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Breaking Barriers in Familial Chylomicronemia Syndrome

Announcer:
You're listening to *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD. Here's your host, Dr. Mary Katherine Cheeley.

Dr. Cheeley:
This is *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD. I'm Dr. Mary Katherine Cheeley, and joining me to explore recent advances in the management of familial chylomicronemia syndrome, or FCS, is Dr. Robert Hegele. He's a Distinguished University Professor in the Departments of Medicine and Biochemistry at Western University in Ontario, and he practices as a staff physician at the University Hospital in London, Ontario. Dr. Hegele, welcome to the program.

Dr. Hegele:
Well, thank you, Dr. Cheeley. Mary Katherine, I'm very happy to be with you.

Dr. Cheeley:

So, let's start. Not a lot of people know about FCS, so can you help walk us through the underlying pathophysiology and why it's historically been so difficult to treat this condition?

Dr. Hegele:
Sure. So FCS is a subset—a very small but clinically relevant and informative subset—of the broader phenotype of severe hypertriglyceridemia. So if we consider severe hypertriglyceridemia using a cutoff of a thousand—there are various definitions, but if we say a thousand—in North America, that is about one in six hundred people will have a triglyceride that high.

Of that, only a tiny percentage actually has FCS, which is the most strongly genetically determined form of that. The estimates range between one in a hundred thousand to one in five hundred thousand. And it's a Mendelian condition. So those patients have triglycerides that high, typically presenting in childhood, because of the genetic deficiency.

And so the problem is, it's always homozygous autosomal recessive: so two copies of a pathogenic variant. We used to call these mutations, but nowadays, the nomenclature has been updated to pathogenic variants. It's a clinically relevant pathogenic variant in a key enzyme that breaks down the large triglyceride-rich particles called chylomicrons, which are from the intestine.

And that enzyme is lipoprotein lipase, or LPL. So about eighty percent of patients with FCS have one copy from each parent of a pathogenic variant in the gene that encodes for that enzyme, and therefore, they're totally not making that enzyme. And then, we've since learned that there are a number of cofactors—actually four clinically relevant cofactors—that have names like APOC2, APOA5, GPIHBP1, and LMF1. And the consequence is the same. So if you inherit the normal gene for the enzyme, but you inherit biallelic or homozygous mutations in both cofactors, then it results in a functional deficiency.

And so the problem is that this is the first step. When we consume a diet, and fat comes in through the lymphatics and then goes into the bloodstream, these chylomicron particles are the first sort of processing enzyme that they encounter—that lipase enzyme on the endothelium. And so, if it is working right, then the triglycerides are released, the fatty acids go into the tissues, it goes into the liver, and then the liver is pretty smart; it recycles them and puts them out later as very low-density lipoprotein, or VLDL.

But in the patients with this condition, that very first step is blockaded, and so then these chylomicrons just pile up. They build up to these enormously high levels. So first of all, that's a biochemical issue, but they also then can result in clinical features. So if there are

the clinical features, that's where we use the term syndrome.

The biggest risk to health is acute pancreatitis. And that is the consequence of having this severe genetically determined enzymatic deficiency. There's something about the chylomicron that predisposes to pancreatitis. So you can have high triglycerides based on other particles—the LDL, the smaller particles—and those won't result in pancreatitis. It's the chylomicrons in particular.

Dr. Cheeley:
Since chylomicrons are the part that causes the worst end result, acute pancreatitis, what unmet needs did we have that have driven forward the need for development of novel therapeutics, which we're now really excited to start to get some of?

Dr. Hegele:
So for the majority of patients who actually have chylomicrons with triglycerides over a thousand, that would not be the familial chylomicronemia syndrome, but the multifactorial adult onset. Those are much more common. We see them in lipid clinics. Basically, if you can get those patients to cut their alcohol, reduce the fat in the diet, lose some weight and treat the diabetes, they will respond and they will normalize.

And you want to get the triglycerides. So we know from administrative data that if you can get the triglycerides down to below five hundred, then the pancreatitis risk basically goes away—or you can get pancreatitis for other reasons, but it's not on the basis of high triglycerides.

So those patients, by and large, then will respond, if they have a garden variety multifactorial chylomicronemia. In he familial chylomicronemia—the childhood-onset Mendelian autosomal recessive—because they lack lipolytic capacity, it is an absolute lack. It's not a relative lack.

So any of these drugs that we use—fibrates, omega-3—do not work. And so then, in fact, the traditional treatment for them has been this really draconian fat restriction, down to 10 percent of their calories as fat, possibly, supplemented by medium-chain triglycerides for a little bit of flavor.

And then, of course, it's our diet, three times a day. We're thinking of our meals more often.

Dr. Cheeley:
And children, we're talking about children.

Dr. Hegele:
Absolutely.

Dr. Cheeley:
It's really hard.

Dr. Hegele:
They’re going to a birthday party, or whatever. That has been the treatment, and so their triglycerides never come down. It's like rare that they'll come down under 1,000. It's the rare child or adolescent that will have that.

But anyway, that's the unmet need. Now, fortunately, the new biologic treatments that we have have been transformational for these patients, in that finally, now, they don't have to be living with the sword of Damocles over their heads, worried every day, am I eating too much fat on this occasion?

Dr. Cheeley:
So take us to school a little bit. Teach us about these new therapies. Let's start with apolipoprotein C3 or APOC3. Why is this such a compelling target, and how is it influencing how we treat FCS?

Dr. Hegele:
So there's a well-known cofactor that causes a form of FCS, which is APOC2. So APOC2 activates lipoprotein lipase like an accelerator. APOC3 is the brake; it’s an inhibitor of lipoprotein lipase. And we need the balance, and they're there for physiological reasons.

And then APOC3 is also involved in the uptake of these particles in the liver that is not lipase-mediated. And then it is also involved in production and secretion of these very large particles from the intestine and the liver. So APOC3 is basically promoting and keeping the chylomicrons around for a longer period of time.

And this has been known; APOC3 has been a logical target. There would be some way of knocking down APOC3. And so it turns out, it's a small peptide, and you can't really target it with an antibody. But with RNA interfering therapies, you can mimic genetic deficiency, and you can either intercept the RNA at the level of the nucleus, which is the small interfering RNAs, or you can interfere in the

cytoplasm, which are then the antisense oligonucleotides.

So now there are these two agents that have been recently approved for use, I think globally. I can attest to the fact they've been absolutely transformational for these patients, and that they finally allow them to come out from under this scourge of having to be so obsessive about their diet and afraid.

And there is another target. There's ANGPTL3. But it turns out the ANGPTL3 inhibitors do not work, or their efficiency in FCS is blunted. There is a lack of efficacy. They work much better in patients that have at least a little bit of lipase activity. But if you give the ANGPTL3 drugs to patients with true genetically proven FCS, it seems not to work.

Dr. Cheeley:
For those just joining us, this is *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD. I'm Dr. Mary Katherine Cheeley, and I'm speaking with Dr. Robert Hegele about novel therapeutic options for familial chylomicronemia syndrome.

So a lot of these therapies have moved through clinical development, and some are available to patients now. So what key efficacy and safety considerations should clinicians think about when they have a patient that they are trying to evaluate which therapy is best for them?

Dr. Hegele:
So one is, does my patient actually have familial chylomicronemia syndrome, or is this just multifactorial chylomicronemia syndrome? It's important to make the diagnosis of FCS, because there are then a fraction of these more garden-variety severe hypertriglyceridemia patients who are refractory. They lose weight, they do everything properly, they come off alcohol, we manage their diabetes, and then they're still running with triglycerides over a thousand. And so this has been variably called persistent chylomicronemia or sustained chylomicronemia. And so they're not really FCS patients, but there is still a medical need for those patients. But the true FCS are the most extreme, where, in fact, there is no other alternative. And that diagnosis is made genetically.

And so then, genetic testing is accessible. And fortunately, you only need to do it once, but it's still expensive. It's not widely available. So there are these clinical tools, these clinical scoring systems, and one is called the NAFCS score: the North American Familial Chylomicronemia Syndrome score. It's eight fairly readily available clinical variables. If the patient has a high enough score, like if it's above forty-five, it's likely. And if it's above sixty, it's definite for FCS. And then, also, if the patient doesn't have a score that high, you can rule out FCS while you're waiting for genetic testing.

So with these agents right now, their indication, their coverage, and their regulatory approval is for FCS—either genetically proven or the clinical equivalent.

Dr. Cheeley:
Are there any adverse effects that we should think about with these new medications?

Dr. Hegele:
Yeah, that's a good question. With all injectables, there is a higher incidence of local injection site reactions. There seems to be a slight increased risk of transaminase elevation, which may be related to fatty liver, but it's a fairly low percentage risk and something that we need to monitor. But again, it's a low percentage, but more than placebo.

And then, also, in some patients, there is a worsening of glycosylated hemoglobin or hemoglobin A1C. But that's, again, subtle, and it may be in patients who are on that trajectory anyway.

Dr. Cheeley:
I want you to pull out your crystal ball and help us figure out where you see us going with these therapies. How are we going to integrate them into clinical practice? What do you think that they might mean for the future of the standard of care in our FCS patients?

Dr. Hegele:
What I've noticed—and I'm sure you've seen the same thing—is that it doesn't let the patient totally off the hook with respect to their diet. The diet is still important, but at least it's a little more normal. They can feel a little more human. They don't have to obsess about a slice of pizza or the tortellini carbonara or whatever.

Dr. Cheeley:
Kids can go to a birthday party.

Dr. Hegele:
Absolutely, yeah. They can have a piece of birthday cake.

These are proven treatments. There may be a longer duration, and I know there's refinements on that pathway and newer drugs in the future, probably, that'll be targeting that. But I think this has already been a big step forward to have both of these drugs available now.

But I think what I'm really interested in is to see that for milder, say, non-FCS severe hypertriglyceridemia, or even mild-to-moderate hypertriglyceridemia, when we have a patient who is refractory or a patient in whom we are still concerned about residual cardiovascular risk. Would these drugs have a place in the algorithm for those patients?

Dr. Cheeley:
That is such a great way to round out our discussion. Thank you so much for your expertise and amazing teaching today, Dr. Hegele. It was lovely having you on the program. Thanks for being here.

Dr. Hegele:
Well, I really enjoyed it, Dr. Cheeley. Thanks again.

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