in fact, combination therapy is not indicated for this genotype.

We've seen that combination therapy has not shown any benefit in patients who carry one copy or who are heterozygous for the F508del *CFTR* mutation. In addition, there is a drug interaction between lumacaftor and ivacaftor and that reduces the amount of ivacaftor that is available in the combination therapy, compared with ivacaftor monotherapy. That in itself might reduce any potential benefit. So for this patient, it really is not indicated to use the combination therapy.

Some new clinical trials in progress are going to assess different combination therapies on CFTR function in patients with gating mutations who are heterozygous for the F508del mutation, and I think we're likely to see some new approaches that might provide greater benefit compared with ivacaftor monotherapy in the future. But for now ivacaftor is the only CFTR modulator therapy available for this patient and others with this genotype.

MR. BUSKER: Dr. Douglas, do you agree with what Dr. Wainwright just said? And if so, what do you think might be going on with this patient?

DR. DOUGLAS: I do agree, because I think ultimately this could be an issue for adherence. But let's just talk about some of the studies: ENVISION and STRIVE. These studies were conducted in patients just like this one, with at least one G551D mutation. These studies showed an increase in FEV_1 of around 10% from baseline and improvements in body weight and reductions in pulmonary exacerbations compared to placebo in the patients who were randomized to ivacaftor.

The effects were apparent as early as two weeks into treatment, and importantly, the effect was sustained throughout the whole 48 week trial period and into the 96th week open label period. So for this patient we would expect ongoing stability.

We also might expect a reduced rate of decline in lung function longer term, as was seen in the trial among patients with a G551D mutation. While the disease modifying effect is very exciting, ivacaftor does not cure CF. There is still a rate of lung function decline of around half of what might be expected without ivacaftor over time. So it is possible that the decline in lung function for this patient is really just part of her ongoing CF disease, but we need to consider whether she has a new airway infection and whether she's developed any complications such as allergic bronchopulmonary aspergillosis or potentially CF-related diabetes.

MR. BUSKER: You said that the decline in this patient's condition might be an issue of adherence. Talk to us a little bit

more about that, please.

DR. DOUGLAS: This is a young lady who is 15 years of age, and from clinical experience we recognize that adolescent patients have difficulties with adherence. There are other things in their lives that often take precedence over their CF care. Trial data also suggest that especially in young people and adults, adherence might not be optimal, even with ivacaftor, which is a relatively simple medication.

Consideration of suboptimal adherence with the standard regular therapies is important as well. We need to have a frank and honest discussion with our patient about how she takes her ivacaftor, making sure that she takes it with fatty food, and whether she's continuing with her standard regular CF treatment.

As her physician I'll sit down and find out what barriers she may have to optimal adherence, what's happening in her life, and how I might be able to navigate and solve these problems with her and her family so she can be in a position to get the best results from ongoing use of ivacaftor. Adherence is very important and must be discussed with all patients regularly, along with barriers to taking therapy and continuing therapy.

Mr. Busker: Thank you for that case and discussion. We'll return, with Dr. Wainwright and Dr. Douglas, in just a moment.

MR. BUSKER: This is Bob Busker; I'm the managing editor of *e*CysticFibrosis Review.

***e*CysticFibrosis Review is a combination newsletter and podcast program delivered by 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 information into practice in the clinic.
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MR. BUSKER: Welcome back to this *e*CysticFibrosis Review podcast. I'm Bob Busker, managing editor of the program. Our guests are Dr. Claire Wainwright and Dr. Tonia Douglas from the University of Queensland. We've been discussing the clinical applications of CFTR modulation. To continue in that vein, Dr. Wainwright, please bring us another patient scenario.

DR. WAINWRIGHT: Tim has just had his 12th birthday. His CF was diagnosed through newborn screening; he's homozygous for the F508del mutation. He loves sports and he's trying out for his school football team. Tim has a BMI on the 50th percentile. He's had normal growth and is just starting to go into puberty. His lung function has been stable over the last couple of years and his FEV_1 is around 85 percent predicted. But his previous best FEV_1 was around 90 percent predicted when he was around 8 years of age.
Tim has cultured *Staphylococcus aureus* intermittently from sputum cultures, and he has had two intermittent infections with *Pseudomonas aeruginosa* in the past, but on each of those occasions he's had successful eradication of the organism.

Now despite stable lung function, he has had around two pulmonary exacerbations per year over the last couple of years requiring admission to hospitals for intravenous antibiotics. Tim also has a history of a little asthma and mild eczema, and he has had the occasional hospital admission for asthma.

Tim also has had intermittently elevated transaminases, up to around twice the normal range since he was 5 years of age, but his physical exam and his liver ultrasound have not indicated any concern for significant liver disease. In particular, there is no evidence that he has any cirrhosis or portal hypertension.

His regular therapy includes pancreatic enzyme supplementation and vitamin therapies; he uses inhaled dornase alfa, some inhaled corticosteroids, and albuterol; and his airways clearance regimen is fairly standard as well.

His parents are aware that he could now start combination therapy with lumacaftor and ivacaftor, but they've been worried about the liver enzyme changes and wonder whether that might be a problem for him if he starts the combination therapy. They've also heard that some patients have had chest tightness when starting combination therapy, and they're worried because of his history of asthma and occasional admissions for asthma. They also feel that his chest has remained very stable for some time, and given his young age they're worried about starting a relatively new therapy that might be taken over a long time.

MR. BUSKER: Is combination therapy with lumacaftor/ivacaftor indicated for this patient at this time? Dr. Douglas, how would you advise the family?

DR. DOUGLAS: We know that combination therapy in patients with CF who are homozygous for del-F508 is associated with a modest improvement in pulmonary function and that improvement was maintained for the duration of the clinical trials. We also know that pulmonary exacerbations and some modest improvement in nutritional status were also observed.
But Tim is starting to go through puberty, and growth and nutrition are going to be very important for him. He's also going to want to avoid any hospitalization during this time so he can maximize his school attendance and keep up with his social life. While his lung function has remained stable over the past few years, it has fallen from his previous best values. An important consideration here is that if he continues to have pulmonary exacerbations, he is at risk of further loss of lung function, because we know that around a quarter of all pulmonary exacerbations are associated with incomplete recovery of previous lung function. He is also at the highest risk of loss of lung function over his adolescent years.
So, yes, I think it is worthwhile starting Tim on combination therapy, and I hope we can prevent further pulmonary exacerbations, reduce the risk of lung function loss, and optimize normal function.

MR. BUSKER: I'd like to focus on this patient's recent exacerbations — you said he's had two a year over the past two years. Dr. Wainwright, do these exacerbations have any impact on your recommendation for combination therapy?

DR. WAINWRIGHT: Even if Tim had not had any exacerbations recently, I would still consider combination therapy. We're now moving to a different, more preventive model of treatment, and we want to maintain health rather than wait for deterioration and evidence of disease progression before starting therapies. You need to do that very carefully and work closely with patients and their families. You have to tailor therapies for them as individuals and you don't want to overburden them with therapies. But the goal of therapy should really be to avoid deterioration and maintain health. I think this is an option for the family to consider.

MR. BUSKER: What about his liver enzymes? He doesn't show significant liver disease, that was made clear, but his levels have been intermittently high over the past seven years or so. How big a concern are these elevated liver enzymes if he starts combination therapy, and what kind of monitoring should be done?

DR. WAINWRIGHT: In the clinical trials of combination therapy, patients with severe liver disease were excluded, but Tim does not appear to have severe liver disease, so he would fit the inclusion criteria for the trials, and I would be happy for him to start the combination therapy. Elevation in transaminase levels is very common in patients with cystic fibrosis, and it does not necessarily indicate significant liver disease.

Elevated liver enzymes are also reported in equal proportions in patients taking placebo or active treatment in the phase 3 trials of combination therapy. However, we did see more severe adverse events in the actively treated group. So I'm reassured that his liver ultrasound and physical exam did not identify any concerns about liver disease, but I would suggest

we check liver function tests before starting the combination therapy with lumacaftor and ivacaftor. I would also check his liver function in the first two to four weeks after starting therapy and then every three months over the first year of use. If all that remains stable, we would go to the recommended annual checking.

MR. BUSKER: The parents expressed concern about the potential side effects of lumacaftor/ivacaftor therapy on their son's asthma. Dr. Douglas, how would you address that?

DR. DOUGLAS: It's a good question. During the phase 3 trials TRAFFIC and TRANSPORT, around 13% to 15% of patients taking combination therapy experienced dyspnea, compared with around 8% of patients taking placebo. Around 9% to 11% of patients taking the combination therapy also experienced chest tightness, compared with around 6% of those on placebo. Those respiratory symptoms were of relatively short duration and resolved after the first few weeks of therapy; they also responded to bronchodilators.
Interestingly, it wasn't possible to predict which patients might experience those symptoms in patients with a previous history of asthma. So my advice to Tim would be to predose with albuterol before starting combination therapy, and we would normally give the first dose of combination therapy in the clinic.

MR. BUSKER: Let's assume you are going to start this patient on lumacaftor/ivacaftor therapy. Overall, what advice would you give to the parents?

DR. DOUGLAS: The family will need a good discussion about the side effects and interactions of the combination therapy with other medications, and also their expectations. They need to be aware that combination therapy can interact with other drugs and medications, so they need to be sure they tell any health care professional that Tim is taking combination therapy before starting other medications — in particular, macrolides such as erythromycin, and antifungals such as parconazole.

They also need to be aware that certain over the counter products can interact, as can some alternative therapies. So we would sit down and run through any medications that Tim is taking, including over the counter therapies and alternative medicines, before we start combination therapy.

This is really important for managing expectations, as we might not expect to notice large changes or improvements in Tim's clinical statements. This is especially the case since Tim has been stable for some time and his lung function is in the normal range. So I will talk about the potential for maintaining health and the importance of continuing his regular medications to optimize Tim's overall health outcomes.

MR. BUSKER: Dr. Wainwright — anything to add?

DR. WAINWRIGHT: Yes. I think managing expectations is going to be very important because we don't really expect to notice large changes in clinical status, especially as Tim has been stable and his lung function has been in the normal range. And I think particularly because of the past, people have very high expectations with taking CFTR modulator therapies.
I will talk about the potential for maintaining health and the importance of continuing regular therapies to optimize Tim's health outcomes. We also need to talk regularly about adherence, not just on this occasion. It will be worth asking how often Tim misses his regular therapies and how he plans to add combination therapy to his regular therapy, especially as he is going to need to take this combination therapy with fatty foods every 12 hours over the long term. We'd really need to have good conversations about how he's going to manage all of that.

MR. BUSKER: Thank you for that case and discussion, doctors. Dr. Douglas, we have time for one more patient scenario.

DR. DOUGLAS: Helen is 27 years of age and she's homozygous for the delta-508 *CFTR* mutation. She has moderately severe lung disease with an FEV_1 of 55 percent predicted and CF-related diabetes. She's had a much more stable course since she's started combination therapy with lumacaftor and ivacaftor. In particular, her nutritional status has improved, and she has gained 1.3 kg in weight over the last 12 months. She has had no admissions to hospital in the last 12 months. Previously she was being admitted around two or three times a year for intravenous antibiotics, so that's an improvement.

Helen has recently married John, who has had genetic testing for CF and is not known to carry any *CFTR* mutation, which is

good news. Helen has also taken on a new job with longer working hours and she's concerned about managing her therapeutic regimen given her changing circumstances. She's also considering starting a family.

Helen's treatment regimen includes insulin through an infusion pump with four to five blood glucose measurements a day, inhaled antibiotics on alternate months, dornase alfa, albuterol, and hypertonic saline. She's taking azithromycin and using PEP and vest therapy for her physio. She is also taking pancreatic enzyme replacement and vitamin supplementations, and in addition to that, the lumacaftor/ivacaftor combination therapy. She is managing to attend the gym between two or three times a week.

MR. BUSKER: I have two questions here. My first is that this patient's therapeutic regimen seems exceptionally time consuming. Dr. Wainwright — any changes she might be able to make to simplify things?

DR. WAINWRIGHT: This is a big issue for patients, but when we look at it, the phase 3 clinical trials of combination therapy with lumacaftor and ivacaftor were conducted with patients taking all their usual CF therapies, so the benefits that were seen with CFTR modulator therapy are really on top of all the usual treatments. We don't yet have any good evidence around what if any therapies can be withdrawn to simplify or reduce the therapeutic burden and make patients' lives easier if they have a good response to these therapies. We know there is always a risk that if patients cut back on therapy, the benefits seen might not continue to be as effective. But chronic disease management is all about working with patients and helping them make choices about their treatment regimens and taking into account their changing circumstances. We need to make sure that Helen understands the evidence around the use of her different therapies and then work with her to make some shared decisions around her therapeutic regimens, and we may need to discuss different treatments according to her health needs.

I think it would be certainly useful clinically in the future to have some evidence around how to do this most effectively, because at the moment we have to do it by trial and error and use individual patient preferences as well.

MR. BUSKER: My second question is about her planned pregnancy. Dr. Douglas, what specific issues should be considered?

DR. DOUGLAS: It's a complicated situation. We know that remaining stable from a health perspective, in particular maintaining nutritional status and avoiding pulmonary exacerbations, are key during pregnancy. Helen's experienced an improvement in her nutritional status, as well as a reduction in the frequency of pulmonary exacerbations with lumacaftor and ivacaftor. However, the difficulty here is that lumacaftor/ivacaftor in CFTR modulated therapy is not recommended during pregnancy, and the clinical trial specifically ensured avoidance of pregnancy for subjects taking part in the trials.

So here I'm going to advise Helen that the combination therapy she has been taking with good effect is not advisable during her pregnancy. We'll discuss with her the options around starting a family and consider how we can maintain her health appropriately if she wishes to start a family, and I'll inform her that she will have to stop her combination therapy prior to conception.

MR. BUSKER: Doctors, thank you both for today's cases and discussion. We've talked about CFTR modification therapies today. I'd like to take a moment now and ask you to focus on tomorrow. Dr. Douglas, what does the future hold for new CFTR modification therapies?

DR. DOUGLAS: Thank you, Bob. It is a really exciting time for new therapeutic development. Lots of new therapies are under development, but there are also some big challenges ahead. One of the major challenges is making sure that the CFTR modulator therapies are available for all patients with CF, including those who may not have been included in phase 3 trials to date. Patients with rare CFTR mutations; those at both extremes of lung function, including those with FEV_1 less than 40 percent predicted or FEV_1 greater than 100 percent predicted; patients who are pregnant; and very young patients from the time of diagnosis through newborn screening — and perhaps in the future, before birth, to prevent disease manifestations becoming established.

We also need approaches for patients who have more severe liver disease.

Additionally, we may see different patterns of disease emerging with earlier use of CFTR modulator therapies, and

consequently we may need to change how we manage our patients over time. We have to develop new approaches and new clinical outcome measures so we can determine how patients will benefit from therapy.

MR. BUSKER: Dr. Wainwright — same question.

DR. WAINWRIGHT: I think we have to find out how best to monitor different patients across their lifetime as well — how we monitor very young children and older patients, and how we juggle very complicated therapeutic regimens over time; which drugs are the best or most needed for patients across different circumstances through their life, which ones they can drop.

We also have to consider the cost and health economic benefits as a society and make sure that the extraordinary benefits these new therapies bring are available globally to all patients with cystic fibrosis. We have no cure for CF yet, although CFTR modulator therapies currently available give us huge hope, but I think we still have a really long road ahead.

MR. BUSKER: Thank you for sharing your insights, doctors. Let's wrap things up now by reviewing the key points of today's podcast in light of our learning objectives. So to begin: the appropriate use of CFTR modulators in clinical practice. Dr. Wainwright?

DR. WAINWRIGHT: We talked about the importance of correct selection of CFTR modulator therapy to address patients' specific genotypes, and in particular we discussed how CFTR modulator therapies can improve lung function, reduce the frequency of pulmonary exacerbations, and improve nutritional status. We also discussed the use of CFTR modulators and monitoring in patients in specific clinical situations such as with CF related liver disease and also in pregnancy.

MR. BUSKER: And our second objective, Dr. Wainwright: the potential barriers to optimal use of CFTR modulators.

DR. WAINWRIGHT: I think adherence is the major issue, both with taking CFTR modulator therapy and in maintaining other therapies. We also need to ensure the correct administration of CFTR modulator therapy with fatty food. We need to have avoidance of medications or foods that may interact with CFTR modulator therapies, including certain macrolides, certain antifungals, and herbal therapies, in particular.

MR. BUSKER: And finally, Dr. Douglas, the role of patient/physician collaboration and communication in the use of CFTR modulator therapies.

DR. DOUGLAS: We've highlighted the importance of exploring patient expectations of CFTR modulator therapy, the importance of education around CFTR modulation therapy, and finally discussing barriers to adherence, particularly among adolescents and young adults and patients with an already complex therapeutic regimen.

MR. BUSKER: From the University of Queensland in Brisbane, Dr. Tonia Douglas, Dr. Claire Wainwright, thank you both for participating in this *e*CysticFibrosis Review Podcast.

DR. DOUGLAS: Thank you, Bob. It was a real pleasure.

DR. WAINWRIGHT: Thank you so much, Bob. I've really enjoyed taking part.

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