American Heart Association (AHA) Scientific Sessions 2014

Promising Treatment for Statin-Intolerant Patients with Very High Baseline LDL-C Levels

Chicago - In the ODYSSEY ALTERNATIVE trial, a PCSK9 inhibitor demonstrated significantly greater LDL-cholesterol (LDL-C) lowering vs. a cholesterol absorption inhibitor after 24 weeks in a statin-intolerant population with very high baseline LDL-C levels. The PCSK9 was well-tolerated, with significantly lower rates of musculoskeletal treatment emergent adverse events than a statin.

Determining Options for Statin-intolerant Patients

Up to 25% of patients have been reported to be statin intolerant, although "personally, over 50% of patients are referred to our clinic as diagnosed with statin intolerance," stated ODYSSEY ALTERNATIVE trial lead investigator and study presenter, Dr. Patrick M. Moriarty, University of Kansas Medical Center, Kansas City. They are a very complex population, very diverse, existing in every practice, he noted. "Unfortunately, there haven't been any large, well-controlled randomized trials of cholesterol-lowering drugs in statin-intolerant patients. The PCSK9 inhibitor alirocumab, currently in development, could be of major benefit for these patients down the road," Dr. Moriarty declared.

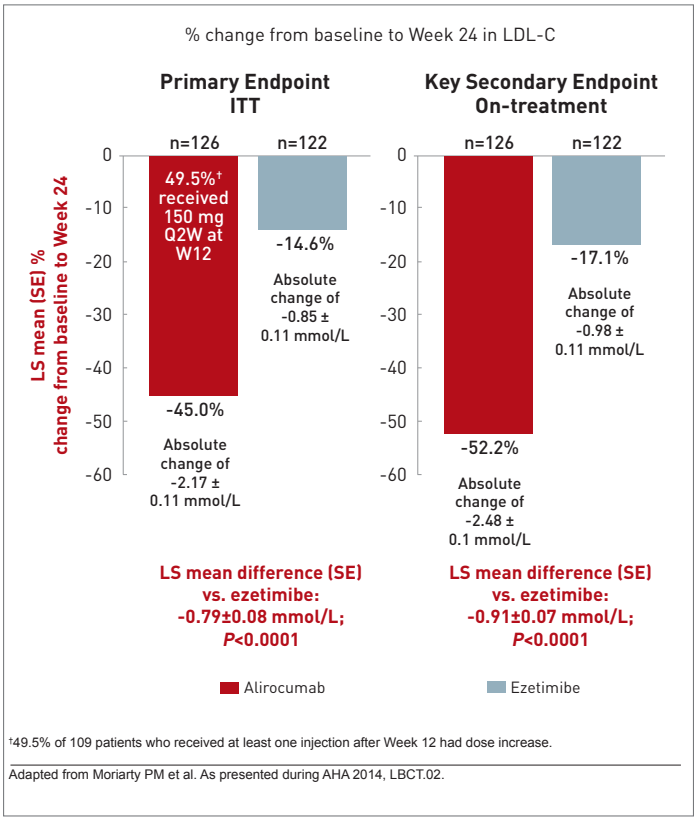
ODYSSEY ALTERNATIVE Trial

The international, multicenter ODYSSEY ALTERNATIVE trial addressed the problem of statin intolerance, which prevents many patients from taking statins and achieving LDL-C goals. It compared alirocumab with ezetimibe, which is recommended as an option for patients with history of statin intolerance due to muscle symptoms (inability to tolerate 2 statins, 1 at the lowest-approved starting dose). Statin intolerance was confirmed after a 4-week placebo run-in and statin rechallenge.

A total of 314 statin-intolerant patients (with CHD/other CV risk factors) were randomized to treatment for 24 weeks with either alirocumab 75 mg sc, self-administered via 1 mL pre-filled pen every 2 weeks, ezetimibe 10 mg/day, or atorvastatin 20 mg/day. The alirocumab dose was increased to 150 mg every 2 weeks at Week 12 depending on CV risk and Week 8 LDL-C level.

Baseline mean LDL-C levels were "extremely high" (4.94- 5.02 mmol/L) in these patients, who included a large proportion with heterozygous familial hypercholesterolemia, type 2 diabetes and a history of coronary heart disease, Dr. Moriarty noted. The PCSK9 produced significantly greater LDL-C reductions vs. ezetimibe at Week 24, the primary endpoint of the study (45.0% vs. 14.6%; *P*<0.0001) on ITT analysis (Figure 1). On-treatment analysis, a key secondary endpoint, showed increased respective reductions in LDL-C (52.2% vs. 17.1% *P*<0.0001). "The difference in effects was consistent between alirocumab and ezetimibe over the 24 weeks of the period."

FIGURE 1 I Significantly Reduced LDL-C from Baseline to Week 24



Adapted from Moriarty PM et al. As presented during AHA 2014, LBCT.02.

Significantly more patients achieved LDL-C goals with alirocumab than with ezetimibe (42% vs. 4%, *P*<0.0001). "This reached over 50% with alirocumab in the on-treatment analysis, where only 6% achieved goal on the ezetimibe arm," Dr. Moriarty reported.

The PCSK9 was better tolerated that atorvastatin (HR 1.63, *P*=0.042) with a significantly lower rate of skeletal muscle adverse events (*P*<0.05).

Almost 80% of randomized patients have entered an ongoing, 3-year open-label extension study, during which all patients receive alirocumab 75 mg every 2 weeks (with possible dose increase to 150 mg at 12 weeks). "At 52 weeks, among these patients that are 100% intolerant to statins, 97% of them have been able to tolerate alirocumab," Dr. Moriarty revealed.

The "incredible difficulty" of treating this population was emphasized by trial discussant, Dr. Karol Watson, David Geffen School of Medicine, UCLA, Los Angeles, CA. "I am very excited about the PCSK9 monoclonal antibody class, and as soon as we see the long-term safety and efficacy studies, I think there is real potential for use," she said.

The ODYSSEY ALTERNATIVE trial is one of 14 ongoing studies in the Phase 3 program with alirocumab, including an outcomes study in over 20,000 patients, Dr. Moriarty noted.