A single infusion of a gene-editing medicine may control inherited high LDL cholesterol

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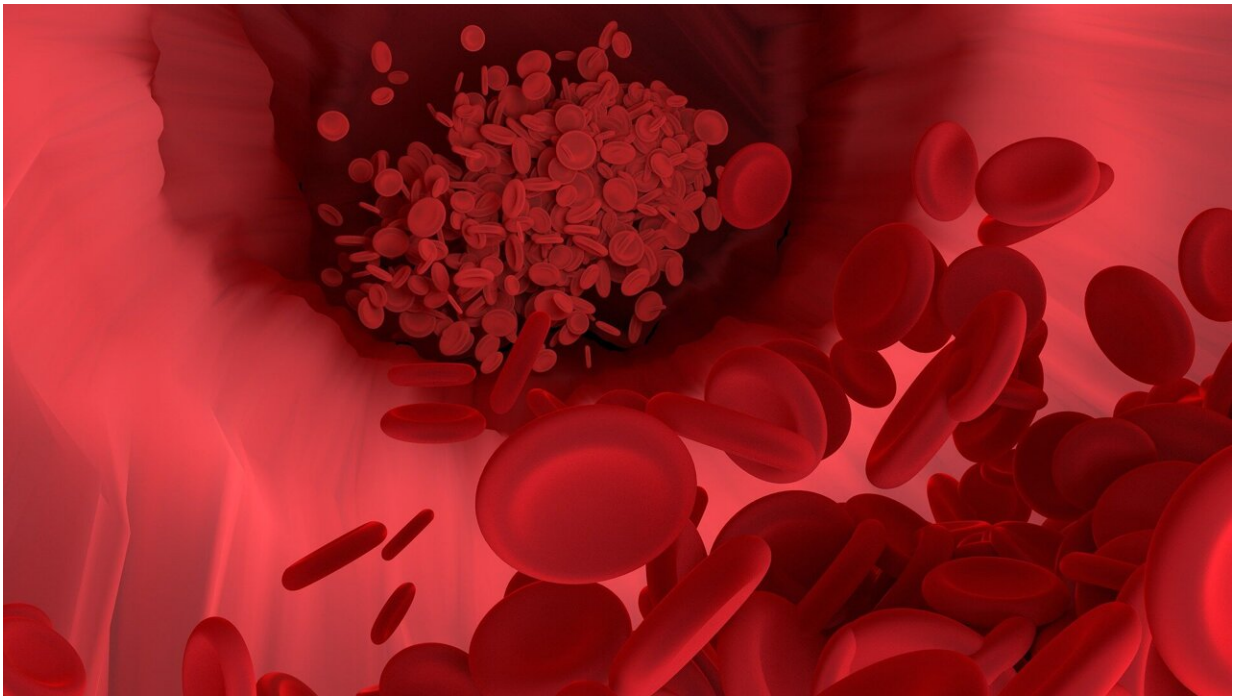

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A single infusion of a CRISPR-based gene-editing therapy significantly reduced low-density lipoprotein cholesterol (LDL, the "bad cholesterol") in people who carry one gene for the inherited condition that results in very high LDL cholesterol levels and a high risk of heart attack at an early age, according to late-breaking science presented today at the American Heart Association's Scientific Sessions 2023. The meeting,

held Nov. 11–13, in Philadelphia, is a premier global exchange of the latest scientific advancements, research and evidence-based clinical practice updates in cardiovascular science.

"Instead of daily pills or intermittent injections over decades to lower bad cholesterol, this study reveals the potential for a new treatment option—a single-course therapy that may lead to deep LDL-C lowering for decades," said senior study author Andrew M. Bellinger, M.D., Ph.D., chief scientific officer at Verve Therapeutics in Boston.

The investigational treatment, VERVE-101, uses DNA-editing technology to permanently turn off the PCSK9 gene in the liver. PCSK9 is a gene that plays a critical role in controlling blood LDL-C through its regulation of the LDL receptor. The study presented Nov. 12 is the first human trial of VERVE-101.

Earlier this year, the results of the researchers' one-year animal study were published in *Circulation*. In that animal study, VERVE-101 lowered PSCK9 levels 67%–83% and bad cholesterol 49%–69%, depending on the dose. After a single dose, the reductions have now lasted 2.5 years, supporting the idea that VERVE-101 may potentially be an effective long-term or permanent treatment for high LDL-C.

The ongoing, first-in-human study included seven men and two women in New Zealand or the United Kingdom: average age of 54 years; eight white adults; and one Asian adult. Each participant was diagnosed with heterozygous familial hypercholesterolemia—meaning they inherited one gene for the disorder from one parent—and had extremely high bad cholesterol levels (average measure of 201 mg/dL) despite taking the maximum-tolerated LDL cholesterol- lowering medication.

"These numbers are consistent with the fact that, despite available treatments, only about 3% of patients living with heterozygous familial

hypercholesterolemia globally have reached target treatment goals," Bellinger said.

The majority of study participants had pre-existing severe coronary artery disease and had already experienced a heart attack, or undergone coronary bypass surgery or stenting to allow adequate blood flow to heart muscle. None were taking PCSK9 inhibitors while enrolled in the study.

Each participant received a single intravenous infusion of VERVE-101, with the first cohort (n=3) receiving a low dose of 0.1 mg/kg and other cohorts receiving escalating doses, after consultation with an independent safety monitoring board. The highest dose received was 0.6 mg/kg.

The study found that the highest-two VERVE-101 doses:

- reduced LDL-C by 39% and 48% in the two participants receiving 0.45 mg/kg of the drug and 55% in the sole participant receiving 0.6 mg/kg;
- reduced blood PCSK9 protein levels by 47%, 59% and 84% in the three participants receiving the 0.45 mg/kg or 0.6 mg/kg doses; and
- reduced LDL-C at six months in the sole participant receiving 0.6 mg/kg, with follow-up ongoing.

"We were thrilled to see that the previous testing we had done of VERVE-101 in animal models translated faithfully to these findings in humans," Bellinger said.

To date, most adverse events that occurred in the study were mild and unrelated to treatment. Serious adverse cardiovascular events, specifically a cardiac arrest, a myocardial infarction and an arrhythmia, occurred in two patients who had underlying advanced coronary artery

disease. "All safety events were reviewed with the independent data safety monitoring board, who recommended continuation of trial enrollment with no protocol changes required," Bellinger said.

Background:

- People with heterozygous familial hypercholesterolemia are currently treated with oral lipid-lowering medications such as statins and sometimes with injections every few weeks of a drug to inhibit the action of PCSK9. Despite these treatments, few people with the disorder may be reaching heart-healthy target levels of LDL cholesterol.
- Target levels of LDL cholesterol are generally less than 100 mg/dL for people without heart disease, 70 mg/dL for people who already have heart disease, and even lower (55 mg/dL) for people with heterozygous familial hypercholesterolemia who already have severe heart disease.
- First-in-human trials are the first-time new medications or treatments are tested in humans and inform future studies with more participants. Studies involving a larger number of patients and with a control group will be required to fully document the efficacy and safety of VERVE-101, noted Bellinger.
- The study is still enrolling patients to receive the highest-two doses of VERVE-101. After a year's follow-up, each participant will go into a long-term follow-up study for an additional 14 years, as required by the FDA for all participants in any human genome editing trials.

Among the study's limitations is that this is an interim report with a few participants who all received the treatment; therefore, no participants receiving an alternate treatment or no treatment were available for direct comparison. Results in the study were measured by reductions in LDL-C, not changes in the occurrence of heart attacks; however, LDL-C

reduction is a well-known, validated endpoint among patients with heterozygous familial hypercholesterolemia and coronary artery disease.

It is estimated that one in about 200 adults have the familial hypercholesterolemia genetic mutation, affecting about 1.3 million adults and children in the U.S. High bad cholesterol contributes to atherosclerotic plaques, leading to a much higher-than-normal risk of heart disease. If left untreated, people with the disorder have 20 times the risk of developing heart disease, according to the American Heart Association. The other type of familial hypercholesterolemia, called homozygous familial hypercholesterolemia, is when someone inherits the gene for the disorder from both parents, and it is rare and more severe.

More information: Safety and Pharmacodynamic Effects of VERVE-101, an Investigational DNA Base Editing Medicine Designed to Durably Inactivate the PCSK9 Gene and Lower LDL Cholesterol—Interim Results of the Phase 1b heart-1 Trial. www.abstractsonline.com/pp8/?_ … 1/presentation/16572

Provided by American Heart Association

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