No benefit of synthetic HDL-C on arterial plaque

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Injection of a novel form of synthetic high-density lipoprotein cholesterol (HDL-C), or good cholesterol, into the arteries of patients who had recently had a heart attack did not reduce the volume of fatty deposits, or plaque, in the arteries, compared with placebo injections, according to research presented at the American College of Cardiology's 66th Annual Scientific Session.

The Phase 2 CARAT trial failed to meet its primary endpoint of change in the volume of fatty deposits in a coronary artery that had previously been shown to be at least 30 percent blocked, said Stephen Nicholls, MBBS, PhD, director of the Vascular Research Centre at the South Australian Health and Medical Research Institute in Adelaide, and the study's lead author.

"In general, CER-001 was well-tolerated, but it had no discernible effect on arterial plaque compared with placebo injections," Nicholls said. "This suggests that low-dose CER-001 does not appear to be a promising agent for use in patients with acute coronary syndrome."

Acute coronary syndrome, or ACS, occurs when blood flow to the heart is suddenly blocked. It may take the form of a heart attack or unstable angina, chest pain that may signal an imminent heart attack. Studies suggest that about 12 percent of patients with ACS will experience another blockage of blood flow to the heart within a year of the first event, despite taking medication to reduce their risk.

Standard treatments to reduce the risk of both heart attack and stroke have focused on reducing blood levels of LDL cholesterol (LDL-C), known as "bad" cholesterol because it contributes to the development of plaque in the lining of arteries, making them narrower, stiffer and more prone to being blocked by a blood clot. However, some researchers have sought to develop treatments that increase HDL cholesterol (HDL-C). Studies suggest that healthy levels of HDL-C (above 40 in men, above 50 in women) may protect against heart attack and stroke, due in part to HDL-C's role in clearing bad cholesterol from the arteries, thereby reducing inflammation and preventing blood clots. Low levels of HDL-C, by contrast, have been shown to increase risk for heart attacks and strokes.

One strategy for increasing HDL-C levels has been to create synthetic HDL-C that mimics the biological structure and function of natural HDL-C. The idea is that the synthetic HDL-C, when injected into the blood, will help to clear more fat and bad cholesterol, shrink arterial plaque, and reduce heart attack and stroke risk.

CER-001 is a form of synthetic HDL-C. Early studies suggested that CER-001 could increase the removal of LDL-C from the arteries and that, in patients with inherited cholesterol abnormalities such as familial hypercholesterolemia, it could reduce arterial plaque. However, other previous studies have found no benefit from CER-001 in reducing fatty deposits in arteries.

In the CARAT trial, researchers enrolled 301 patients (average age about 60, 80 percent male) who had had a recent heart attack and who had at least one coronary artery that had been shown in an ultrasound examination to be more than 30 percent blocked with fatty deposits (that is, to have atheroma volume of more than 30 percent). Patients with uncontrolled diabetes, extremely elevated triglyceride levels, heart failure, or liver or kidney disease were excluded. The study was

conducted in Australia, Hungary, the Netherlands and the United States.

Trial participants were randomly assigned to receive 10 weekly infusions of either CER-100 or a placebo. One to three weeks after the last infusion, they underwent a second ultrasound examination of the same coronary artery that had previously been shown to be at least 30 percent blocked. In addition to comparing the two ultrasounds and measuring the change in the volume of fatty deposits (the primary study endpoint), Nicholls and his colleagues also looked at additional measures of plaque volume, cholesterol levels, and safety and tolerability.

Results showed the primary endpoint decreased by 0.41 percent in the placebo group and by 0.09 percent in the CER-001 group, a non-statistically significant difference. Analysis of the major secondary endpoints revealed a reduction in total atheroma volume of 6.6 mm3 in the placebo group and 5.6 mm3 in the CER-001 group and regression of percent atheroma volume in 57.7 percent of placebo patients and 53.3 percent of CER-001 patients. Neither of these findings met the cutoff for statistical significance. Levels of LDC-C declined equally in the CER-001 and placebo groups. Rates of adverse events were low and were similar in both groups.

"We are disappointed that low-dose CER-001 did not show a benefit in a patient population at elevated risk for an ACS event," Nicholls said. "We will continue to analyze the CARAT data in order to fully understand the study's findings, and we will continue to search for effective therapies targeting residual risk for ACS events."

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