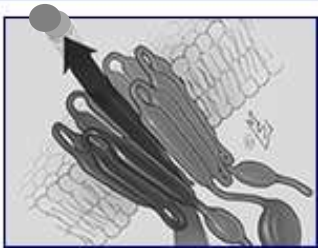

Transcript: Clinical Cases: Christopher Goss, MD & Peter Mogayzel, MD

So with that we're going to present some clinical cases and I think the room is going to be divided down the line, and we're going to try to be interactive. I have my assistant, Dr. Mogayzel, and his job is to run around and we're going to give you some time to sort of with your table try to come up with some answers to some of these questions we'll pose. And we would like to actually, it is hard to be interactive in a room this size, but we hope we can induce some interaction because I think these are challenging questions. And I can tell you these are challenging questions that you are going to start to face in the next year or two years.

So I have two cases and I have several questions associated with each case. The first case is a 23 year old CF patient with an FEV1 of 55 percent of predicted who is sputum culture positive for *Pseudomonas.* The patient qualifies for three different ongoing trials that are open for enrollment at your site.

So we're going to divide the room in two, so is there a clear division, left side, right side, right down the middle. If you are on my left you are now the CFTR modulators, if you are on my right, you're the mucus clearers.

So the patient is reluctant to enroll in the research study because she does not want to get placebo. She thinks she'll lose ground and have disease progression if she's on the study and gets placebo. So for the group on the left I would like you to answer this question, the study agent is an investigational drug and not FDA approved, what are you going to do as a site PI or as a care provider in that center?

And for the group on the right, I would like you to address the question, the study agent is FDA approved for another indication, and this has been a common phenomena in CF, what should the PI do? Again, this is a patient who doesn't want to participate in a clinical trial because she is concerned that her risk of progression

will be higher if she gets a placebo. So left side is the CFTR modulators, this side is the mucus clearers. So I would like you to think about it. There is a pad of paper at your table, but talk amongst yourselves, coffee-talk, I don't hear a lot of chitchat.

Dr. Mogayzel: We are just going to take a couple of minutes to chitchat and then we'll get your opinions on this, and then dessert. Okay, gang, we have an FDA approved drug, your patient is concerned about being in the study, doesn't want to get the placebo, so may think that the drug is useful, and the drug is FDA approved, what do you do?

MALE VOICE: I would try and work some magic and try and convince this patient that even though it's FDA approved for another indication, we don't know if it will be efficacious, so we really don't know if she is going to gain any ground using it for this particular indication, whatever it may be, and that it potentially might be harmful in that subset of patients because it hasn't been studied in that group of patients. That's what this group is for. So that would be my first attempt would be to try and convince her that going the study route would be the appropriate way to go.

Dr. Mogayzel: Any other thoughts for you mucusy people?

MALE VOICE: I agree with what was just said. There is another point though which is all patients tend to do better in studies by having more regular, more careful follow-up, and maybe more frequent visits. So I would reassure her that even in the placebo group she might do better than if she was not in the study at all.

Dr. Mogayzel: That's a very good point. So are there people in this group that would just give her the medicine, it might work, it might not, or is everybody going to try to convince her to be in the study?

DR. CHRISTOPHER GOSS: This is a very "researchy" group.

I can actually tell you from personal experience I have patients who shop around for physicians who will treat with FDA approved non-indication drugs for other diseases to find a physician who will prescribe. I have had this in at least three lung diseases recently. So the patients will potentially move to find physicians who will provide those therapies.

Dr. Mogayzel: How about if it's not FDA approved, any thoughts on that?

MALE VOICE: I think this one is a little bit more straightforward because the person doesn't have access to medication in the first place. But I think this is a situation of educating the person that they are not going to lose ground because they are simply going to be continuing what they're taking even if they get the placebo. But it's an issue of I think expectation that when an exciting medication comes out that because they don't get that medication they think they might lose ground. So it's an issue of trying to educate a person to understand that even if they get the placebo that their current care will not change.

The other aspect is what has already been brought up that when you are enrolled in a study that you are followed much more closely and there is a placebo effect just from participating in the study.

DR. CHRISTOPHER GOSS: And I agree entirely. I think this issue, they really will have no access to the drug otherwise, but it is really a question of educating patients about clinical research. Obviously clinical research is always volunteer, there is consent involved and you have to know the risks and benefits of participating in a study. And I also emphasize to patients that, you know, that though it may appear that the drug is exciting, clinical research is needed to show it is actually truly effective. So earl studies, there are many examples of early studies where we found that it wasn't effective, had we not done the study, had patients started taking that drug out of, had you not actually been able to enroll the study you would never know it wasn't or was effective. So for the CF community, we studied the percent of patients participating in clinical research in CF and they presented a much higher rate than even cancer.

So we have a very educated population but sometimes it's just that kind of education about that your care will be potentially, your overall care may benefit, and that this is how we advance the science of CF. And again, CF patients, I've been amazed at the proportion of patients who participate in clinical research.

Even if you look at 16 percent of a site, and actually there's the numbers that are actually greater than that, there are some sites that are participating up to 25 percent of all their patients are investigational study drugs in this recent report that we're not reporting on here. But I agree with you entirely.

Dr. Mogayzel: So there is more to this case.

DR. CHRISTOPHER GOSS: So the next case, the patient wants to be in the study and is eligible for three studies, one of which his under enrolled. And this is for the left side of the room, how does the PI present the clinical research at the site to the patient. That's for the CFTR modulators. And the mucus clearers the patient really wants to participate in a study but is on an excluded agent and for many of you who if you have participated in a study, there's a number of excluded agents, what should the PI do? So talk amongst yourselves. We'll give you a few minutes to just sort of think about this question.

So remember CFTR modulators, the first question, mucus clearers on the right, second question.

Dr. Mogayzel: Let's hear some thoughts about these questions.

DR. CHRISTOPHER GOSS: So let's start on the left side of the room, the modulators. So the patient wants to be in a study but there are three studies, one of which is under enrolled at your site, how do you present the research to the patient?

Dr. Mogayzel: Any volunteers? This is a very common problem I would think, that you have one study that you haven't got enough patients enrolled in but there are other studies that the patient may be wanting to participate in.

FEMALE VOICE: Well you should present all three, I mean you have to explain all three to the patient, not because one is under enrolled, you can't just tell that one. I mean ethically we have to present all three.

Dr. Mogayzel: Is that what most people do? It's a challenge, it is, when there is pressure from the TDN or other groups to say you need to make your enrollment and you have three choices. And I think it is something that it's expected that you do present all three possibilities to patients, but I think we all know that there are patients that are more interested in doing one type of study than another, as well.

And the other group, the mucus --

DR. CHRISTOPHER GOSS: And I would also add that there are some studies, and we do the same thing, we present all studies to the patients. And patients self select

often for the studies that they can do. We have patients who can't do nasal potential difference, they just, we know they can't, they've tried it, they hate it. Others don't mind it.

So there are clearly patient, I think you have to leave it to the patient to try to decide, but it is quite challenging and I think I agree entirely with presenting. We actually have the research nurses present all the studies to the patient, we don't actually, the physicians don't present them and they come in later.

But how about the right side of the room, the patient really wants to participate but is on an excluded agent?

MALE VOICE: It gets back down to making sure that you keep the patient well and you have to explain to the patient that we would love to have you participate but this medication is important. So if there is really good strong evidence that it helped the patient out, we have to sort of clearly express how that has helped him in the past. I might go ahead and say you really want to be on this study, we'll go ahead and try perhaps and hold this medication for a period of time, one week, two weeks, something like that. And if your outcome comes back, you come back and are reevaluated and if you have any clinical findings that show that your outcomes are worse, then we have got a medication that we know is helping you versus a medication that we don't know whether it's going to do anything, whether you are going to be on placebo or not, and that it would be our recommendation under those circumstances that your health is more important than being involved in this study.

FEMALE VOICE: We run clinical trials, too, and I think in a case like this, and we have had this sort of thing where there have been patients who have been taking an exclusion, they have been under the exclusion criteria. And what I would do is I would call the medical director of the product and tell them I've got this situation and would they like to provide it on a compassionate use, if they think it would work. And we've done that before.

DR. CHRISTOPHER GOSS: So that is almost like getting to the point of a non-FDA approved agent in a patient research. And again, that's common. We tend to do, what the first speaker, if patients really want to participate we do a test period where we go off the agent and the most common, we even counted recently, is hypertonic saline.

Patients are on stable hypertonic saline and seem to have had benefit, if they really want to participate we do a test period off. And honestly the patients who do well do worse when they're off and when you restart it they do better. So it is a real challenge.

The other point I think that's really important is to get back to people who design the studies and companies who do the studies, that our studies should include these agents, if possible, because they become standard of care.

Dr. Mogayzel: So the next case?

DR. CHRISTOPHER GOSS: So we have the next case where we're venturing into a realm that I pretend not to know anything about, which is pediatrics. This is a family meets with a CF team regarding their two and a half year old child. He was diagnosed at newborn screening and has no symptoms and a normal chest x-ray. The FDA has just approved a novel agent for CF which improves CFTR function in adolescents and adults.

So the modulators, I would like you to answer the question, the family requests that their child receive this novel treatment, no further clinical trials are planned in this patient population, two and a half year old, what should the physician do?

And with the mucus clearers on the right, I would like you to answer this question, a new study has just started to enroll patients age 2 to 14, so covering that gap that this patient includes, in a randomized controlled study with this FDA approved agent. The family requests that the CF team treat the patient outside of the clinical trial.

DR. CHRISTOPHER GOSS: So we'll start on the left side of the room and we'll start with the family requests that the child receive this therapy and no further trials are expected in this age group, what should the physician do?

MALE VOICE: I was handed the microphone, so I'll guess that I would ask the first question is why does the family want to do this to their child, I mean what is the motivation for this? I mean have they heard about it, et cetera. And I guess in explaining risks and benefits, I would ask the question what were their expectations in terms of risks and what were their expectations of benefits? Because to my understanding, this would be comparable to somebody asking for an opioid or

whatever because they thought they would feel better with it. And I'm not sure that my obligation is to provide what they are requesting, my obligation is to provide a risk/benefit assessment and then give them what my assessment was at that time. And it depends upon what I know about and actually it depends more on what I now about the drug, itself. If I had, rhDNase was a good example because they were doing studies in much older children, but it's profile of safety versus risk was very high that it was safe. The second was that the data showed that it was better given earlier than later. So you didn't treat moderate or severe disease, you were doing it to prevent, a preventative.

So there are a number of factors and this would take several visits for me to sort out and I guess I would want to know the patient/family expectations.

DR. CHRISTOPHER GOSS: Yes, and I really like that answer, and I think understanding their expectations of risk and benefit, their expectations of risk are probably under estimated, and their expectations of benefit are over estimated. I can guarantee you with the advent of some of these new agents, they're successful in adolescents and adults, this will land in the pediatrician's lap and this will be a frequent question.

So we're going to move, should we move to the right side of the room, and talk about this, now there is an ongoing trial in small children, much like the adult case before, there is a randomized controlled, this is an FDA approved agent but it is not FDA approved for these small children and the family requests that the CF team treat the patient outside the clinical trial.

What would the mucus clearers do?

MALE VOICE: Peter gave me the microphone kindly. I think you have to again balance what you think the risks and the potential benefits are in making a decision like this and how likely you think there may be some benefit to it. We were talking, there was an example this morning or yesterday, I think it was this morning that there are some potential anti-inflammatory agents that are out there that are approved. So I think the statins was one of the classes of drugs that was discussed. And there is some theoretical and maybe some clinical evidence that perhaps they do have an anti-inflammatory benefit, and they may help in CF.

So this is an FDA approved agent, that you, there may be a study of it and you might think that it could help and you would have to balance it against the risks. The risks are very low probably with a statin, which would lead me in the direction of saying well maybe I would go along with the request. But on the other hand, the clinical evidence that it might be beneficial is still so sketchy at this time that the benefit is also very low. So I think it would put me in a very ambivalent situation and again, in this case, I would probably say that I -- I would probably say no because I just don't have enough confidence in the potential benefit of the agent even though there is very little risk. You can look at it the other way.

DR. CHRISTOPHER GOSS: This is very challenging. I actually have the, I think one of the flipsides of this is if physicians start doing a lot of treatment of drugs outside of FDA, FDA approved drugs, these studies will never be enrolled, and this will happen very quickly. And I can tell you this is happening with something called the MILES trial for Lymphangioleiomyomatosis. Patient advocacy groups have realized that sirolimus, which is a potent anti-inflammatory immunosuppressant drug seems to shrink the kidney lesions in this disease, we don't know if it works. And right now they're having a hell of a time enrolling because patients are taking this existing FDA drug off label. So I think it's a really challenging question and I think you have to really tussle with this because there as a physician your goal is to treat the patient, you are the patient's advocate and you want to give them the best care they can possibly have. But I think emphasizing the lack of knowledge of risk/benefit I think is important for the patients to know.

But anyway, I just think these are intriguing questions, they don't have clear answers, but I am pretty sure in the next two to five years this could be a real theme in CF, particularly in small children. And hopefully these agents will be tested in small children, because I think that's where most of us feel that if you actually could intervene in these small children you may actually create a normal lung phenotype later in life.

But that is all I have for cases, I have one more case we're going to skip and we're going to go to Dr. Mogayzel's wrap-up. But thank you very much.