RNA inhibitor is shown safe and effective in reducing a wide range of cholesterol and triglyceride levels in the blood

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A small interfering RNA (siRNA) investigational therapy that inhibits a gene involved in lipoprotein metabolism has been shown in a clinical

trial led by Mount Sinai researchers to significantly reduce levels of different types of cholesterol and triglycerides in individuals with mixed hyperlipidemia, a condition in which fats build up in the blood.

In addition to seeing promising preliminary results related to safety and efficacy in clinical trials, the Mount Sinai researchers found the RNA interference (RNAi)-based therapy zodasiran to be a potentially promising option for substantially reducing a number of atherogenic lipoproteins while requiring less frequent dosing than conventional therapies. The results were presented as a late-breaking clinical trial at the European Atherosclerosis Society Congress on Wednesday, May 29, in Lyon, France, and simultaneously published in *The New England Journal of Medicine*.

Zodasiran (Arrowhead Pharmaceuticals) targets a specific gene expressed in hepatocytes known as angiopoietin-like protein 3 (ANGPTL3), which plays a role in regulating levels of low-density lipoprotein (LDL), non-HDL cholesterol (a measure of all the "bad" cholesterol in the blood including LDL), and triglycerides. Various research has identified these components as increasing risk of atherosclerotic cardiovascular disease.

"Our study represents one of the first trials of an RNA inhibitor of ANGPTL3 with advantages like durable gene silencing and infrequent dosing," says lead author Robert Rosenson, MD, Professor of Medicine (Cardiology) at the Icahn School of Medicine at Mount Sinai, and Director of Lipids and Metabolism for the Mount Sinai Health System.

"For patients with mixed hyperlipidemia and persistent elevations in LDL cholesterol and non-HDL cholesterol, zodasiran could expand the opportunities for lowering 'bad' cholesterol beyond conventional therapies such as statins, potentially leading to more favorable outcomes for patients."

Mixed hyperlipidemia is characterized by the build-up of fats in the blood and is often hereditary. Individuals with this condition may be overweight and more prone to prediabetes or diabetes.

In the phase 2b global trial (known as ARCHES-2) of 204 participants with mixed hyperlipidemia who received zodasiran (50, 100, and 200 mg) and background therapy of standard of care medications including statins, the researchers observed substantial reductions in all lipid level parameters monitored.

These included lowering triglycerides by 54 to 74 percent compared to placebo, LDL cholesterol by up to 20 percent, non-HDL cholesterol by up to 36 percent, and remnant cholesterol by 73 to 82 percent. Remnant cholesterol measures the amount of "leftover" or remnant very-low-density lipoprotein (VLDL) particles. It is measured by adding up HDL and LDL and subtracting that sum from the individual's total cholesterol.

The reduction in remnant cholesterol is particularly important because those remnants may contain up to four times more cholesterol per particle than LDL. Moreover, prior research has demonstrated an association between elevated remnant cholesterol and increased risk of cardiovascular disease.

The Mount Sinai researchers suggested that based on prior genetic studies the magnitude of remnant cholesterol reduction evidenced by zodasiran in their study could translate into a 20 percent decrease in recurrent major cardiac events.

The ARCHES-2 study also found zodasiran effective in lowering apolipoprotein B, a lipid-transporting protein in the body which has been linked to increased risk of heart disease at high levels.

"In contrast to fibrates and fish oils, zodasiran lowers apolipoprotein B

and thus may be a more promising potential therapy for reducing the risk of cardiovascular events," Dr. Rosenson notes.

The findings from this study in patients with mixed hyperlipidemia build on prior efforts to modulate ANGPTL3 with evinacumab, the fully human monoclonal antibody against the ANGPTL3 protein, approved by the U.S. Food and Drug Administration to treat patients with homozygous familial hypercholesterolemia (HoFH).

"It's our contention," emphasizes Dr. Rosenson, "that based on these promising results, further studies are warranted to determine the potential of zodasiran, an investigational drug has the potential to reduce the risk of cardiovascular events in a broad range of patients through a single therapy that targets all the lipoprotein fractions."

More information: Robert S. Rosenson et al, Zodasiran, an RNAi Therapeutic Targeting ANGPTL3, for Mixed Hyperlipidemia, *New England Journal of Medicine* (2024). DOI: 10.1056/NEJMoa2404147

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