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Plozasiran (ARO-APOC3) Decreases APOC3 and Triglycerides (TG) in Patients With Mixed Hyperlipidemia: MUIR Final Results

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Ballantyne:
This is CME on ReachMD, and I'm Dr. Christie Ballantyne, here to talk to you about a hot topic, triglyceride-rich lipoproteins.

High triglycerides are associated with increased risk of ASCVD [atherosclerotic cardiovascular disease]. Some of the variants with lower triglycerides have less risk. And this has identified genetic targets. And once you get a target, biotechnology takes off. And this is an example of how targeting messenger RNA, small interfering RNA molecules, that target APOC3.

What does APOC3 do? APOC3 inhibits the catabolism of triglyceride-rich lipoproteins, so they hang around a long time. The levels go up, particularly in the postprandial state. There's an LPL-dependent and -independent pathway. And if you block the production with an siRNA, you never make the protein. And what do we see? A big reduction in these triglyceride-rich lipoproteins. Triglycerides go down, and also the cholesterol content in those particles, that's gone too.

So what was done here was a phase 2b, placebo-controlled, dose-ranging study. And the name of the drug is plozasiran. This is an sRNA that targets APOC3. And the patients had mixed hyperlipidemia, so that was defined as triglycerides elevated between 150 and 499, and also some elevation of either LDL cholesterol greater than or equal to 70, or non-HDL greater than or equal to 100 mg/dL.

The primary endpoint was triglyceride changes. Key secondaries was a change in APOC3, the protein it's targeting, non-HDL cholesterol, apoB, LDL, HDL cholesterol, and also safety. Now there were 4 dosages, 10, 25, 50 mg every 12 weeks, and then there was a 50 mg every 24 weeks. Some of the sRNAs have a long duration of biological activity. And there was a placebo group to compare to these.

Okay, so what kind of patients were in the study? About 40% women, mostly white. They were overweight, average BMI, which is commonly seen with mixed hyperlipidemia, was over 30. They had high triglycerides, around 240 to 250 on mean averages. Remnant cholesterol was increased, that's the cholesterol in those triglyceride-rich lipoproteins, around 45. Non-HDL was elevated around 150, and LDL was around 100.

What were the results? Triglycerides went down very dramatically, as did APOC3. So what was seen at 24 weeks? So you got a dose at 0, 12 weeks, so 24 weeks later after that 12-week dose there was a reduction in triglycerides ranging from 52% to 64%. APOC3 was reduced 59% to 80%. And a reduction in remnant cholesterol of 48% to 53%.

If we look at the changes in non-HDL cholesterol, which is an important number when we look at cardiovascular trials for lipid-lowering therapy, 19% to 27% reduction. LDL didn't change much, -1% to -10%; apoB was reduced 10% to 18%, and a very large increase in HDL cholesterol, 38% to 51%.

What about adverse events? This was done during COVID, some of it, so that was the most common adverse event, including the placebo group. But we really didn't see any signals here. There was nothing with platelets.

There was a signal of some worsened glycemic control at the 50-mg dose.

All right, so let's summarize. What were the effects of plozasiran? By targeting APOC3 protein production, you reduce APOC3 up to 80%, triglycerides went down 64%, remnant cholesterol 54%, non-HDL cholesterol up to 27%, apoB up to 18%, HDL cholesterol increased up to 51%. Overall, a favorable safety profile.

It's the first RNA interference investigation molecule, substantial reductions in triglyceride-rich lipoproteins in this mixed hyperlipidemia population. And so this appears to be a promising treatment for increased ASCVD, and it further supports development in a larger phase 3 program for plozasiran, including, based upon this data, doing a program large enough to look at clinical outcomes and outcomes trial.

Thank you very much.

Announcer:
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