Injectable biologic therapy dramatically reduces triglycerides

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When an adult gets an annual physical, physicians commonly check the levels of fat cells, known as triglycerides, in their blood stream. Triglycerides are a type of fat, or lipid, which are consumed when you eat, and are normally stored in fat tissue to be used later as an energy source. However, some people accumulate fat in the blood that should otherwise be stored in the fat tissue, causing high triglycerides. Extremely high triglycerides can lead to inflammation of the pancreas - pancreatitis - and moderate elevations are associated with higher risk for heart disease such as atherosclerosis.

Today at the American Heart Association Scientific Sessions 2016, Richard Dunbar, MD, an assistant professor of Translational Medicine and Medical Genetics in the Perelman School of Medicine at the University of Pennsylvania, will present early data from a study which evaluated the use of a new injectable biologic drug therapy for reducing triglyceride levels.

"In this study, we tested a new approach for lowering triglycerides using an injectable drug that inhibits a specific protein which enables high triglycerides - Angiopoietin-like 3 (ANGPTL3). As expected, suppressing AngPTL3 resulted in a profound drop in triglyceride levels, as compared to a placebo," said Dunbar. "Encouragingly, the kinds of drops we saw appear to push beyond the boundaries of what is usually experienced with current oral medications."

Researchers conducted this phase I, first-in-human, placebo-controlled,

double-blind study to test the safety and efficacy of the injectable biologic drug, Evinacumab, an investigational monoclonal antibody specifically engineered to inhibit ANGPTL3. Results from 41 participants, 32 of whom received Evinacumab and nine the placebo, showed the biologic therapy was well-tolerated by participants with only mild adverse events being reported, including headaches in seven participants. Triglyceride levels were monitored for at least five months following the injection, with the maximum reduction seen on day four. Six doses were tested, and in the top three dose-groups, triglycerides were lowered by 64 to 73 percent.

"Current medications such as fibrates or prescription fish oils effectively lower triglycerides, but leave much to be desired, each only lowering levels by 20 to 50 percent," Dunbar said. "Validating a drug that lowers triglycerides well beyond that range would undoubtedly take us to the next level, particularly since it could be combined with current oral medications for those patients with extraordinarily high triglycerides who often can't achieve safe levels with our usual medications. A similar approach has been taken for lowering certain cholesterol with the advent of PCSK9 inhibitors, which utilize a similar monoclonal antibody mechanism."

Dose-dependent reductions in cholesterol were also observed, most notably cholesterol from low-density lipoproteins (LDL), which is thought to contribute significantly to atherosclerosis - plaque buildup and the narrowing of the heart's arteries. Curiously, the drug also lowered cholesterol from high-density lipoproteins (HDL) - the "good" cholesterol - consistent with the drug's mechanism targeting the AngPTL3 protein.

"Though the preliminary results give us a lot of hope that we could significantly improve triglyceride management, there is still a lot of work to be done to validate this approach," Dunbar said. "If all goes well and

if this therapy makes it into clinical practice, the implications of this research are twofold. In the short term, profoundly lowering triglycerides may render hospital admissions less frequent in patients prone to pancreatitis, while long term, lowering triglycerides and associated cholesterol could also help reduce the risk of certain heart disease."

While the team notes it is gratifying to see more attention being paid to triglycerides, the 'other' bad lipid, and that these early results are promising, more research is needed in order to evaluate the safety and efficacy across a larger patient population, particularly with multiple doses.

Provided by Perelman School of Medicine at the University of Pennsylvania

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