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From Evidence to Action: Advancing Care in Severe Hypertriglyceridemia and Familial Chylomicronemia Syndrome

Chapter 1

Dr. Watts:

Hello from ESC here in Munich. This is CE with GLC, and I'm Dr. Gerald Watts.

Dr. Gouni-Berthold:

And I'm Dr. Ioanna Gouni-Berthold, and we're going to discuss some new data that came out or presented in this congress about the management of severe hypertriglyceridemia.

So, Gerald, you presented yesterday some very interesting data about SHASTA-3 and SHASTA-4 on patients with severe hypertriglyceridemia. Can you tell us a little bit about why you did the study and a little bit about the patients that took part, and, yeah, why did you do it?

Dr. Watts:

Well, this is a gap in medical care. Severe hypertriglyceridemia, which we define as a persistent triglyceride level above 5 mmol/L or 500 mg/dL, is quite a relatively common condition present in about 1 in 100 people. The issue is that when persistent, is associated with a number of comorbidities, obesity and type 2 diabetes, and it has a number of medical sequelae, the most important of which is acute pancreatitis.

The clinical gap arises from the fact that standard therapies, as we all know, with diet and oral agents, fibrates, and high-dose EPA, are relatively ineffective in preventing acute pancreatitis. So we had to close this gap in care. The opportunity comes from the discovery of the role of APOC3 in triglyceride metabolism.

So the trial was carried out. In fact, there were 2 trials carried out as mandated by the FDA in people, and patients with hypertriglyceridemia greater than 5 mmol/L on 2 occasions and multi-morbidities. That was the group. The treatment comprised 4 injections of plozasiran over 12 months. The primary endpoint, and this is important to note, that the primary endpoint, this is a

lipid trial, actually. It wasn't a clinical endpoint trial. We must keep that quite clear. The trial was powered to demonstrate a 70% reduction in plasma triglyceride at 12 months, which was the primary endpoint.

And lo and behold, we actually achieved in both trials. Remember, the trials were the same type of design: the same treatment, the same 80% reduction

within group, obviously adjusted for placebo. Because the placebo improved, which is good for placebo. On average, a 55% to 60% reduction, placebo-adjusted, which is important information for the clinical trial.

There were some secondary endpoints, remnant cholesterol, non-HDL cholesterol, and they fell by about 50% and 30%, respectively, but of course,

managing hypertriglyceridemia means nothing, effectively, for the patient really, unless you prevent something that affects their life, like acute pancreatitis.

So the impact of triglyceride reduction of about 80% in an individual was explored in a secondary endpoint analysis. So an analysis in that group, looking at the cumulative incidence of acute pancreatitis in 2 dimensions, the new cases and total cases both showed a significant reduction in the incidence of acute pancreatitis of about 80%, really, and a delay of about 5 months in terms of new acute pancreatitis over time.

So that was a subsidiary analysis, secondary endpoint there was an additional analysis an exploratory analysis in the high-risk group with acute pancreatitis.

And everyone who'd had acute pancreatitis actually showed a much larger absolute risk reduction than in the overall trial.

Now this is important, and I think it's a takeaway message for clinicians that they should actually focus on patients in their clinic with hypertriglyceridemia with a previous history of acute pancreatitis because this is the utmost clinical implication of this study.

Dr. Gouni-Berthold:

Can I ask you something? I think this group that had the maximal benefit are the ones that had, as you said, acute pancreatitis, but also the ones that had what we in Europe consider severe hypertriglyceridemia, TGs more than 880.

So they were this mega-risk group. Very high triglycerides. You found a subgroup that has the best the maximum benefit. I found this very interesting.

Dr. Watts:

Well, it's a very intuitive comment that you make, a perceptive one. But when you actually look at the data, the benefit really was across the whole range of plasma from 5 and above, really. So provided you had acute pancreatitis, your number needed to treat was actually the same if you were above 5 mmol/L, 500, as if you're above 1,000. But a slightly better relative risk reduction, above 800. And they were; they did. But that's a take-home message, really, that almost irrespective of the level of plasma triglycerides in the severe range, that the number needed to treat is small if you've had previous acute pancreatitis.

Dr. Gouni-Berthold:

What about safety?

Dr. Watts:

The safety there was nothing particularly novel seen that we hadn't seen before in this study. The 2 to 3 most important side effects lumped together was hyperglycemia, seen in 9% of placebo-treated patients, and 14% in active treatment. A little bit of nausea and diarrhea. Liver enzymes, there were no significant changes in liver enzymes, and that's a point of distinction from the olezarsen studies. Renal function was normal. And when we delved into hepatic side effects—because that is an issue that we worried about when you're breaking down triglycerides going to the liver. Does it actually result in fat storage?

There was a sub-study of about 25 patients or so in which we looked at magnetic resonance imaging to see whether there's a growth of triglyceride in the liver, hepatic steatosis, and there was no significant difference there at all.

A point of difference also with a CORE trial, that they saw a slight increase in HbA1c and increase in liver fat. But overall, it was exceptionally well tolerated.

And of course the other matter of duration of the study. I mean, we have a 12-month intervention. I think the open-label extension is absolutely critical. It goes on to 3 years, so we can see whether any new adverse events or any small signals that we've seen here have been sustained.

Dr. Gouni-Berthold:

I know you cannot compare trials because the design is different, but CORE and

CORE2 were also done in patients with severe hypertriglyceridemia with olezarsen. How do you see a physician has a patient, how would you differentiate between the 2 studies, and is there one you would say, "Hmm,

I think this, the data here are better," or?

Dr. Watts:

Well, it's very difficult to say. I mean, I think what we can say, that we now have a therapy, an RNA therapeutics, that if your patient has persistent severe hypertriglyceridemia. It's important to say that really because they needed at least 2 measurements to be elevated. Then if you actually offer them that treatment and if they meet the criteria and they're being followed according to guideline recommendations, and it's got a label, that you've got a good chance really of inhibiting acute pancreatitis and that it's particularly most beneficial if you've had previous acute pancreatitis, and that's exactly what the CORE investigators found.

Unfortunately, they had quite a significant increase in HbA1c that we didn't see. And also, there was a significant increase in liver enzymes, ALT, and liver fat by MRI. The other point, of course, that it means 1 injection a month versus an injection every 3 months, which can go either way, actually. I mean,

obviously not 3 months is more convenient for people who are fearful of side effects and reversibility. They may want an injection every month, really.

And there was an interesting presentation yesterday of an injectable that gives you durability over 12 months, which that's for the future actually.

I see them both as supporting the notion and hypothesis that we now have a new tool for addressing this gap in care. The right drug for the right patient by the right doctor in the right place, in a timely way, and in an equitable way, actually, so that everyone can access this all the way across the social strata.

Dr. Gouni-Berthold:

So, Dr. Watts, thank you so much for this very interesting discussion.

Dr. Watts:

Pleasure's mine.

Dr. Gouni-Berthold:

And in Chapter 2 we will shift our focus on FCS, familial chylomicronemia

syndrome, and what recent advances do we have in this area? What are the new trials? What are the new drugs coming? So stay tuned.

Chapter 2

Dr. Watts:

Welcome back. In Chapter 1, we explored the new SHASTA-3 and SHASTA-4 data presented here at the ESC and the evolving evidence for targeting APOC3 in severe hypertriglyceridemia.

So as part of the severe hypertriglyceridemia continuum, we actually have familial chylomicronemia syndrome, or FCS, where the treatment landscape is rapidly evolving. So, Ioanna, a question for you here, and what better person to answer than Ioanna Gouni-Berthold. So when you look beyond the efficacy numbers in these trials actually, what did PALISADE change or clarify about what may be achievable in adults with FCS?

Dr. Gouni-Berthold:

Yeah. Thanks for this question. I will just give for our viewers a small introduction on FCS. Of course, yeah. It's a very rare disease, so they're people that have severe hypertriglyceridemia, and no treatment can help them. You can give fibers, you give even omega-3 fatty acids. You can give statins. Nothing works. A minimal decrease, less than 20%.

So finally, in the last couple of years, we have 2 drugs that target, as you previously mentioned, this totally nasty protein, APOC3. Yes. And they've shut it off almost—not completely, but almost completely enough to decrease the triglycerides also in this really hard-hit population. They almost all get pancreatitis, so they are really suffering. So anyway, now we have 2 drugs approved to treat, FCS. Both decrease acute pancreatitis.

And to go back, this is olezarsen and plozasiran. And you asked me about the plozasiran study on FCS the PALISADE trial. So I found the PALISADE trial extremely interesting because usually FCS is a genetic diagnosis. And what you did, you were the first author in this wonderful *New England Journal* paper. You didn't only include genetically defined FCS, but also clinically defined FCS, and you have the famous now PALISADE criteria that do not require genetic diagnosis to get the treatment.

And this is, of course, yeah, a big benefit for our patients because we all have patients that have one pancreatitis after the other, sky-high triglycerides, but we cannot find a genetic because we need a biologic genetic effect. And you don't know what to do with them, and they are covered in the PALISADE trial.

So that is the unique fact in PALISADE, not only genetically defined FCS, but also clinically defined

Dr. Watts:

So, Ioanna, access is all to do with diagnosis and detection. So we have these clinical criteria from Europe called by Philippe Moulin and the other one from North America from Robert Hegele, actually. Would you like to tell us a little bit about those and how useful those may be in identifying FCS, and how do they compare with the with the Palisade criteria?

Dr. Gouni-Berthold:

If one can put it simply, the Moulins score is for Europe and the score of Hegele, the NAFCS score, is for the US because it was done in North America, mainly Canadian individuals. For me, pragmatically, these scores are academically very interesting, but pragmatically, no score will allow me to treat a patient if he doesn't have either a genetic diagnosis or fulfills the PALISADE criteria. The sensitivity and specificity show for both that they are good in excluding patients, yes, but not really good in diagnosing patients.

Dr. Watts:

Yeah, so the specificity is good.

Dr. Gouni-Berthold:

But the sensitivity is—

Dr. Watts:

—low. So if you applied them to predict or select people for balance, really, you would be missing many. So the evidence runs with the PALISADE criteria.

Shall we just visit the PALISADE criteria again as you see them and how you use them in Europe so the audience—

Dr. Gouni-Berthold:

They're actually not extremely strict. They require a screening TG more than 880. Yeah. Then 2 values of TGs of more than 1,000. And then one of the following, and one of the following is either a positive genetic testing or multiple acute pancreatitis episodes or multiple admissions because of abdominal pain of unclear etiology or family history of acute pancreatitis due to hypertriglyceridemia or acute pancreatitis in childhood.

Dr. Watts:

But so it's a concept of persistent chylomicronemia confirmed and at least 1 of 5 criteria. And there was benefit in that group, as I gather, as well as in the genetic group, really, or at least no difference, really.

Yeah. So in terms of comparing and contrast, if one may ask the question, the use of olezarsen and plozasiran in FCS, what are the restrictions in Europe concerning access, and how do they compare in terms of effectiveness in preventing pancreatitis, in your experience?

Dr. Gouni-Berthold:

So let's start with the approval. It was very interesting. Olezarsen is approved in Europe for the treatment of FCS in patients with a

genetically proven FCS.

And we were all surprised, positively surprised that plozasiran is approved in Europe for patients with genetic or also clinical FCS.

So a large number of FCS patients with no genetics, but clinical FCS can get the drug. In the US it's just stated patients with FCS. But in Europe, there is this distinction. Now regarding efficacy and safety, I would say there are not massive differences. As you pointed out, they both prove, and I'm very grateful that they invested so much, that APOC3 is an excellent target to decrease triglycerides.

Olezarsen is an antisense oligonucleotide injected once a month, while plozasiran is injected every 3 months because it's a small interfering RNA. The safety profile there is one question mark with increase in hepatic fat with

olezarsen and a little bit of a question mark about hyperglycemia with plozasiran. The open-label studies will show that. The TIMI group presented the open-label extension data of olezarsen, and it was very reassuring. Of course, we need the paper that it went down after 1 year, the hepatic fat, which would be good for the patients. Yeah, yeah. But I think both drugs are quite good.

Of course, plozasiran has the benefit that you can give it in patients with no genetics.

Dr. Watts:

Okay, Ioanna, we talked about effectiveness, but just to get a bit of idea on the percentage reduction in triglycerides and how this translated into clinical benefit.

Dr. Gouni-Berthold:

Yeah. Both drugs massively decrease triglycerides. But to be honest, I'm not really so much interested in triglyceride reduction. I want a significant reduction in acute pancreatitis. The patients also don't really care if they have 2,000 or 1,800 if they have pancreatitis. And what was wonderful is that both medications decrease the incidence of acute pancreatitis, which of course translates to extreme benefit for our patients.

Dr. Watts:

So just trying to take a bird's-eye view on this. We've talked about severe hypertriglyceridemia in both studies, in SHASTA-2, CORE, and the PALISADE, BALANCE trials. What, in your experience—and you've had tons of experience, right, probably greater than most in Europe—really, what would be your call to action now for clinicians?

Dr. Gouni-Berthold:

Yeah. Let's focus on FCS. What I would like to tell my colleagues is that now this obscure disease, FCS, has a treatment. There are 2 drugs that massively help individuals. So don't just disregard high triglycerides as something you cannot do a lot anyway. There are 2 very good treatments, and please be aware, don't just ignore the disease.

Dr. Watts:

Excellent. Thank you very much.

Dr. Gouni-Berthold:

Thank you.

Dr. Watts:

Thank you, Ioanna, and thanks to our audience for joining us here at the ESC.

Dr. Gouni-Berthold:

Yes. Thank you, Gerald, and thanks to our audience. Thanks so much.