Evolocumab plus statin triggered plaque regression

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NEW ORLEANS – Adding the PCSK9 inhibitor evolocumab to maximum tolerated statin therapy in subjects with symptomatic coronary disease induced atheromatous plaque regression of a previously unheard-of scale in the phase III GLAGOV trial, Steven E. Nissen, MD, reported at the American Heart Association scientific sessions.

Over 18 months of follow-up, percent atheroma volume was unchanged in patients treated with maximum tolerated statin therapy. But in patients on maximum tolerated statin therapy plus evolocumab, mean atheroma volume decreased by 0.95%.

A reduction in atheroma volume as small as 0.5% has been associated with a reduced rate of cardiovascular events in previous studies, said GLAGOV principal investigator Stephen J. Nicholls, MBBS, PhD, of the University of Adelaide (Australia).

Total atheroma volume was reduced by 5.8 mm^3 with dual therapy, compared with a nonsignificant 0.9-mm^3 decrease in patients on statin monotherapy.

Among 423 patients on statin monotherapy, 47% had regression and 53% had progression of atheroma volume. In contrast, 64% of 423 patients on a statin plus evolocumab had atheroma regressions and 36% had atheroma progression.

"We've never seen levels of atheroma regression of this magnitude in any study previously. This is really quite extraordinary," said Dr. Nissen, chairman of the department of cardiovascular medicine at the Cleveland Clinic and chair of the GLAGOV trial.

What's more, plaque regression was directly related to declines in LDL levels.

"We saw a linear relationship between lower LDL and greater regression with no tailing off of benefit at very low LDL levels. Down to 20 mg/dL, it's continuous and linear," the cardiologist said. "I thought there might be diminishing return at low LDL levels. We don't see that."

GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) was a double-blind, placebo-controlled, randomized trial including 846 evaluable patients with symptomatic CAD at 197 centers. All were on a stable maximum tolerated dose of a statin at baseline, at which point they underwent intravascular ultrasound (IVUS) and were assigned to subcutaneous evolocumab (Repatha) at 420 mg once monthly or placebo injections while continuing on their statin. At 18 months, participants had a follow-up IVUS of the originally imaged target vessel.

The mean LDL cholesterol level was 93 mg/dL at the start of the study. With the addition of evolocumab, the mean LDL level dropped to 37 mg/dL; that's a 60% further reduction below the level on statin alone.

The investigators conducted a post hoc exploratory subgroup analysis confined to 144 patients whose baseline LDL on statin monotherapy was less than 70 mg/dL. In this group, the addition of evolocumab caused the mean LDL level to plunge to 24 mg/dL.

Mean atheroma volume in dual-treatment patients with a baseline LDL below 70 mg/dL decreased by 1.97% – double the reduction seen in the overall statin/evolocumab study arm. Further, 81% of patients on dual therapy who started out with an LDL below 70 mg/dL showed IVUS evidence of plaque regression, compared with 48% of those on statin monotherapy. For those whose baseline LDL level was below 70 mg/dL and who remained on statin monotherapy, there was no change in atheroma volume over time.

No signals of any safety concerns arose in the group on a statin plus evolocumab. Of particular interest, there was no increase in new-onset diabetes, neurocognitive dysfunction, or myalgia in patients given dual therapy, compared with patients on a statin alone.

Discussant Raul D. Santos, MD, said the GLAGOV findings "suggest the start of a new era in lipid management." Dr. Santos, of the University of São Paolo, Brazil, noted that GLAGOV wasn't powered to provide evidence of long-term safety or of hard clinical endpoints such as acute MI. For those outcomes, physicians must await the soon-to-come results of the nearly 28,000-patient FOURIER clinical outcomes trial.

The GLAGOV trial was sponsored by Amgen, the maker of evolocumab.

Dr. Santos reported serving as a consultant to and paid researcher for the company. Dr. Nissen reported serving as a consultant to Amgen and several other companies; any resultant consultant fees are directly paid to charities. Dr. Nicholls reported receiving research support from and serving as a consultant to Amgen and several other drug companies.

The GLAGOV results were published online (JAMA. 2016 Nov 15. doi: 10.1001/jama.2016.16951).

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