Background

In Canada, an estimated 5.2 million adults have hypercholesterolemia, 1.3 million people are living with heart disease, and cardiovascular disease (CVD) is a leading cause of morbidity and mortality.\(^2\) Since increased low-density lipoprotein (LDL) cholesterol (LDL-C) levels predispose patients to cardiovascular disease, lowering of LDL-C is a primary goal.\(^3\) HMG-CoA reductase inhibitors (i.e. statins) are the first-line therapy for lowering LDL-C levels and have been shown to reduce the risk of cardiovascular events.\(^2\)\(^4\)\(^5\) However, some patients on statin therapy are still unable to achieve target LDL-C levels and statin intolerance or concerns regarding adverse effects may limit statin use.\(^3\)\(^6\)

Additionally, patients with familial hypercholesterolemia (FH) are often unable to achieve sufficient LDL-C reduction with statins, even when used in combination with other lipid-lowering therapies.\(^2\) FH occurs due to genetic abnormalities that affect the synthesis, function, or disposition of the LDL-receptor (LDLR), a receptor that normally acts to clear LDL from the circulation, thereby reducing plasma LDL-C.\(^7\)\(^8\) FH can exist in heterozygous (HeFH) or homozygous (HoFH) forms.\(^7\) Approximately 1 in 500 Canadians has HeFH, which can result in LDL-C levels that are 2-3 times higher than normal, whereas HoFH occurs in about 1 in 1 million people worldwide and results in LDL-C elevations 4-8 times over normal values.\(^7\)\(^9\) In patients with untreated HeFH, the likelihood of experiencing a coronary event by 50 years of age is up to 44% in men and 20% in women; atherosclerosis is even more accelerated in patients with HoFH, with the possibility of experiencing CVD manifestations in childhood or adolescence.\(^7\)\(^9\)

The discovery and characterization of proprotein convertase subtilisin/kexin type 9 (PCSK9) in the early 2000s revealed a key regulator of cholesterol homeostasis.\(^10\)\(^11\) PCSK9 interacts with LDLRs resulting in the degradation of these receptors.\(^10\) This led to findings that gain-of-function mutations in PCSK9 can cause autosomal dominant hypercholesterolemia and loss-of-function mutations are associated with low LDL-C levels and decreased CVD risk.\(^10\) Alirocumab and evolocumab are medications with a novel mechanism of action that antagonize PCSK9 and lower LDL-C levels.\(^7\)\(^10\)

Indications

Alirocumab and evolocumab are indicated in adult patients (≥18 years of age) with HeFH or clinical atherosclerotic cardiovascular disease (ASCVD) who need further reduction in LDL-C. Both are indicated as adjunctive therapy to diet and maximally tolerated statin therapy.\(^8\)\(^12\) In addition, evolocumab is indicated in adult and adolescent patients (≥12 years of age) with HoFH who require additional LDL-C lowering; in this population, it is indicated as adjunctive therapy to diet and other LDL-C-lowering therapies (e.g. statins, ezetimibe, LDL apheresis).\(^12\) For both medications, efficacy and safety data in patients over 75 years of age are limited.\(^9\)\(^12\)
Pharmacology

PCSK9 is a protein that helps regulate plasma LDL-C by modulating the density of LDLRs in many organs, particularly the liver. LDLRs act to clear LDL from the circulation. At the surface of hepatocytes, LDLRs bind circulating LDL, leading to intracellular lysosomal degradation of LDL but recycling of the LDLR. LDLR-binding circulating LDL promotes lysosomal destruction of the LDLR itself. Both alirocumab and evolocumab are fully human monoclonal antibodies that bind circulating PCSK9 and prevent its interaction with the LDLR. PCSK9 inhibition prolongs LDLR lifespan and increases the number of LDLRs available to clear LDL, ultimately resulting in a reduction in the plasma LDL-C level.

Pharmacokinetics

Following subcutaneous administration of alirocumab, maximum serum concentration (t_max) is reached in 3-7 days and the absolute bioavailability is approximately 85%. Steady state is reached in 2 to 3 doses. At steady state (with subcutaneous administration of 75 mg or 150 mg every 2 weeks), the median apparent half-life of alirocumab is 17 to 20 days; the half-life is reduced to 12 days when administered concomitantly with a statin. Alirocumab is a protein with expected degradation into peptides and amino acids; therefore, metabolism studies have not been performed. Elimination occurs through saturable binding to PCSK9 (the target) at low concentrations and largely via a non-saturable proteolytic pathway at higher concentrations.

Following subcutaneous administration of evolocumab, t_max is reached in 3-4 days and the absolute bioavailability is approximately 72%. With subcutaneous dosing of evolocumab at 140 mg every 2 weeks or 420 mg monthly, steady state is reached by 12 weeks. The effective half-life is approximately 11 days with biweekly dosing and 17 days with monthly dosing. Catabolic pathways are expected to degrade evolocumab into small peptides and amino acids. Evolocumab is eliminated through saturable binding to PCSK9 (the target) at low concentrations and largely via a non-saturable endogenous immunoglobulin G clearance mechanism at higher concentrations.

Efficacy

Phase 3 clinical trials have evaluated the effect of PCSK9 inhibitors as adjunctive therapy or as monotherapy on LDL-C levels in a variety of patient populations with hypercholesterolemia. Both alirocumab and evolocumab trials showed reductions in LDL-C levels versus placebo at weeks 78 and 124, respectively. A meta-analysis of pooled populations (representing various hypercholesterolemia types) reported lowering of LDL-C by 47% (95% CI = 25% to 70%, P < 0.001) with PCSK9 inhibitor therapy. A greater LDL-C reduction was seen when PCSK9 inhibitors were compared with placebo than when they were compared with ezetimibe. Of note, a phase 3 trial of evolocumab in patients with HoFH (who were also on other lipid-lowering therapies) showed that the efficacy of evolocumab was related to the extent of LDLR function; patients with HoFH who lacked any functioning LDLRs did not respond to therapy.

To determine the applicability of alirocumab or evolocumab studies to specific hypercholesterolemic patient populations, readers can find a summary of individual phase 3 trials in Appendix A (Table A-1) of the CADTH document. For the Treatment of Hypercholesterolemia (download the pdf from: https://www.cadth.ca/dv/pcsk9-inhibitor-monoclonal-antibodies-treatment-hypercholesterolemia).

To date, trials have not sufficiently evaluated long-term efficacy and have not been powered to assess whether these LDL-C reductions translate to improved cardiovascular outcomes. Post hoc analyses and meta-analysis of evolocumab and alirocumab trials suggest favourable cardiovascular outcomes, however, this requires confirmation. Phase 3 trials assessing this endpoint are currently ongoing, with results expected in 2017 and early 2018.

Contraindications, Warnings, Precautions, & Adverse Effects

Both alirocumab and evolocumab are contraindicated in patients who have a hypersensitivity to the active ingredient or to any component of the product’s formulation or container.

Warnings and precautions for PCSK9 inhibitors include that hypersensitivity reactions have occurred. Patients experiencing signs or symptoms of serious allergic reactions should discontinue PCSK9 inhibitor therapy and receive treatment for the reaction and monitoring as necessary. The most common adverse effects observed in clinical trials of PCSK9 inhibitors were:

- **Alirocumab**: Local injection site reactions (e.g., redness, swelling, pain), upper respiratory tract signs and symptoms (e.g., nasopharyngitis, influenza), and pruritus.
- **Evolocumab**: Upper respiratory tract infection, influenza, nasopharyngitis, back pain, arthralgia, and nausea (injection site reactions, urticaria, and rash have also been observed).

For a complete list and explanation of warnings, precautions, and adverse effects, refer to the respective product monographs.
Clinical trials have generally demonstrated short-term safety and tolerability of alirocumab and evolocumab, however, these trials did not have enough participants to detect rare adverse effects and were not of adequate duration to provide long-term safety data.\(^2^{,}10\) Phase 3 trials have not demonstrated adverse events from low LDL-C, however, concerns exist over prolonged low LDL-C levels, including increased risk of neurocognitive adverse effects or hemorrhagic stroke. Long-term trials continue to monitor for these effects.\(^2\)

**Drug Interactions**

Studies have not been performed to evaluate interactions between alirocumab and other drugs, food, herbal supplements, or lifestyle. With concomitant administration of alirocumab and atorvastatin or rosuvastatin, no relevant changes in statin levels were observed.\(^8\)

Like alirocumab, studies have not been performed to evaluate interactions between evolocumab and other drugs. Interactions between evolocumab and food, herbal products, or lifestyle have not been established. With concomitant administration of evolocumab and statins in clinical studies, there was an increase in evolocumab clearance of approximately 20%. However, this increased clearance did not negatively affect the action of evolocumab on lipids and no statin dose adjustment is required when used adjunctively with evolocumab.\(^12\)

**Dosage, Administration, & Monitoring**

Both alirocumab and evolocumab are administered subcutaneously into the thigh, abdomen, or upper arm. Rotation of the injection site is recommended with each injection.\(^8,12\) Alirocumab should not be administered in areas of skin injury or active disease.\(^8\) Evolocumab should not be injected into areas with scars or stretch marks or into skin that is tender, hard, bruised, or red.\(^8,12\) Neither alirocumab nor evolocumab should be co-administered at the same injection site as other injectable medications.\(^8,16\) Detailed administration instructions are available in the respective product monographs.\(^8,12\)

The starting dose of alirocumab is 75 mg subcutaneously once every 2 weeks, which may be increased to a maximum dose of 150 mg subcutaneously every 2 weeks if needed. LDL-C reduction is sufficient for most patients at the 75 mg starting dose. To determine response or the need for dose adjustment, monitor LDL-C level 4 to 8 weeks after starting or changing the dose of alirocumab.\(^8\)

In the treatment of HeFH or clinical ASCVD, the recommended dose of evolocumab is either 140 mg subcutaneously every 2 weeks or 420 mg subcutaneously once per month. For HoFH, the starting dose of evolocumab is 420 mg subcutaneously once monthly, which can be titrated after 12 weeks to 420 mg every 2 weeks if needed. HoFH patients on apheresis may start treatment with 420 mg every 2 weeks (to allow evolocumab to correspond with their apheresis schedule).\(^12\)

For both alirocumab and evolocumab, no dosage adjustment is required for patients with mild to moderate renal impairment, mild to moderate hepatic impairment, or in geriatric patients (however, data are limited in patients >75 years of age). Data are not available regarding the use of these medications in patients with severe renal or hepatic impairment. Dosage adjustment of alirocumab or evolocumab based on body weight is not recommended.\(^8,12\)

**Availability, Storage, & Cost**

Alirocumab is available as a clear, colourless to pale yellow solution for injection in single-use prefilled pens. Pens hold a volume of 1 mL and are available in concentrations of either 75 mg/mL or 150 mg/mL. They are supplied in a pack size of 2 pens per carton. Alirocumab pens should be stored in the outer carton (to protect from light) and in the refrigerator at 2°C to 8°C. They should not be frozen or exposed to extreme heat.\(^8,17,18\)

Evolocumab is available as a clear to opalescent, colourless to yellowish solution for injection in a single-use prefilled autoinjector. The autoinjector holds 1 mL of solution and is available in a concentration of 140 mg/mL. Autoinjectors are supplied in a pack size of 2 per carton. Evolocumab autoinjectors should be stored in the original carton in the refrigerator at 2°C to 8°C. They should be protected from light and temperatures >25°C. They should not be frozen or shaken.\(^12,19\)

For complete composition, storage, and stability information, refer to the respective product monograph.\(^8,12\)

The price of one alirocumab pen (either strength) or one evolocumab autoinjector from a national wholesaler is approximately $295, which is much higher than standard LDL-C-lowering therapies.\(^7\) Neither alirocumab nor evolocumab is a benefit under the Ontario Drug Benefit Program (at the time of this publication).\(^20\)

**Discussion**

Updated recommendations to the Canadian Cardiovascular Society guidelines on the management of dyslipidemia suggest considering the use of alirocumab or evolocumab for LDL-C lowering in patients with ASCVD who do not achieve their LDL-C goal despite maximally tolerated statin (± ezetimibe) therapy. Note that PCSK9 inhibitors as add-on to statin therapy have not been adequately evaluated in patients with diabetes or other comorbidities. Evolocumab is suggested for addition to background therapy in patients with HoFH (and for continued therapy if LDL-C lowering is achieved) and
either PCSK9 inhibitor is suggested for HeFH patients with above-target LDL-C levels despite maximally tolerated statin therapy. These guidelines recognize the present lack of clinical trial cardiovascular outcome data but note that phase 3 efficacy trials showed reduced cardiovascular event trends (although not powered for this outcome).4

Expert consensus from the American College of Cardiology on the role of non–statin therapies for LDL-C lowering states that addition of a PCSK9 inhibitor may be considered in certain patients with clinical ASCVD taking a statin for secondary prevention when LDL-C reduction is not achieved with a maximally tolerated statin plus a non–statin medication (either ezetimibe or a bile acid sequestrant). Replacement of the non–statin medication with a PCSK9 inhibitor may also be considered in this scenario. In patients with primary, severe elevations of LDL-C (i.e., those who are more likely to have HeFH or HoFH) with or without clinical ASCVD, a PCSK9 inhibitor can be added (if needed for further LDL-C lowering) following maximally tolerated statin therapy.21

Guidance from the United Kingdom National Institute for Health and Care Excellence (NICE) recommends evolocumab (at a dosage of 140 mg every 2 weeks) and alirocumab as treatment options for patients with CVD who have primary non–familial hypercholesterolemia or mixed dyslipidemia and high or very high risk of CVD as well as patients with primary HeFH with or without CVD. These recommendations apply only to patients whose LDL-C levels are persistently elevated above pre–specified thresholds despite maximally tolerated lipid-lowering therapy.22,23

Further details pertaining to these recommendations can be found in the respective guidelines.4,21-23

PCSK9 inhibitors are additional therapeutic options for reducing LDL-C. Potential advantages of this novel class include substantial LDL-C lowering ability,3 short-term tolerability and safety, and infrequent administration. The need for subcutaneous delivery is a potential disadvantage and the high costs of alirocumab and evolocumab may limit their use.14 Important data on the long-term safety and efficacy of PCSK9 inhibitors and their effects on cardiovascular morbidity and mortality are currently lacking. Future research is also required to answer questions regarding PCSK9’s other physiologic roles and the implications of long-term inhibition of PCSK9.10

References


19. Amgen Canada Inc. Customer Care. [Verbal communication; 2016 Nov 1]


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