radcliffe cardiology

Title: ACC.24: Olezarsen for Hypertriglyceridemia and ASCVD
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Dr Brian Bergmark

"My name is Brian Bergmark. I'm an investigator at the Timmy study group at Brigham and Women's Hospital.

Reasoning for this Study

Elevated triglyceride rich lipoproteins, including chylomicrons and VLDL, continue to be a clinical issue in need of drug therapy. They are associated with heightened cardiovascular risk, and severe hypertriglyceridemia is also directly clinically important, including risk of acute pancreatitis. And so there are need for additional therapies to target triglyceride rich lipoproteins.

Olezarsen Overview

Olezarsen is an antisense oligonucleotide that targets apolipoprotein c three. Apolipoprotein c three is a protein made in the liver that sits on the triglyceride rich lipoproteins and blocks the breakdown of them by lipoprotein lipase. So we know from genetic data that people who have loss of function mutations in the apOC three gene have lower triglyceride levels as well as lower risk for cardiovascular events. It is a distinct mechanism of action, certainly compared to other agents, but the hope is that with that, that you can get a much larger reduction in triglycerides than is currently available.

Study Design

This particular study enrolled patients who had either moderate hypertriglyceridemia plus elevated cardiovascular risk or severe hypertriglyceridemia, meaning levels of 500 milligrammes per deciliter or more. And the goal was to look at the effect on

triglycerides. At six months, we were looking at two doses, 50 milligrammes given every four weeks, or 80 milligrammes given every four weeks compared to placebo.

Results

Both doses of olezarsen significantly reduced triglyceride levels rapidly and in a sustained way through twelve months. So for the 50 milligramme dose, that was 49% compared with placebo, and for the 80 milligramme dose, by about 53% compared with placebo.

Safety Profile

In terms of the major things that have been seen with this class of medication prior, in terms of platelets, et cetera, things look good for low level elevations in ALT and AST, for instance, there are slightly more with the drug compared to placebo, but for the clinically significant changes, three times the upper limit of normal or more, no difference across the treatment arms. So the important thing is there's a reduction in triglycerides that is greater than can be achieved with currently available therapies in what appears to be with a safe drug.

Outstanding Questions

One of the outstanding questions is about the efficacy for cardiovascular risk reduction. So, in addition to the triglyceride lowering, there were reductions in apolipoprotein B and non HDL cholesterol, which are markers of atherogenic risk. And so we're fortunate to have some upcoming data that are really gonna flesh this out.

Ongoing Trials

There are two ongoing trials, specifically in people with severe hypertriglyceridemia. So we're gonna get some more efficacy, some more safety data, specifically in that population. And there actually are hepatic MRIs that are being incorporated into that.

Future Directions

And then in terms of cardiovascular risk reduction, specifically, there's a large trial of over 1300 patients underway in a population similar to this one that also has a coronary CT substudy, where there's a coronary ct at baseline and after twelve months, that I think will really help inform the degree to which this might help with cardiovascular risk reduction.