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FCS and SHTG: Are We Meeting the Need?

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Chapter 1

Dr. Ray:
Hello everybody. My name is Kausik Ray. I'm Professor of Public Health and a Cardiologist at Imperial College London. Welcome to this educational series. And in our first chapter, we're going to discuss the unmet needs in patients with familial chylomicronemia syndrome, or FCS. And we're also going to look at novel therapies and investigational drugs in patients with this particular condition. This is a CME on PACE-CME and ReachMD. And I'm joined today by Dr. Ira Goldberg. Welcome, Ira.

Dr. Goldberg:
Hi there. I'm Ira Goldberg. I'm the Director of Endocrinology at New York University.

Dr. Ray:
And also joining us today is Dr. Christie Ballantyne from Houston. Welcome, Christie.

Dr. Ballantyne:
Hi. I'm Christie Ballantyne. I'm the Chief of Cardiology and Cardiovascular Research at Baylor College of Medicine in Houston, Texas.

Dr. Ray:
Great. So maybe I can start with Ira. Ira, could you please just maybe just remind us what is FCS? And when we talk about chylomicronemia syndrome, or patients with this condition, what are we talking about? And what is the unmet need?

Dr. Goldberg:
So I've taken care of patients like this for more than 3 decades. This disorder is exclusively due to a defect in the clearance of triglycerides from the bloodstream via the lipoprotein lipase. Most commonly, it's a molecular defect in the lipoprotein lipase enzyme, so it doesn't function normally. It's also due to defects in several other proteins that are either important in LPL synthesis or its binding to the endothelial cell surface or facilitating its activity.

These patients either have to be on a very restricted diet, so low in fat intake. I often have them exercise a lot. And even then, sometimes they get recurrent episodes of pancreatitis. They do not respond to the usual medical therapies of fibric acids or fish oils or the third-line therapies, which are niacin and statins. So we need a better way to treat them.

Dr. Ray:
So that's clearly a huge unmet need. And so we've seen some exciting data in the PALISADE trial and we'll review other trial data. I mean, so what did the PALISADE trial show? What was the therapy? How does it work?

Dr. Goldberg:
So about 20 years ago, a group at University of Maryland studying the Amish population in Pennsylvania discovered that a protein called ApoC-III, a small protein stuck on the chylomicrons, was defective in that population. And the people who had the defect had lower levels of triglycerides and they also had less cardiovascular disease. People had known for a long time that the C3 protein regulated the lipolysis enzyme, and so it made sense that they could – or pharmaceutical companies could try to target the C3 as a way to drop triglycerides. And in fact, they did that. Surprisingly, reduction in C3 also reduced triglycerides in people who had no lipoprotein lipase enzyme, and that fit with some old data suggesting that C3 affected the uptake of triglyceride particles by the liver.

So reducing C3 does two things: it makes the lipoprotein lipase reaction work better, and for people who don't have lipoprotein lipase activity like most of the patients in the FCS category, it reduces triglycerides probably to a great extent by increasing their uptake in the liver.

So studies have been done using two different approaches, an antisense and a silencing RNA. The recently published PALISADE trial showed that the silencing RNA dropped ApoC-III levels in the bloodstream over 90% and reduced triglyceride levels even in patients who were LPL deficient by over 80%, and also decreased the incidence of pancreatitis by over 80%. So now we have a treatment where there was no real effective treatment except for stringent diet for people with this disease.

Dr. Ray:
The mechanism of action of the silencing RNA and the antisense, what's the difference between those two in terms of how they work?

Dr. Goldberg:
Well, in some ways they work similarly in that they both bind to messenger RNA. One is a piece of DNA, one is a piece of RNA. They make a double complex, which is then degraded by the cells. The silencing RNA lasts longer than the antisense.

Dr. Ray:
Thank you. Christie, so we've heard from Ira about the PALISADE trial. I mean, there's other data as well with the antisense oligonucleotides, notably BALANCE, and there were essentially first-generation antisense. Maybe you want to comment on those. What are your thoughts?

Dr. Ballantyne:
Yeah, so there was a first-generation antisense called volanesorsen, and it had some side-effect profile, it was never approved by the FDA. It was approved by the EMA. And the more modern approach is basically using this GalNAc structure. So an N-acetylgalactosamine targets the liver, you can use a much lower dose. It's avoided the side effects and allowed much lower doses to be used, which has been helpful.

So the BALANCE study ended up using two doses. It was in a very similar design in terms of, except these people were all biallelic FCS, so they all had genetically confirmed FCS, which was a little different. And I like the approach personally in PALISADE, where they also allowed some people with persistent chylomicronemia who were very high risk, for example, had pancreatitis beforehand, and there were two doses. Now, one of the doses did not meet its endpoint on triglyceride reductions, so as a result, the analyses, because of hierarchical testing on pancreatitis, was all post hoc. But it did show a reduction, once again, overall in pancreatitis.

So very consistent to what Ira said, it looks like this is a great target. It's effective for lowering triglycerides. You've got to get the dose right. It looks like for the ASO, it takes a higher dose, about 50 mg than it did for the siRNA. But it looks like you lower triglycerides. And for the first time, we've had trials where you see reductions in pancreatitis. It's really exciting.

I want to point out, I personally think that these people having persistent chylomicronemia, very important because a lot of them, they may not have biallelic, but they actually have a pathogenic variant. They may have, for example, a bad PRS score with multiple snips, diabetes. The other one is, there's another group that's not that small, and these are people with partial lipodystrophy who were really severe, Ira, and they were also very hard to treat. We know that C3 works there, so I do think there's even a little bit bigger than just pure FCS for people who are hard to treat that can benefit.

Dr. Ray:
So Christie, maybe you can tell us about what the status is of these therapies. And you mentioned earlier on that one therapy was approved in Europe, but not in the US. So where are we?

Dr. Ballantyne:
Yeah, we're very excited in terms of this approach to our targeting ApoC-III.

The side effect profile is far superior to what we saw in the prior round with volanesorsen. And basically, these are breakthrough

technologies. So the designation has been given to both of these therapies. I am very hopeful that we're going to be able to use these in the next year. I mean, I'm not the FDA, but I think the data is extremely strong. The safety looks good. And as Ira pointed out, these are very hard to treat conditions where we don't have anything right now that can touch them.

Dr. Ray:
Ira, do you want to add anything?

Dr. Goldberg:
Growing up with this disorder makes you different. You cannot go eat pizza with your friends, you cannot go to McDonald's. And having patients on both of these trials, these are therapies that are going to change people's lives.

Dr. Ray:
I mean, that's a really salient point. And in both of those trials that we talked about and discussed, the principle of infrequent dosing, maintaining that sustained reductions in triglyceride over and above good practice, good clinical care, and maintaining triglycerides well below the thresholds we typically think about pancreatitis and also reducing the incidence of pancreatitis, I think, is a great thing for the field.

So I want to thank both of you for this fantastic discussion. I want to thank the audience as well. So in Chapter 2, we're going to move on and focus on severe hypertriglyceridemia and discuss the trial evidence and the therapeutic options. So stay tuned.

Chapter 2

Dr. Ray:
Welcome to this educational series. In our second chapter, we're going to discuss the unmet needs of patients with severe hypertriglyceridemia and novel therapies and data around investigational agents. This is a CME on PACE-CME and ReachMD. My name is Kausik Ray. I'm Professor of Public Health at Imperial College London. Joining me today are doctors Ira Goldberg and Dr. Christie Ballantyne. Ira, do you want to introduce yourself and say hello?

Dr. Goldberg:
Yes. I'm Ira Goldberg. I'm the Director of Endocrinology at New York University.

Dr. Ray:
Christie, nice to see you again.

Dr. Ballantyne:
I'm Christie Ballantyne. I'm the Chief of Cardiology and Cardiovascular Research at Baylor College of Medicine in Houston, Texas.

Dr. Ray:
Well, it's great to have you both here. In our previous chapter, we talked about FCS, so we're going to move the needle a little bit and now move to talk about severe hypertriglyceridemia. So perhaps in some scenarios people might want to know about what the difference is between severe hypertriglyceridemia versus FCS in those patients with pancreatitis and what the unmet needs are. So maybe I can start with you, Christie. What do these people look like? And what are the unmet needs?

Dr. Ballantyne:
So I think the first thing is, how do we define severe hypertriglyceridemia? And we usually talk about it, at least in the United States, as people who are persistently over 500 mg/dL. And we call chylomicronemia 1,000 mg/dL; in Europe, slightly different, 10 mmol would be chylomicronemia, it's 880.

So the issue that comes up is the person who you'd be seeing is 600 or 700 or 800 fasting, now, unfortunately, what ends up happening – that's in the fasting state, and in the postprandial state, so once you get to a certain saturation threshold, you can actually get your triglycerides, particularly when you throw in alcohol, to very high levels. So there is a risk of pancreatitis.

Now, the other thing that comes up, there's a risk for cardiovascular disease. And particularly as we talk about more and more focus on, you know, those are ApoB lipoproteins. So you have VLDL, that's ApoB-100, chylomicrons are ApoB-48 but the thought ends up is that these people, if you look at ApoB-100, they have increased levels. And, in fact, there's increased cardiovascular disease. And there's been an increasing focus on maybe thinking about remnant cholesterol, the particles are also carrying cholesterol. And if we look at remnant cholesterol, which is partially captured by non-HDL cholesterol, we know that's associated with cardiovascular risk.

So what was fascinating was in this same study mentioned with the Amish is that they had lower calcium scores. And also ApoB was lower. There was other favorable changes on LDL particles. So a lot of interest on ApoC-III. And the same thing has been done, for example, there was a recent trial with plozasiran, enrolling people with high triglycerides. And as expected, there was a very favorable

reduction in triglycerides of 60% but there was also a very robust reduction in remnant cholesterol, almost about 60%. ApoB went down more modestly. You do see some increase in LDL cholesterol. But ApoB going down, big reductions in remnant cholesterol. That is not what we saw when we added pemafibrate to statins. We saw that actually LDL went up some, ApoB went up some; it didn't go down at all. And then we didn't see the big drops in remnant cholesterol.

So the data is interesting here that might be cardiovascular benefit, very good in terms of reducing triglycerides, keeping you out of the risk for pancreatitis. So I think there's a lot of excitement about potentially this approach having some ramifications towards maybe not just the pancreatitis part.

Dr. Ray:
That's really exciting. So that was the SHASTA-2 trial, I think, right?

Dr. Ballantyne:
That's correct.

Dr. Ray:
So Ira, there have been other trials, I mean, so the two therapies in this space are antisense oligonucleotides and small interfering RNAs, and Christie's mentioned plozasiran, a small interfering RNA, but what about we've got olezarsen has been tested as well I think in this patient population. What do we know about the ASOs?

Dr. Goldberg:
Pretty similar except looks like they're slightly less effective. The C3 levels don't go down quite as much, and neither do the triglyceride levels, but they're effective therapy. They work. They're once a month, rather than once every 3 months. So it's a good therapy. It's been probably used in a little more patients, so there's a little more patient data on it.

Dr. Ballantyne:
There's a SHASTA-3, the phase 3 program will be pursuing plozasiran, the 25-mg dose. And there's some large studies that are ongoing also with olezarsen. And one interesting one is, Kausik, one of those studies has a CTA substudy. So CT angiography to look at coronary disease, which will be quite interesting in this. And there's also been looking at lower triglyceride populations like MUIR looked at 150 to 500. So these are robust programs, very exciting target. And it goes back to genetic studies. We've seen this now PCSK9, but ApoC-III was a very intriguing target from the genetics. And then, you know, Ira, you've done so much work in this area, but it was exciting to see that the ApoC-III playing a role not only enhancing lipolysis but in removing particles by the liver. So it's an intriguing target. And hopefully we'll see something different than we've seen with the fibrates.

Dr. Ray:
No, absolutely. And I mean, it sounds very much like these – both siRNAs in particular, I mean, the big difference is that infrequency of dosing, maybe four times a year and ASOs monthly is what it looks like. But I mean, essentially these injectable RNA-based therapies that are really targeting these relevant proteins were previously not thought to be druggable, and that's really the huge advance. I mean, going from pills to injectable therapies, and with probable advantages as well maybe in terms of adherence, that we can find ways of people to remember these. I mean, it really sounds like a really exciting time.

Dr. Ballantyne:
Kausik, that's a really good point though, because what ends up happening is, is remember every 3 months, but that effect is still going afterwards. So if someone's a month late, they're still having a nice drug effect.

Dr. Ray:
That level of protection is something that we've never really seen before with small molecules, right? So I think this is an incredibly exciting time.

So I want to thank you both for a very engaging discussion covering some exciting data. And I want to thank the audience for joining us today, and thank you both for sharing your expertise. So thank you.

Dr. Goldberg:
Thank you for having me.

Dr. Ballantyne:
Thank you for having me, Kausik.

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