New class of drugs lowers cholesterol in first human trial

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A single dose of the small interfering ribonucleic acid (siRNA) drug candidate ALN-PCS cut levels of LDL cholesterol (bad cholesterol) in healthy volunteers by up to 57%, and 40% on average more than those given a placebo, according to the new research published in *The Lancet*.

"These phase I results pave the way for RNA interference (RNAi) therapeutics as a potential treatment for high cholesterol", explains trial investigator Kevin Fitzgerald from Alnylam Pharmaceuticals who helped develop the new siRNA.

"If successfully developed, this class of drugs could be an alternative for the one in five people who are resistant to statins, or be combined with statins to produce even greater effects for the many others for whom the current first line treatment does not lower cholesterol enough."

ALN-PCS works by blocking the production of the cholesterol regulator PCSK9 (proprotein convertase subtilisin/kexin type 9)—a protein that destroys low-density lipoprotein (LDL) receptors that normally clear LDL cholesterol from the blood.

Genetic studies have shown that mutations resulting in a rise in PCSK9 concentration or activity lead to a major increase in LDL cholesterol which contributes to the build up of plaque inside blood vessels, while mutations causing less PCSK9 activity lower cholesterol dramatically. What is more, evidence suggests that statins increase the production of PCSK9, which could limit their effectiveness.

Building upon a series of successful preclinical studies, researchers from the USA and UK recruited 32 healthy volunteers, 18 to 65 years old, with mildly to moderately raised LDL cholesterol. Volunteers were randomly assigned to receive one of six doses of intravenous ALN-PCS, or matching placebo (normal saline).

ALN-PCS was generally well tolerated, with similar proportions of volunteers in both groups experiencing mild to moderate adverse events (79% vs 88%). The researchers noted no clinically significant changes to markers of liver function or inflammation.

Infusion of ALN-PCS led to a rapid, dose-dependent reduction in plasma PCSK9, with higher doses having longer lasting effects. For those given the highest dose of ALN-PCS (0.400mg/kg), plasma PCSK9 levels dropped up to 84% (average 70%), and LDL cholesterol dropped up to 57% (average 40%), compared with placebo.

According to Fitzgerald, "This marks the first time that the effect of an RNAi drug candidate has been demonstrated on a clinically validated endpoint (LDL cholesterol), performing as well as statins that provide about 36% to 53% drops in LDL cholesterol. The next step will be larger multidose studies without the use of premedication to address long-term safety and tolerability of ALN-PCS in various patient populations, including those on statins and those who are statin intolerant."

Commenting on the study, John R Burnett and Amanda J Hooper from the University of Western Australia say, "PCSK9 inhibition is shaping up to be an effective means of lowering LDL cholesterol in patients with severe or refractory hypercholesterolaemia who are not able to tolerate statins or have not reached target concentrations of LDL cholesterol. Since statins upregulate PCSK9, potentially limiting their effectiveness, combination treatment with the addition of a PCSK9 inhibitor could enhance the LDL-lowering effect of statins alone."

More information:
www.thelancet.com/journals/lan … (13)61914-5/abstract

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