DYSLIPIDAEMIA

1-Year results from OSLER trial of anti-PCSK9 monoclonal antibody evolocumab

The 1-year findings of a randomized, controlled trial of a human monoclonal antibody against PCSK9 were presented at the 2013 AHA Scientific Sessions. After the success of multiple phase II trials in which the effects of anti-PCSK9 monoclonal antibody use for up to 20 weeks (most ≤ 12 weeks) were assessed, the OSLER trial was designed to test the safety and efficacy of longer-term administration of one of these antibodies—evolocumab—in patients with hypercholesterolaemia. The 1-year results of the trial are promising, and longer-term follow-up of the OSLER cohort, as well as ‘hard’ outcome data for long-term PCSK9 inhibitor use, are eagerly awaited.

Evolocumab, previously known as AMG 145, was tested in four phase II trials presented at the 2012 AHA Scientific Sessions—GAUSS, LAPLACE-TIMI 57, MENDEL, and RUTHERFORD. Patients from these phase II trials made up the patient cohort for OSLER. Regardless of their treatment assignment in the 12-week phase II study in which they were initially enrolled, patients were randomly assigned in a 2:1 fashion to standard care plus a subcutaneous injection of 420 mg evolocumab every 4 weeks ($n = 736$), or to standard care alone (the control arm; $n = 368$) in the OSLER trial. Most eligible patients (88%) were assigned to their treatment within 3 days of the patient’s end-of-study visit for the phase II trial. Patients in the evolocumab group visited the study centre every 4 weeks during the OSLER trial. The control group was also followed up every 4 weeks, but only the appointments at weeks 4, 12, 24, 36, 48, and 52 were conducted at the study centre (the remainder were conducted via telephone).

Compared with their baseline measurement at the beginning of the phase II trial in which they participated, patients assigned to the evolocumab group in the OSLER trial demonstrated a 52% reduction in their LDL-cholesterol level,

which was maintained from the initial week 12 measurement to the measurement taken at week 52. In line with this finding, apoB levels fell by about 42% over the 52 weeks, Lp(a) levels were reduced by one-third, and triglyceride levels fell by about 9% in the evolocumab-treated patients. Additionally, at 1 year, levels of HDL cholesterol and apoA1 were increased by about 9% and 4–5%, respectively, in the antibody-treated group. By comparison, the control patients demonstrated a 2–3% reduction in LDL-cholesterol levels over the 1-year period, and changes in the other lipid parameters were also far smaller than those seen in the evolocumab-treated group.

In total, 73.1% of controls and 81.4% of the evolocumab-treated patients experienced adverse events over the 52 weeks; investigators classified 5.6% of all adverse events as being possibly related to evolocumab. Injection-site reactions were reported in 5.2% of the evolocumab group. The rate of serious adverse events was similar for the two treatment groups (6.3% and 7.1% for the control and evolocumab groups, respectively), and none was considered to be possibly related to evolocumab. When presenting the study findings at the AHA Scientific Sessions, Michael Koren highlighted that the broadly similar rates of adverse events occurred “despite the fact that the evolocumab-treated patients had more face-to-face visits, which could arguably increase the reporting rate of adverse events”.

When talking to us about the need for the OSLER trial, John Kastelein (who has been involved in the development of monoclonal antibodies against PCSK9) pointed out that “every lipid-lowering therapy needs to be assessed for longer than the 12-week and 20-week time frames used in phase II studies”. He says this need is especially important in the case of lipid-lowering therapies, because they are usually used for very long periods of time, and drugs that affect metabolism are sometimes associated

with waning effects. Robert Eckel made a similar point when he acted as discussant for the OSLER study at the 2013 AHA Scientific Sessions: “When we think about LDL-lowering therapy, we are thinking about therapy that is going to be sustained [in the] long term”. With regard to the 1-year findings, Eckel said, “1 year is nice, but 1 year is not 20 years or even 5 years, but it is interesting to see that this study is going to be continued for additional time periods”. The total duration of OSLER is anticipated to be 5 years.

John Kastelein is very enthusiastic about the idea of using injections in the setting of secondary prevention, rather than adding another oral drug to the mix. He acknowledges that the therapy will be expensive, but says that injections are “something we really need to get used to in our field,” because they “solve the compliance problem, especially if the injection frequency can be reduced to once every 2 or even 3 months”. “Of course,” he qualifies, “this is if the patient isn’t scared of needles.”

Interestingly, by 12 months, adjudicated cardiovascular clinical events occurred in 1.2% and 2.2% of the evolocumab and control groups, respectively, in OSLER. Whether the promising findings in the OSLER trial will translate into positive outcome data in trials powered to assess hard end points remains to be determined. Robert Eckel assured delegates of the AHA meeting that “three companies making [anti-PCSK9 antibodies]—that’s Amgen, Pfizer, and Regeneron-Sanofi—... have outcome trials that have been designed, and two are actively recruiting”.

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Original article Koren, M. J. et al. Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the open-label study of long-term evaluation against LDL-C (OSLER) randomized trial. *Circulation* doi:10.1161/CIRCULATIONAHA.113.007012