DYSLIPIDAEMIA

Assessing the efficacy and safety of evolocumab and alirocumab

Monoclonal antibodies to proprotein convertase subtilisin-kexin type 9 (PCSK9) have been shown to be effective in lowering LDL-cholesterol levels. The efficacy and safety of the PCSK9 inhibitors evolocumab and alirocumab were assessed in the OSLER and ODYSSEY trials.

Investigators of the OSLER-1 and OSLER-2 trials aimed to obtain long-term data on the safety and efficacy profile of evolocumab in patients completing phase 2 and phase 3 trials, respectively, who had completed the short-term parent trials involving evolocumab. Eligible patients of each trial were randomly assigned to receive evolocumab plus standard therapy, or standard therapy alone. The primary end point of the two trials was the incidence of adverse effects. In total, 1,324 patients were enrolled in the OSLER-1 trial and 3,141 in the OSLER-2 trial. At 12 weeks, evolocumab plus standard therapy, compared with standard therapy alone, reduced LDL-cholesterol levels by 61% (95% CI 59–63, $P < 0.001$). LDL-cholesterol levels were reduced to below 100 mg/dl in 90.2%, and below 70 mg/dl in 73.6% of patients in the evolocumab group, in comparison to 26.0% and 3.8%, respectively, in the standard-therapy group. During a mean follow-up of 11.1 months, the incidence of adverse events was 69.2% and 64.8% for the patients who did and did not receive evolocumab, respectively. The incidence of cardiovascular events at 12 months was lower in the evolocumab group than in the standard-therapy group (0.95% vs 2.18%; HR 0.47, 95% CI 0.28–0.78; $P = 0.003$). Although this analysis was based on a small number of events, the authors reiterate that this was a prespecified but exploratory analysis, and their findings are “consistent with the large reduction in LDL cholesterol levels, the mechanism of action, and the PCSK9 genetic data.”

The ODYSSEY LONG TERM trial was a double-blind study performed to collect long-term data on the safety and efficacy of alirocumab in reducing LDL-cholesterol levels. All participants had LDL-cholesterol levels < 70 mg/dl, were taking statins, and had a high risk of a cardiac event. Participants were randomly assigned to receive alirocumab or placebo, administered subcutaneously, every fortnight for 78 weeks. At week 24, the mean percentage change in LDL-cholesterol levels from baseline was -61% with alirocumab versus 0.8% with placebo; this treatment effect was sustained throughout the 78-week treatment period. Total rates of adverse events were similar for the two groups, but patients receiving alirocumab experienced more injection-site reactions, myalgia, and neurocognitive events. A *post hoc* safety analysis revealed that the incidence of major adverse cardiac events was significantly lower with alirocumab treatment compared with placebo (1.7% vs 3.3%, HR 0.52, 95% CI 0.31–0.90, nominal $P = 0.020$). The authors conclude that “although the ODYSSEY LONG TERM trial followed patients for a longer period than most other trials of PCSK9 inhibitors, the duration of follow-up is still relatively short ... and longer-term studies will be needed.”

Karina Huynh

Marek Uliasz/Stock/ThinkStock

Original articles Sabatine, M. S. *et al.* Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N. Engl. J. Med.* doi:10.1056/NEJMoa1500858 | Robinson, J. G. *et al.* Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N. Engl. J. Med.* doi:10.1056/NEJMoa1501031

CORRECTION**Assessing the efficacy and safety of evolocumab and alirocumab**
Karina Huynh

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In the version of this Research Highlight initially published online, the incidence of cardiovascular events at 12 months for the standard-therapy group was cited as 2.15% instead of 2.18%. This error has been corrected for the print and online versions of the article.