ASSURE study of experimental agent to raise HDL yields 'disappointing and surprising' results

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The search continues for an agent that increases high-density lipoprotein (HDL) and reduces arterial plaque, after the experimental apolipoprotein A1 (apoA1) inducer, RVX-208 failed to do so in the ApoA1 Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation (ASSURE) study.

The lack of efficacy of RVX-208 is "disappointing and surprising, given promising earlier findings," noted lead investigator Stephen Nicholls MBBS, PhD, Deputy Director at the South Australian Health and Medical Research Institute, Professor of Cardiology at the University of Adelaide and Consultant Cardiologist at the Royal Adelaide Hospital in Adelaide, Australia.

However, the failure of RVX-208 to incrementally impact atherosclerotic plaque should not be interpreted as a failure of the hypothesis that increasing the level and activity of HDL could result in this benefit, he said.

"RVX-208 represents the first epigenetic foray into the metabolic treatment of cardiovascular disease, and ongoing clinical trials will evaluate the potential cardiovascular efficacy of other agents that target HDL."

ASSURE was a prospective, randomized, double-blind clinical trial

carried out at 60 centers.

It randomized 323 patients with low HDL and coronary disease who had a target blood vessel for imaging with less than 50% stenosis.

All patients received treatment with either atorvastatin 10-40 mg daily or rosuvastatin 5-20 mg daily during the study and were also randomized to receive either RVX-208 100 mg (n=244) or placebo (n=80) twice daily for 26 weeks.

The primary and secondary outcomes of the study were change from baseline in percent atheroma volume (PAV) and normalized total atheroma (TAV), both measures of the amount of plaque present in the coronary artery.

Intravascular ultrasonography was used at baseline and the end of the study to measure these outcomes.

Of the 281 patients that remained in the study and had this imaging, while a trend towards plaque regression was observed with RVX-208 compared with baseline, there was no significant difference in efficacy outcomes between the groups, said Dr. Nicholls.

However, there were more discontinuations due to adverse events in the RVX-280 group (3.7% vs. 2.5%) as well as significantly more elevations of liver enzymes at triple the normal limit or more (7.0% vs. 0%, P=0.009).

In terms of efficacy, PAV decreased by 0.40% in the RVX-208 group compared to 0.30% in the placebo group (P=0.81) and TAV decreased by 4.2 mm3 vs 3.8 mm3 respectively (P=0.86).

HDL cholesterol increased by 10.9% in the RVX-280 group compared

to 7.7% in the placebo group (P=0.32), and LDL cholesterol decreased by 16.0% vs 17.6% with placebo (P=0.72).

There were no significant differences in cardiovascular events between the groups (13.8% in the RVX-2008 group vs 7.4% in the placebo; P=0.09), and all liver enzyme elevations occurred within the first 2 months of treatment with spontaneous resolution when the study drug was discontinued.

Additionally, the impact of RVX-208 on apoA1 levels from baseline was not significantly different from placebo (P=0.18). The levels increased by 10.6% (P