Praluent (Alirocumab): First PCSK9 Inhibitor Approved by the FDA for Hypercholesterolemia

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Coronary heart disease, more often referred to as cardiovascular disease (CVD) today, is a leading cause of illness and death in the United States.[1] Many risk factors contribute to CVD, including age, family history, obesity, lack of physical activity, diet, smoking, high blood pressure, and high blood cholesterol (hypercholesterolemia).[2] Despite the availability of effective preventive strategies, the burden of CVD is expected to increase as the population ages.

Because it is a modifiable risk factor for CVD, the effective management of hypercholesterolemia, specifically low-density lipoprotein cholesterol (LDL-C) levels, has been an important clinical priority. Statins (or HMG-CoA reductase inhibitors) reduce LDL-C levels and the risk for cardiovascular (CV) events in patients with and without CVD.[3-6] This drug class includes atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Generic versions are available for many of these agents.

Compared with moderate-dose statin therapy, high-dose statin therapy further lowers LDL-C levels and reduces the rates of nonfatal CV events.[7-11] However, safety concerns associated with high-dose statin therapy have prompted evaluations of adjunctive lipid-modifying therapies, including niacin and ezetimibe.[12-15] Most recently, a large clinical study, IMPROVE-IT, demonstrated that adding ezetimibe to statin therapy incrementally lowers LDL-C levels and improves CV outcomes in patients who were recently hospitalized for acute coronary syndrome.[16]

In 2013, new guidelines for cholesterol management were developed by the American College of Cardiology (ACC) and American Heart Association (AHA) in conjunction with the National Heart, Lung, and Blood Institute.[17] These guidelines abandoned the use of targets for LDL-C levels, such as <100 mg/dL, citing the absence of data regarding the titration of drug therapy to specific goals.[17]

The ACC/AHA guidelines identify 4 groups of patients for primary and secondary prevention in whom clinicians should focus efforts to reduce CV events (**Table 1**).[17] The recommendations specify the appropriate intensity of statin therapy needed to achieve particular relative reductions in LDL-C.[17]

The ACC/AHA guidelines have not been altered to include specific recommendations regarding the use of ezetimibe or other new adjunctive therapies for patients who do not achieve their LDL-C goals with statins.

Alirocumab Approved for Heterozygous Familial Hypercholesterolemia

On July 24, 2015, the US Food and Drug Administration (FDA) approved alirocumab (Praluent; Sanofi), the first proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor.[18] This novel injectable monoclonal antibody therapy is indicated for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or those with clinical atherosclerotic CVD who require additional lowering of LDL-C as an adjunct to diet and maximally tolerated statin therapy.[18,19] Alirocumab's effects on CV events, including CV morbidity and mortality, have not been determined.[19]

According to John Jenkins, MD, Director of the FDA's Office of New Drugs, Center for Drug Evaluation and Research, "Praluent provides another treatment option for patients with HeFH or with known CVD who have not been able to lower their LDL-C enough on statins."[18]

Mechanism of Action

Alirocumab represents a new class of cholesterol-lowering medications that inactivate a protein in the liver called PCSK9. The relevance of PCSK9 as a biologic target for drug development first emerged when the protein and its gene were identified in 2003.[20] People with genetic mutations that cause a loss of function in PCSK9 have lower plasma levels of LDL-C and are protected from CVD, whereas some patients with familial hypercholesterolemia have a missense or gain-of-function mutation in the *PCSK9* gene.[21]

When PCSK9 binds to low-density lipoprotein receptors (LDLRs) on the surface of liver cells, it promotes the degradation of these receptors by the liver. Because LDLR is the primary receptor that clears circulating LDL, a decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-C.[19]

By preventing the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs that are available to clear LDL and lowers the blood levels of LDL-C.[19]

Dosing and Administration

The recommended starting dose for alirocumab is 75 mg given subcutaneously once every 2 weeks. If the LDL-C response is inadequate, alirocumab can be titrated to 150 mg subcutaneously every 2 weeks, which is the maximum recommended dose.[19]

Within 4 to 8 weeks after initiating or titrating alirocumab therapy, LDL-C levels should be tested to determine the response and the need for (additional) dose adjustments.[19]

Each dose of alirocumab is provided in 2 single-dose forms, including a prefilled pen or an autoinjector and a prefilled syringe. Each form delivers 1 mL of solution in either 75 mg/mL or 150 mg/mL.[19]

Alirocumab should be stored in the refrigerator in the carton to protect from light and be allowed to come to room temperature for 30 to 40 minutes before use.[19]

Clinical Trials

The development program for alirocumab included 5 double-blind placebo-controlled clinical trials.[19] Approximately 3500 patients enrolled in these trials, of whom 54% had nonfamilial hypercholesterolemia and clinical atherosclerotic CVD.[19] A total of 36% of the patients were diagnosed with HeFH.[19]

All patients enrolled were taking maximally tolerated doses of a statin, with or without other lipid-lowering drugs. Each trial lasted for at least 52 weeks. The primary efficacy end point was the mean percent change in LDL-C level from baseline, which was measured at week 24.[19]

Among the 5 studies, 3 used an initial dose of 75 mg of alirocumab every 2 weeks. Criteria-based uptitration to 150 mg every 2 weeks was considered at week 12 for patients who did not achieve their predefined target LDL-C level at week 8. The majority of patients who received alirocumab 75 mg every 2 weeks for at least 12 weeks did not require a higher dose.[19] The other 2 studies evaluated 150 mg of alirocumab be given every 2 weeks.[19]

The average age of the patients ranged from 51 to 63 years, with baseline LDL-C levels ranging from 102 mg/dL to 198 mg/dL.[19]

Table 2 summarizes the efficacy results of the 5 clinical trials. At week 24, the treatment difference (alirocumab minus placebo) in mean LDL-C percent change ranged from –58% to –36%.[19]

The proportion of patients who prematurely discontinued alirocumab therapy before the 24-week end point ranged from 6% to 11% in these 5 clinical trials.[19]

Adverse Events

The safety of alirocumab was evaluated in 2400 patients in 9 placebo-controlled clinical trials.[19] The median duration of treatment with alirocumab was 65 weeks.[19]

The patients' mean age was 59 years, and 60% were men. At baseline, 37% of patients had a diagnosis of HeFH, and 66% had clinical atherosclerotic CVD.[19]

Adverse reactions reported in ≥2% of patients receiving alirocumab and more frequently than in those receiving placebo included nasopharyngitis (11.3%), injection-site reactions (7.2%), influenza (5.7%), urinary tract infection (4.8%), diarrhea (4.7%), bronchitis (4.3%), myalgia (4.2%), muscle spasms (3.1%), sinusitis

Table 1 Target Populations for CVD Prevention Based on the ACC/AHA Cholesterol Guidelines

Target populations of primary and secondary prevention	Recommendations
Patients with clinical atherosclerotic CVD	Use high-intensity statin therapy (ie, rosuvastatin 20-40 mg or atorvastatin 80 mg) to achieve ≥50% reduction in LDL-C, unless otherwise contraindicated
Patients with LDL-C levels ≥190 mg/dL, such as those with heterozygous familial hypercholesterolemia	Use high-intensity statin therapy (ie, rosuvastatin 20-40 mg or atorvastatin 80 mg) to achieve ≥50% reduction in LDL-C, unless otherwise contraindicated
Patients with diabetes aged 40-75 years with LDL-C levels 70-189 mg/dL and no evidence of atherosclerotic CVD	Use moderate-intensity statin therapy (ie, atorvastatin 10-20 mg, simvastatin 20-40 mg, or others) to lower LDL-C by 30%-49%
Individuals without evidence of CVD or diabetes, but with LDL-C levels 70-189 mg/dL, and a 10-year risk for atherosclerotic CVD ≥7.5%	Use moderate-intensity or high-intensity statin therapy (ie, rosuvastatin 20-40 mg or atorvastatin 80 mg) to achieve ≥50% reduction in LDL-C, unless otherwise contraindicated

ACC indicates American College of Cardiology; AHA, American Heart Association; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.
Source: Stone NJ, et al. *J Am Coll Cardiol.* 2014;63(25 pt B):2889-2934.

Table 2 The 5 Clinical Trials Findings: Alirocumab versus Placebo in Patients with Nonfamilial Hypercholesterolemia or with Heterozygous Familial Hypercholesterolemia

Study	Total patients in study, N	Patient type	Average baseline LDL-C, mg/dL	Alirocumab starting dose	Week 24 treatment difference[a]: alirocumab versus placebo: mean LDL-C percent change
Study 1	2341	Non-FH, 69% HeFH, 18%	122	150 mg every 2 weeks	–58% (95% CI, –61% to –56%) *P* <.001
Study 2	316	Clinical atherosclerotic CVD, 84%	102	75 mg every 2 weeks; 17% (of 191 patients receiving alirocumab) uptitrated to 150 mg every 2 weeks at week 12	–43% (95% CI, –50% to –35%) *P* <.001
Study 3 and 4 (pooled)	735	HeFH, 100%	141	75 mg every 2 weeks; 42% (of 469 patients receiving alirocumab) uptitrated to 150 mg every 2 weeks at week 12	–54% (95% CI, –59% to –50%) *P* <.001
Study 5	107	HeFH, 100%	198	150 mg every 2 weeks	–36% (95% CI, –49% to –24%) *P* <.001

[a]Difference of alirocumab minus placebo.
CI indicates confidence interval; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.
Source: Praluent (alirocumab) injection prescribing information; October 2015.

(3.0%), cough (2.5%), contusion (2.1%), and musculoskeletal pain (2.1%).[19]

Adverse reactions led to treatment discontinuation in 5.3% of patients receiving alirocumab and in 5.1% of patients using a placebo.[19] The most common reactions leading to the discontinuation of alirocumab were allergic reactions (0.6%) and elevated liver enzymes (0.3%).[19]

Neurocognitive events. Neurocognitive events were similar in patients receiving alirocumab (0.8%) or placebo (0.7%).[19] However, confusion and memory impairment were noted more often among patients receiving alirocumab (0.2% for both) than in patients receiving placebo (<0.1% for both).[19]

Liver enzyme abnormalities. Liver-related disorders were reported in 2.5% of patients receiving alirocumab and in 1.8% of patients receiving placebo, leading to treatment discontinuation in 0.4% and 0.2% of the patients, respectively.[19] The elevation of serum transaminases to >3 times the upper limit of normal was 1.7% with alirocumab and 1.4% with placebo.[19]

Low LDL-C values. In pooled analyses of placebo-controlled and active-controlled clinical trials, 796 patients receiving alirocumab had 2 consecutive calculated LDL-C values that were <25 mg/dL.[19] A total of 288 patients had 2 consecutive calculated LDL-C values <15 mg/dL.[19] No changes were made to lipid-altering therapy or to alirocumab dosing. Although no very low LDL-C adverse events were identified in these trials, the long-term effects of very low LDL-C levels induced by alirocumab are not known.[19]

Immunogenicity. In a pooled analysis of 10 placebo-controlled and active-controlled trials, 4.8% of patients had newly detected antidrug antibodies after initiating alirocumab treatment compared with 0.6% of patients receiving placebo.[19] Patients with antidrug antibodies were more likely to experience injection-site reactions relative to those without antidrug antibodies (10% vs 6%, respectively).[19]

Among patients treated with alirocumab, 1.2% had neutralizing antibodies on at least 1 occasion but none in the control group.[19] Positive neutralizing antibodies in addition to transient or prolonged loss of efficacy were observed in 0.3% of patients.[19] The impact of long-term alirocumab treatment in the presence of persistent neutralizing antibodies is unknown.[19]

Because immunogenicity data are dependent on the sensitivity and specificity of the assay, as well as other factors, comparing the incidence of antidrug antibodies with alirocumab and with other biologics can be misleading.[19]

Contraindications

The use of alirocumab is contraindicated in patients

who have had a serious hypersensitivity reaction to alirocumab in the past.[19]

Warnings and Precautions

Allergic reactions. Hypersensitivity reactions, such as pruritus, rash, and urticaria, have been reported with alirocumab. Some serious events required hospitalization. Alirocumab should be discontinued if serious allergic reactions occur.[19]

Specific Populations

Pregnancy. There are no adequate studies of alirocumab in pregnant women. Alirocumab should only be used during pregnancy if the potential benefit outweighs the potential risk to the fetus.[19]

Nursing mothers. Whether the components of alirocumab are present in human breast milk is not known. Either nursing or alirocumab should be discontinued based on the importance of the drug to the mother.[19]

Pediatric use. The safety and effectiveness of alirocumab in pediatric patients have not been established.[19]

Geriatric use. In clinical studies, the efficacy and tolerability of alirocumab in older patients (aged ≥65 years) were similar to younger patients.[19]

Renal impairment. No adjustment of alirocumab dosing is needed for patients with mildly or moderately impaired renal function; no data are available regarding patients with severe renal impairment.[19]

Hepatic impairment. No adjustment of alirocumab dosing is necessary for patients with mild or moderate hepatic impairment; no data are available regarding patients with severe hepatic impairment.[19]

Conclusion

Alirocumab is a safe and effective adjunct to diet and maximally tolerated statin therapy in patients who require additional lowering of LDL-C levels. By inhibiting the action of PCSK9 in the liver, this first-in-class injectable drug lowers circulating LDL-C in patients with HeFH or uncontrolled CVD despite maximum-dose statin therapy.

Multiple clinical trials have demonstrated that statins lower the risk for CV events, including myocardial infarction and stroke.[3-6] Post hoc analysis of data from the ODYSSEY LONG TERM study showed that the rate of major adverse CV events (ie, death from CVD, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower for alirocumab compared with placebo (1.7% vs 3.3%, respectively; $P = .02$).[22] Additional efforts are under way to learn the impact of adjunctive alirocumab therapy on the rate of CV events.[22] ■

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