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Media Contacts Below

Evinacumab Could Help Some Patients with Severe Hypertriglyceridemia

Patients' genetic profile strongly influences size of effect in early-phase trial

WASHINGTON (May 16, 2021) — People with extremely high levels of triglycerides (a type of fat in the blood) and a specific genetic profile saw a substantial reduction in triglycerides after taking the human monoclonal antibody evinacumab compared with those taking a placebo, in a study presented at the American College of Cardiology's 70th Annual Scientific Session.

Severe hypertriglyceridemia is a rare disorder that causes extremely high levels of triglycerides, an accumulation of fat in the blood that can lead to heart, liver and pancreatic disease. People with severe hypertriglyceridemia commonly have triglyceride levels of 1,000 mg/dL (less than 150 mg/dL is considered normal and above 200 mg/dL is considered high) that cannot be adequately controlled with dietary restrictions or available medications.

“This trial has important clinical implications for this population with severe hypertriglyceridemia,” said Robert S. Rosenson, MD, professor of medicine in cardiology and director of metabolism and lipids for the Mount Sinai Health System and the study's lead author. “It also demonstrates the importance of genetic testing in people with severe hypertriglyceridemia because by performing genetic testing you are able to tell which individuals will respond to this therapy and which are unlikely to respond.”

Evinacumab is a monoclonal antibody currently approved for treating familial hypercholesterolemia (FH), a condition that causes extremely high cholesterol. Previous clinical trials found that evinacumab reduced triglycerides, as well as LDL or “bad” cholesterol, in people with FH. Evinacumab works by binding to angiopoietin-like protein 3 (ANGPTL3), a protein regulating cholesterol and triglycerides.

To study evinacumab's effects on triglycerides, the new phase 2 trial enrolled 51 patients with hypertriglyceridemia at 17 sites in four countries in North America and Europe. The patients did not have FH and had a history of triglyceride levels of 1,000 mg/dL and prior hospitalization for acute pancreatitis. At the time of screening, patients' triglyceride levels were 500 mg/dL or higher despite maintaining a strict diet. Acute pancreatitis is a common complication of hypertriglyceridemia.

Two-thirds of the trial participants were randomly assigned to receive evinacumab via intravenous infusion at a dosage of 15 mg/kg every four weeks for a total of 24 weeks. One-third received a placebo for the first 12 weeks (the double-blind portion of the study) and then received evinacumab for the second 12 weeks. All participants underwent genetic testing to assess mutations in LPL pathway genes, which provide instructions for making an enzyme called lipoprotein lipase that plays a critical role in breaking down triglycerides.

At the end of the 12-week placebo-controlled double-blind period, the median triglyceride level dropped by more than 800 mg/dL (57%) in patients taking evinacumab, compared with an overall increase of 50

mg/dL (1.8%) in participants taking a placebo. The magnitude of triglyceride lowering with evinacumab was highly dependent on participants' genetic profile. Those with a double copy of certain mutations in LPL pathway genes had essentially no benefit from evinacumab, whereas patients with a single mutation or no mutations in LPL pathway genes saw triglyceride reductions of around 80%. Among patients with no identifiable LPL mutations, changes in the double-blind treatment and single-blind treatment (primary endpoint) showed a mean reduction in triglycerides of 27.1% and a median reduction of 68.8%.

While other therapies will be needed for patients with the double copy of certain LPL mutations, researchers said these new findings suggest evinacumab may be a promising therapeutic option for those with the appropriate genetic profile.

“Severe hypertriglyceridemia is a severe, unrelenting condition that impairs quality of life,” Rosenson said. “Many patients have their first episode of pancreatitis in their teenage years and often end up in intensive care. Most lipid-lowering therapies don't work in these individuals, and that's why we need alternative therapies for them.”

Adverse events such as abdominal pain, acute pancreatitis and headache occurred in about 70% of patients in both groups, but there was no significant difference in the rate of adverse events between those taking evinacumab and those taking a placebo. While the trial was not designed to determine an effect on the occurrence of acute pancreatitis, the majority of acute pancreatitis events occurred either when patients were receiving placebo or more than four weeks after completing evinacumab treatment. A separate study is now underway to determine whether evinacumab reduces recurrent pancreatitis by lowering triglycerides.

Rosenson said future studies could investigate evinacumab's potential benefits for patients with elevations in both triglycerides and LDL cholesterol, a combination often seen in patients with diabetes. “By lowering triglycerides by 60-80% and LDL cholesterol by 50% on top of statins and other medications, this agent has an opportunity to impact cardiovascular disease in these very high-risk individuals,” Rosenson said.

As a phase 2 trial, the study was limited by its small sample size. Further studies with a broader patient population and larger sample size could further elucidate evinacumab's potential benefits for lowering triglycerides.

The study was funded by Regeneron Pharmaceuticals Inc.

Rosenson will be available to the media in a virtual press conference on Sunday, May 16, at 9:45 a.m. ET / 13:45 UTC.

Rosenson will present the study, “A Phase 2 Trial of the Efficacy and Safety of Evinacumab in Patients with Severe Hypertriglyceridemia,” on Sunday, May 16, at 8 a.m. ET / 12:00 UTC, virtually.

ACC.21 will take place May 15-17 virtually, bringing together cardiologists and cardiovascular specialists from around the world to share the newest discoveries in treatment and prevention. Follow [@ACCinTouch](#), [@ACCMediaCenter](#) and [#ACC21](#) for the latest news from the meeting.

The American College of Cardiology envisions a world where innovation and knowledge optimize cardiovascular care and outcomes. As the professional home for the entire cardiovascular care team, the mission of the College and its 54,000 members is to transform cardiovascular care and to improve heart health. The ACC bestows credentials upon cardiovascular professionals who meet stringent qualifications and leads in the formation of health policy, standards and guidelines. The College also provides

professional medical education, disseminates cardiovascular research through its world-renowned *JACC Journals*, operates national registries to measure and improve care, and offers cardiovascular accreditation to hospitals and institutions. For more, visit ACC.org.

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