PCSK9 inhibitors – Clinical viability and practical considerations

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ABSTRACT

The U.S. Food and Drug Administration and other regulatory bodies recently approved Praluent (alirocumab) and Repatha (evolocumab) for patients with hereditary forms of high cholesterol and those with cardiovascular disease. These drugs belong to a potent new class of injectable LDL-lowering drugs known as PCSK9 inhibitors. Repatha was approved to treat patients with heterozygous familial hypercholesterolemia (HeFH) and patients with the rarer homozygous (HoFH) form of the disease. It was also approved for patients with cardiovascular disease including heart attack or stroke, who require additional cholesterol lowering. The scope of the approval was similar to the approval given to the Regeneron drug, Praluent (alirocumab), which was approved for patients with cardiovascular disease and those with HeFH.

Keywords: PCSK9 inhibitors, Praluent®, alirocumab, Repatha®, evolocumab, LDL, HDL, cholesterol

INTRODUCTION

Statins have been the first-line drugs for lowering cholesterol since the late 1980s. They’ve been shown to prevent repeat heart attacks in people who have already had one and first heart attacks in a wide range of at-risk individuals. In about one in five people, though, a statin doesn’t lower cholesterol enough. Adding a second drug that lowers cholesterol by a different mechanism doesn’t always help. And some people can’t take a statin because of side effects like muscle pain, liver damage, or the development of diabetes.1

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PCSK9 INHIBITORS

Monoclonal antibodies, target and inactivate a specific protein in the liver. Knocking out this protein, called proprotein convertase subtilisin kexin 9, dramatically reduces the amount of harmful LDL cholesterol circulating in the bloodstream. Lower LDL translates into healthier arteries and fewer heart attacks, strokes, and other problems related to cholesterol-clogged arteries. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that plays an important role in lipid metabolism by modulating the density of LDL cholesterol receptors in multiple organs. The enzyme is synthesized in the nucleus, and after intramolecular autoproteolytic cleavage of its N-terminal prosegment in the endoplasmic reticulum, it is secreted from hepatocytes, where it binds to the surrounding LDL cholesterol receptors. The complex is then subject to endocytosis and degradation of its entire structure in lysosomes.2 This physiologic function leads to an inverse relationship between the level of PCSK9 in the blood and the number of LDL receptors; inhibition of PCSK9 prevents LDL receptor degradation within lysosomes and preserves receptor recycling.

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to the hepatocyte surface. Each receptor normally recycles approximately 150 times. Thus, monoclonal antibody binding and inhibition of PCSK9 prevents PCSK9 binding to the LDL cholesterol–LDL receptor complex and subsequent lysosomal degradation of the LDL receptor. The LDL-receptor recycling is preserved, with a consequent increase in receptor density on the hepatocyte surface and LDL cholesterol clearance.

How do they work
PCSK9 is predominantly produced in the liver.1-3 PCSK9 binds to the low density lipoprotein receptor (LDL-R) on the surface of hepatocytes, leading to the degradation of the LDL-R and higher plasma LDL-cholesterol (LDL-C) levels.4,5 Antibodies to PCSK9 interfere with its binding of the LDL-R leading to higher hepatic LDL-R expression and lower plasma LDL-C levels (figure 1).21

There are several strategies to lower free plasma PCSK9, including antisense, silencing ribonucleic acid (RNA), and monoclonal antibody strategies. PCSK9-antibodies are the first of these therapies approved for clinical use. These antibodies are specific for PCSK9 and do not bind to other members of the PCSK enzyme family.7,8 Alirocumab and evolocumab are fully humanized monoclonal antibodies that bind free plasma PCSK9, promoting degradation of this enzyme.9-12 As a result, less free PCSK9 is available in plasma to bind to LDL-R. This results in a higher fraction of LDL-R recycling towards the hepatocyte surface. As a direct consequence, the liver has the capacity to remove more LDL-C from the circulation, resulting in lower LDL-C plasma levels.

Evidence
Results from seven multi-centre, double-blind, placebo- and/or active (ezetimibe)-controlled, randomized phase 3 trials evaluating evolocumab in more than 4,500 patients have been reported.13-19 The co-primary outcomes of five trials were the percent change from baseline in LDL-C at 12 weeks and averaged between weeks 10 and 12 (to more accurately reflect average LDL-C reduction over the entire dosing interval).13-15,19 This bulletin reports data for the treatment difference at 12 weeks. The primary outcomes for the other two trials were percent change from baseline in LDL-C at 12 weeks or at 52 weeks.20

Five of the trials evaluated evolocumab administered at a dose of 140 mg every two weeks or 420 mg every month in patients with primary hypercholesterolemia (non-familial and heterozygous familial hypercholesterolemia) and mixed dyslipidemia.13-15,17,18 A heterogeneous population was assessed in these trials, in which approximately 20% had a history of coronary heart disease and fewer than 50% of participants were considered to be at moderate to high cardiovascular risk at baseline. One trial evaluated evolocumab administered at a dose of 420 mg every month in patients with homozygous familial hypercholesterolemia.19 Approximately 43% of these patients had established coronary artery disease. One trial evaluated evolocumab at a dose of 420 mg every month in patients with a range of cardiovascular risks.15 The majority (64%) of participants in this trial were at low or moderate cardiovascular risk. Patients enrolled in the evolocumab phase 3 clinical program (who were not considered statin intolerant) were not all required to be taking maximally tolerated statin background therapy prior to the addition of evolocumab, which may not be well aligned with the proposed future use of evolocumab in clinical practice.

Adverse Effects
Overall, patients treated with PCSK9 inhibitors had higher rates of nonspecific side effects, such as arthralgia, headache, limb pain and fatigue, compared with placebo-treated patients. Adverse events were reported in 69 percent of people taking evolocumab in the clinical trials. Injection-site swelling or rash, limb pain, and fatigue were some of the reported side effects. Less than one percent reported mental confusion, difficulty focusing, or other neurocognitive issues.8

In the alirocumab trials, adverse events were reported in 81 percent of participants taking the drug. These included injection-site reactions, muscle pain, and eye-related events. Slightly more than 1 percent of participants reported
neurocognitive adverse events. These included memory impairment and confusion. 20

However, clinicians were most concerned about neurocognitive events. Overall, 1% to 1½% of patients experienced treatment-related neurocognitive effects, mainly confusion and some memory loss. However, it’s important to note that the neurocognitive issues were not related to the amount of LDL-C decrease.

CONCLUDING REMARKS

PCSK9 inhibitor monoclonal antibodies have the potential to fill an important treatment gap in patients with harder-to-treat hypercholesterolemia. The results from trials, which mainly focus on surrogate markers of cardiovascular outcomes, showed that PCSK9 inhibitor monoclonal antibodies produce statistically significant reductions in LDL-C regardless of background lipid-lowering therapy. Based on the relatively short-term evidence that is currently available, these drugs appear to be safe, although the FDA has identified a potential signal for neurocognitive adverse effects. Given that cardiovascular disease is still one of the most important causes of death in Canada, despite the availability of statins for 25 years, PCSK9 inhibitor monoclonal antibodies are expected to be rapidly adopted if approved, particularly for patients with harder-to-treat hypercholesterolemia. However, long-term safety and the effect on cardiovascular outcomes remain to be established. Findings from long-term outcomes trials will not be available until 2017 or 2018.

Given the potential broad clinical use of this new drug class, the high price, and the long time frame required for the introduction of less expensive subsequent entry biologics, the introduction of PCSK9 inhibitor monoclonal antibodies may potentially have a substantial budgetary impact on the Canadian health care system. Careful patient selection will be necessary. The requirement to self-administer the drug subcutaneously may also impact long-term patient acceptability and adherence. In order to determine the clinical impact and value of this new drug class on the potentially broad and diverse population of patients with difficult-to-treat hypercholesterolemia, the long-term safety, efficacy, and cost-effectiveness of PCSK9 inhibitor monoclonal antibodies need to be clarified. 22

DISCLAIMER

This article is based on a report by Canadian Agency for Drugs and Technologies in Health. 22

REFERENCES

Commentary


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