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An In-Depth Look at the Evolution of Cystic Fibrosis Treatments

Dr. Dogramji:

Even though there currently isn't a cure for cystic fibrosis, there may finally be hope on the horizon for the more than 70,000 people around the world who are living with this debilitating disease thanks to the emergence of several new players in the therapeutic playing field. And what those options are and how they can help these patients will be the focus of today's discussion.

Welcome to *Clinician's Roundtable* on ReachMD. I'm Dr. Paul Dogramji, and here with me to talk about recent advances in cystic fibrosis is Dr. Gregory Sawicki, Director at the Cystic Fibrosis Center and Assistant Professor of Pediatrics at Harvard Medical School. Thanks for joining us today, Dr. Sawicki.

Dr. Sawicki:

Thanks for having me.

Dr. Dogramji:

Excellent. So, Dr. Sawicki, before we dive into those exciting updates, can you tell us a bit about how cystic fibrosis has traditionally been treated?

Dr. Sawicki:

Sure. So, as you mentioned, we really are in a place where there are new and emerging therapies that will really change the landscape and how we as pulmonologists practice with our patients with cystic fibrosis. You know, up until a few years ago, really what we were doing with our patients was paying close attention to the symptoms and comorbidities that are associated with CF. CF is traditionally thought of as primarily a pulmonary or airway disease in which mucus is quite thick, and infections and chronic inflammation result from that thick mucus, and so many of our therapies prior to some of these newer therapies that we'll talk about, we'll focus on thinning out mucus, improving airway clearance, hydrating airways. You know, these are therapies such as dornase alpha, a typical mucolytic, bronchodilators, inhaled antibiotics, and oral antibiotics. In addition, as CF clinicians, we spend a lot of time thinking about infections, and we use a lot of antibiotics; both in terms of in hospital or outpatient. And so the main thing of therapy really is focused on these downstream effects that result from having thick mucus that is present in the CF airway.

Dr. Dogramji:

Now that we have that base knowledge, let's take a look at where we are. What are some of the new treatment options that have been introduced within the last few years, Greg?

Dr. Sawicki:

Great. So the major class of medications that has been introduced are so-called CFTR modulators. And this terminology comes from the fact that the states of genetic defect that underlies cystic fibrosis is a faulty protein, which is called CFTR. CFTR is a chloride channel that is present in epithelial cells, present in the sinuses, in the airways, in the intestinal tract, in the pancreatic duct, in the biliary tract, and in the sweat glands primarily. And dysfunction in the CFTR protein leads to chloride imbalance, which leads to thick mucus throughout the body; not just in the lungs, but also in the GI tract. And the so-called CFTR modulators were identified a few decades ago and then brought through clinical trials to help improve the function of the CFTR protein. The first of these was approved in 2012, and this was called Kalydeco, or ivacaftor, which is a generic name. And this was identified in a study in a very small subgroup of people with CF with very particular CFTR mutations. Those that encompass only about 3 to 4 percent of our population. And when this drug was first studied over a decade ago, it was found to improve the function of the CFTR protein, improve lung function, improve symptoms, and improve weight. However, it was only available for a very small subset of the CF population. The most common CFTR mutation is something called delta f508. And this is a mutation in which about 50 percent of our population in the U.S. has two copies of

this mutation leading to CF, and about 80 percent has at least one copy of this mutation. In this mutation, the CFTR protein is functional because it doesn't make its way to the cell surface. And so, Vertex pharmaceuticals, which helped develop and study these CFTR modulators that are now available, has now studied several different compounds that have become approved over the last several years to help patients with the delta f508 mutation, either in two copies or one copy. So the first was something called Orkambi, or lumacaftor/ivacaftor. This was first, approved in 2015 for people with two copies of delta f508 mutation. These studies showed really only a modest benefit in lung function of about 3 percent to 4 percent improvement after one year of therapy, but it was a step in the right direction. This was followed by a medication called tezacaftor/ivacaftor, also the trade name called Symdeko. This was approved in 2017 for people with two copies of the delta f508 mutation, as well as some other more rare mutations. Again, from an efficacy perspective, this drug had about a 3 to 4 percent improvement in lung function over one year. But this has some fewer side effects than lumacaftor/ivacaftor, the first modulator approved. But all of this led to the basis of what's now, the newest medication that was approved this past fall; it's so-called triple combination CFTR modulator therapy. And this is a combination of three compounds; ivacaftor, tezacaftor, and something called elexacaftor. And the trade name is Trikafta here in the United States. This was approved now for people with either one or two copies of the delta f508 mutation, so it's far broad in the indication that was present for the prior therapy. So now upwards of 80 to 85 percent of people living with CF in the United States who are 12 and above are now eligible to receive this medication.

Dr. Dogramji:

So if we look at this triple drug combination medication specifically, Dr. Sawicki, what can you tell us about the role of CFTR genes in cystic fibrosis, and how this recently approved treatment option aims to address that?

Dr. Sawicki:

So again, these medications, the CFTR modulators, and particularly this combination CFTR modulator, function at the level of the protein that, is really made dysfunctional by particular genetic mutations. And as I was mentioning, the particular, mutation that Trikafta is, focused on is this delta f508 – it's a protein-folding or trafficking problem. And so in vitro, prior to being studied in clinical trials, this drug was shown to improve the trafficking of the CFTR protein, and also the stability of a CFTR protein at the cell surface. When we brought it into clinical trials, what it did actually show is that not only did you have an improvement in CFTR function, as measured by a sweat test. And the sweat chloride level is a great biomarker and proxy for CFTR protein function. It also showed a significant improvement in lung function with an FEV-1 improvement of over 12 to 13 percent, even after two weeks of therapy compared to a placebo group. It also showed an improvement in weight, an improvement in quality of life scores, and a reduction in hospitalizations and the reduction of what we call CF pulmonary exacerbation. So across the board, in these studies looking at the triple combination therapy, we saw very impressive outcomes in terms of short-term pulmonary and non-pulmonary results.

Dr. Dogramji:

So for those just tuning in, this is *Clinician's Roundtable* on ReachMD, and I'm Dr. Paul Dogramji, and today I'm speaking with Dr. Gregory Sawicki about recent advances in cystic fibrosis.

So, Greg, now that we've covered the latest additions to the treatment landscape, I'd like to take look a little bit about the big picture. Obviously these advancements are great for our patients with cystic fibrosis, but from your perspective, what are some gaps in the care that still exist? So, for instance, do we have treatment options for all patients who are diagnosed with cystic fibrosis? Or only select patient groups?

Dr. Sawicki:

So this is a really important question because the population of people living with cystic fibrosis in the United States and across the world have been rapidly changing; mostly for the good in that people have been surviving for much longer, even before the advent of some of these therapies. So in about 2015 in the United States, that was the first year in which there were more adults living with CF in the U.S. compared to children. And so prior to that, CF really was considered a pediatric disease, and there was significant limitation in life, with average mortality occurring in the late 20s, early 30s, extending up to near 40 at this point. With the growth of the adult population, this leads to challenges, not just around therapeutics, but about where patients with CF get their care; at adult hospitals with adult pulmonologists, with internal medicine or family medicine physicians who are familiar with adult issues related to healthcare. It also means that patients and people who treat patients with CF need to think about other comorbidities, not just CF-related diabetes, which occurs at a higher incidence in older adults with CF. There has been more recent concern around different infections that can be emerging in people with CF. And, in fact, adults are living longer with CF. We even are starting to think about routine screening for malignancies such as colon cancer that is now recommended for people with CF 40 and above. And as you mentioned, we also have to think about appropriate treatments based on genotype, based on symptoms, and even though these new drugs, are available for a larger group of people with CF, there will still be a population of people with CF who are either unable to receive these drugs because they do not have the common mutation. and in particular, there is a group of patients that are known to have what are called SPOP

mutations, and about 10 percent of populations have these particular mutations. But also it could be people with other comorbidities or drug-drug interactions because of other medications they're taking that they may not be eligible for some of these meds. In addition, as a pediatrician, I think a lot about early intervention, and ideally getting these kind of CFTR modulator drugs to younger kids is a goal that we all have in the CF clinician community. The idea being that if we could identify and treat patients with these drugs when they're even infants, that we could prevent some of the later complications or, in fact, in short, a normal life expectancy without a lot of the comorbidities that we currently are treating. So right now these drugs are really only available for adolescents and adults with CF, and we are hoping that through clinical trials and work over the next couple of years that the availability of these drugs will go down in age such that we can be treating younger kids and, in fact, newborns when they're first diagnosed.

Dr. Dogramji:

So based on those gaps, what would you like physicians to know so that they can better inform and care for their patients with cystic fibrosis?

Dr. Sawicki:

So I think there are a couple of really important things, particularly for physicians out in the field in primary care, family medicine, internal medicine, and pediatrics who do care for perhaps a smaller number of people with cystic fibrosis. First is that it is recommended that all people with cystic fibrosis regardless of their mutation, and regardless of the severity of their illness, be followed at the CF Care Center. The CF Care Foundation nationally accredits centers, and there are over 130 different centers throughout the United States that do provide comprehensive multidisciplinary care for patients. That doesn't obviate the need for primary care and routine care in pediatrics. It's important that patients with CF get routine immunizations. It's important for patients with CF to get annual influenza vaccinations. It's important for us to pay attention to the mental health comorbidities and the behavioral comorbidities that can come with living with a chronic disease. As patients transition from pediatric age to adult age, we think a lot about other things that can happen for young adults with a chronic disease, whether it be around mental health, challenges around taking their medications on a regular basis, moving out of the house, and having their own health insurance as opposed to being relying on their parents. You know, it's establishing primary care, which is important for young adults and older adults. And again, as I said, as patients get older, not forgetting that they also need to have the routine screening that other adolescents, young adults, and adults will need to have in terms of other types of their health. And so it's important that I think primary care physicians of all sorts who take care of people with CF develop a partnership with the CF Care Program in their area to make sure that all of these screening tests are done; either by the CF Program or by the primary care clinicians themselves.

Dr. Dogramji:

So before we wrap up, Dr. Sawicki, although there isn't a cure for cystic fibrosis, are you hopeful that there will be within the near future?

Dr. Sawicki:

So that's a really excellent question, and it's one that is asked of me not just by my colleagues, but by patients and family that I care for, as well. You're absolutely right that these newer advances and these new therapies are not cures, but they're a step in that direction in that they will likely improve longevity, improve life expectancy, even in the background of needing to take other therapies. That said, there are a lot of ongoing efforts to think about the cure. And that cure would be essentially correcting the dysfunctional gene, and so even though we're still years away from gene therapy in cystic fibrosis, there are efforts underway to try to really understand whether that is possible. And I meant to tell you that as a clinician who has now been taking care of people with CF for over 10 years, my conversations with families when a baby is first diagnosed with CF has definitely changed from one of we need to be quite concerned about monitoring for complications, and we need to make sure that we are maintaining really good attention to nutrition, respiratory health, you know, chronic therapies, et cetera, to one of we need to do all of that, but we're doing it in the background of real hope that your child will grow up to have a full and successful and normal lifespan. And I think that even without a cure, we are moving in that direction, and I think within the next five to ten years, the science behind understanding cystic fibrosis, and particularly correcting the gene completely will rapidly advance such that we've had these rapid advances that we've already discussed today.

Dr. Dogramji:

Well, Greg, considering the far-reaching impacts of this debilitating disease, it's great knowing that there are finally some treatment options we can offer our patients and even the potential for a cure in the future. So I'd like to thank you, Dr. Gregory Sawicki, for joining me to get us up to date on those advances. It was great speaking with you today, Dr. Sawicki.

Dr. Sawicki:

Thank you very much. It was a pleasure.

Dr. Dogramji:

And I'm Dr. Paul Dogramji, and you've been listening to *Clinician's Roundtable* on ReachMD. To access this episode and others in this

series, visit ReachMD.com/cliniciansroundtable where you can be part of the knowledge. Thanks for listening.