ORION-8: one step closer to understanding the safety and efficacy of inclisiran

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The discovery of the role of proprotein convertase subtilisin/kexin type 9 (PCSK9) as a key regulator of low-density lipoprotein cholesterol (LDL-C) levels has represented a fundamental opportunity for the treatment of patients at high risk of atherosclerotic cardiovascular disease (ASVCD). Since then, several approaches targeting PCSK9 have been developed, including a small interfering RNA (inclisiran) that specifically inhibits the hepatic synthesis of this protein. Inclisiran is administered twice a year and several clinical trials have shown a ~50% reduction in LDL-C levels under various clinical conditions. Therapy with inclisiran has been approved based on its efficacy in reducing LDL-C levels and its safety profile. Inclisiran and monoclonal antibodies differ in their mechanisms of action and pharmacokinetic profiles. Furthermore, the role of PCSK9 in extrahepatic tissues such as the brain, kidney and immune system is not well understood. Inclisiran reduces plasma PCSK9 levels by about 80%, therefore the results of cardiovascular outcome trials may be somewhat different from those of monoclonal antibodies. The demonstration that therapy with inclisiran also reduces the incidence of major adverse cardiovascular events is still awaited and is currently being investigated in the ORION-4, VICTORION-1 Prevent and VICTORION-2 Prevent trials.

The studies published to date on the lipid-lowering effect of inclisiran are of short duration. To determine both the safety and long-term efficacy of treatment with inclisiran, two studies were designed to investigate these two aspects in patients who had participated in the original studies and subsequently participated in open-label extension studies. A pooled analysis of data from 7 clinical trials showed that treatment with inclisiran is well tolerated when administered in combination with other lipid-lowering therapies in patients at cardiovascular risk. Prolonged treatment with inclisiran was safe and was not associated with any specific safety events other than adverse reactions at the injection site.

The ORION-8 trial was run to investigate the effect of long-term administration of inclisiran in patients with elevated levels of LDL-C and high cardiovascular risk. This trial included 3274 patients who had completed 4 previous clinical trials of inclisiran (ORION-3, ORION-9, ORION-10 and ORION-11), with a mean follow-up of 2.6 years (3.7 years if the exposure to inclisiran in the parent trials is included). This trial has the longest cumulative exposure to inclisiran to date, with a maximum of 6.8 years.

The key finding of this study was that the efficacy of inclisiran administered twice a year persisted throughout the observation period. Overall, a 49.4% reduction in LDL-C levels was observed at the end of the study, regardless of whether patients were on placebo or inclisiran in the parent trials. ASCVD patients achieved the largest reduction (-51% compared to -42.4% in patients with ASCVD risk equivalent). The proportion of patients with ASCVD (categorised as very high risk) or ASCVD risk equivalent (categorised as high risk) who achieved the pre-specified LDL-C goals (<70 mg/dL for ASCVD patients and <100 mg/dL for patients with ASCVD risk equivalent) was 79.4% and 74.3% respectively. However, when analysed based on the more stringent LDL-C
goals included in the current ESC/EAS guidelines for these categories of patients (LDL-C <55 mg/dL and <70 mg/dL, respectively), the proportion of patients achieving these goals was 66.3% and 46.6%, respectively. Of note, the mean baseline LDL-C level in the overall population was 112 mg/dL; LDL-C value was 104 mg/dL in ASCVD patients and 147 mg/dL in patients with ASCVD risk equivalent.

By comparison, in the FOURIER-OLE trial, with a median follow-up of 5.0 years (and a maximum exposure of 8.4 years), the median LDL-C level was 30 mg/dL (LDL-C at baseline was ~90 mg/dL), regardless of the original treatment assignment, with 87.3% of patients achieving an LDL-C level <70 mg/dL and 80.3% achieving an LDL-C level <55 mg/dL. Long-term lowering of LDL-C levels with evolocumab was associated with a persistently lower rate of cardiovascular events over a period of more than 8 years. As expected, patients who were randomised to evolocumab in the FOURIER trial had a greater benefit in terms of major cardiovascular events than patients randomised to placebo during the open-label extension trial.

In the ORION-8 study, an exploratory analysis showed that earlier therapy with inclisiran was associated with a lower incidence of treatment-emergent MACE-related safety events. It is encouraging to see that, similar to FOURIER-OLE, the benefit with inclisiran was accrued over time. Although this study was not designed to answer this question, and specific trials evaluating the clinical outcomes in patients treated with inclisiran are ongoing, an indication of clinical benefit deriving from earlier significant LDL-C lowering can be drawn from these observations. Nevertheless, the fact the majority of patients that in this trial were white, male and obese highlights the need for greater diversity in clinical trials.

In summary, the results of the ORION-8 study confirm the long-term safety and efficacy of inclisiran. The results of the outcome trials with inclisiran are awaited to translate sustained LDL-C lowering into cardiovascular protection.

Conflicts of interest

GDN reports grants from Amgen, Novartis, Pfizer; consultant to Amarin, MSD and Viatris. LT reports honoraria or consulting fees from Abbott, Amgen, Astra Zeneca, Bayer, Daiichi Sankyo, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, Pfizer, Ultragenyx
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