AIM-LO: PCSK9 inhibition (mAbs and siRNA): Efficacy & Safety
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Introduction

A major advance over the last few years has been the availability of highly effective LDL-lowering drugs that target PCSK9. PCSK9 is a protein secreted by hepatocytes that interferes with LDL receptor recycling. The fundamental mechanism of action is that decreased levels of PCSK9 will lead to increased recycling of the LDL receptors and therefore greater clearance of LDL-cholesterol from the bloodstream.

Monoclonal Antibodies: Efficacy and Safety

There are two main classes of drugs that target PCSK9, the monoclonal antibodies and, more recently, small interfering RNA. The first two drugs targeting PCSK9 were the monoclonal antibodies or 'mABs,' evolocumab and alirocumab. These drugs are administered by subcutaneous injection every 2 to 4 weeks and both have been shown to lower LDL levels by about 50 to 60%.

Two large outcome studies have been completed with these agents, FOURIER which included over 27,000 patients with stable cardiovascular disease, and ODYSSEY OUTCOMES, which included about 19,000 patients with a relatively recent acute coronary syndrome. Inclusion criteria included an LDL-cholesterol level above 1.8 mmol/L despite treatment with moderate to high dose statin therapy. In both studies, PCSK9 inhibition reduced the primary MACE-plus endpoint by about 15% and also reduced the traditional MACE outcome, MI, stroke, CV mortality, by about 20%. The only notable side effect observed was a small increase in injection site reactions, typically mild erythema or hematoma.

We now have the results of a 5-year open-label extension of FOURIER. After the initial 2 years of the parent trial, all patients received open label evolocumab for an additional 5 years. Patients who received evolocumab during the randomized phase continued to show significant benefits in terms of the MACE-plus and MACE outcomes, and they also had a significant 23% relative reduction in CV mortality. There was no loss of efficacy with regards to the LDL-C lowering, and no new safety signals emerged, even in those patients who achieved LDL levels as low as 0.5 mmol/L.

Inclisiran: Efficacy and Safety

More recently, we've seen the introduction of inclisiran in Canada. Inclisiran is a small interfering RNA molecule that's administered subcutaneously. The inclisiran molecule is bound to an amino sugar derivative called GalNAC, which gives it high specificity for the liver. While inclisiran is cleared from the blood within about 48 hours, it has prolonged action in the liver and this allows for a relatively infrequent dosing schedule with doses at baseline, at 3 months, and only every 6 months thereafter.

We have results from three completed Phase 3 trials with inclisiran in patients with either heterozygous familial hypercholesterolemia or Atherosclerotic Cardiovascular disease. In these trials, inclisiran lowered LCL by an average of about 51% and, once again, the only notable side effect increased relative to placebo was a small increase in local injection site reactions. We don't yet have a completed outcome trial with inclisiran, these trials are underway, but an analysis of pooled Phase 3 data that examined unadjudicated safety events showed a 26% reduction in the rate of cardiovascular events. In another pooled safety analysis that was recently presented at the American College of Cardiology in March 2023, there were no new safety signals that emerged with over 10,000 patient-years of follow-up. Inclisiran's twice-yearly injections provided consistent and persistent LDL-cholesterol reduction over up to about 4 years.

Conclusion

The bottom line is that we now have another class of effective PCSK9 targeted agents that are very helpful for getting the vast majority of our difficult-to-treat patients with known ASCVD or heterozygous FH to LDL cholesterol levels that are well below the current CCS Guideline recommended threshold of 1.8 mmol/L.