

Update on PCSK9 Inhibitors and New Therapies

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Abstract

Proprotein convertase subtilisin/kexin type 9 (PCSK9), first described in 2003, binds to the low-density lipoprotein receptor (LDLR) resulting in its degradation. Inhibition of PCSK9 results in increased LDLR recycling and a reduction in LDL-cholesterol (LDL-C). The clinical development of monoclonal antibodies (mAbs) that bind to circulating PCSK9 has been rapid with large phase II and III trials demonstrating substantial reductions in LDL-C when given to a very broad group of patients including those with familial and non-familial hypercholesterolemia, diabetes, heart disease, and in those intolerant to statins. Despite sub-cutaneous administration these mAbs are well tolerated and have demonstrated good safety. Two agents, alirocumab and evolocumab, received regulatory approval in 2015 in the US and Europe and evolocumab in 2016 in Japan.

Keywords

PCSK9, low-density lipoprotein (LDL) cholesterol, LDL receptor, cardiovascular disease, familial hypercholesterolemia

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Statins, first approved for general use in 1987 based on their low-density lipoprotein cholesterol (LDL-C) lowering ability, took another decade to demonstrate cardiovascular disease (CVD) benefit.^{1–4} Since 1990 there have been more efficacious statins but only one other modestly effective LDL-C-reducing drug, ezetimibe, has been shown to significantly reduce CVD events compared to statin alone.^{5–8}

There remains an unmet need for patients, many at high CVD risk, who are unable to achieve 'optimal' LDL-C targets with statin therapy, or are intolerant to statins. Two new drugs were approved in 2013–2014 both of which inhibit production of LDL, or its precursor very (V)LDL; mipomersen, an apolipoprotein B antisense agent, and lomitapide, an inhibitor of microsomal triglyceride transport protein.⁹ However their use is strictly limited to the rare orphan population with homozygous familial hypercholesterolemia (HoFH) with prescribing controlled by a Risk Evaluation and Monitoring Strategy in the USA and a 'named patient' program in other countries.⁹ Thus the proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs), alirocumab and evolocumab, approved in late 2015, now provide a new class of drugs which substantially and safely decrease LDL-C.^{10–13}

Proprotein convertase subtilisin/kexin 9 inhibitors

PCSK9 plays a key role in regulating LDL-C clearance by binding to the LDL receptor (LDLR) resulting in its degradation.¹⁴ Loss-of-function (LOF)

mutations resulting in small lifelong LDL-C reductions are associated with a ~40% reduction in CVD risk.^{15,16} In 2006, Legace discovered that circulating PCSK9 interacted with the LDLR providing a rationale for development of mAbs to inhibit PCSK9.¹⁷ The first two PCSK9 mAbs, alirocumab and evolocumab, entered clinical trials in 2009 and have since demonstrated dramatic, rapid and persistent reductions in LDL-C in patients with a wide variety of lipid pheno- and genotypes, comorbidities and on a variety of background therapies.^{18–39} This resulted in both compounds receiving US Food and Drug Administration (FDA) and European Medicine's Agency (EMA) approval in late 2015. evolocumab received approval in Japan in early 2016.^{10–13,40} A third mAb, bococizumab, is still in phase III clinical development.⁴¹

Pharmacokinetic and pharmacodynamics

Following subcutaneous (SC) injection mAbs are rapidly absorbed into the circulation, bind to PCSK9, reducing free PCSK9 and reduce LDL-C within days. At a dose of ~150 mg LDL-C plateaus at roughly 60%, which is maintained for two weeks.^{18,19} A three-fold increase to 420 mg provides no additional LDL-C reduction but does suppress PCSK9 and LDL-C for four weeks.¹⁹

Low-density lipoprotein cholesterol in nonFH patients and influence of background therapy

As statins cause an increase in synthesis and circulating PCSK9, it was suggested that inhibition of PCSK9 would be synergistic when added to

Table 1: US Food and Drug Administration-approved indications, dosing and LDL-C reductions for Alirocumab (Praluent®) and Evolocumab (Repatha®)^{21,22,43}

	Alirocumab (Praluent®)	Evolocumab (Repatha®)
Indications	Primary hyperlipidemia: Indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C	Primary Hyperlipidemia: Indicated as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with HeFH or clinical ASCVD who require additional lowering of LDL-C HoFH: Indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients ≥13 years with HoFH who require additional lowering of LDL-C.
Dosing Instructions	Recommended starting dose is 75 mg SC Q2W. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg Q2W. Measure LDL-C levels within 4 to 8 weeks of initiating or titrating drug, to assess response and adjust the dose, if needed	Recommended dose in patients with HeFH or patients with primary hyperlipidemia with established clinical ASCVD is either SC 140 mg Q2W OR 420 mg Q4W. For the 420 mg dose, give 3 injections within 30 minutes. When switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen. In HoFH the recommended dose is 420 mg Q4W with LDL-C measured 4 to 8 weeks after starting, as response will depend on the degree of LDL-receptor function
LDL-C reductions	75 mg Q2W dose: 48% 150 mg Q4W dose: 60%	140 mg Q2W or 420 mg Q4W: 60% HoFH 420 mg Q4W: 31%
Drug storage and stability	Store refrigerated at 36°F to 46°F (2°C to 8°C) in the outer carton in order to protect from light. Do not freeze. Warm to room temperature for 30 to 40 minutes prior to use. Do NOT use if it has been at room temperature (77°F [25°C]) for ≥24 hours	Store refrigerated at 36°F to 46°F (2°C to 8°C) in the outer carton. Warm to room temperature for ≥30 minutes. The drug can also be kept at room temperature, up to 25°C (77°F) in the original carton but must be used within 30 days.

Extracted and Summarized from references 21,22,43. ASCVD = atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SC = subcutaneous

statins. However, numerous trials performed in patients on diet alone, on existing statin therapy or randomized to various doses of statins have shown PCSK9 mAbs provide a consistent additional 50 to 60% decrease in LDL-C.^{20–39} This implies that there may be a limit to the upregulation of LDLR activity at the higher doses of statins. Included in these trials have been a large number of elderly, diabetics, women, patients with CVD and other CVD risk factors making the results applicable to the likely population in which mAbs will be used.^{20–39}

While mAbs were well tolerated in short-term eight- to 12-week phase II trials, concern remained regarding longer term adherence given that this was the first mainstream SC therapy for lowering LDL-C.^{20–22,29} This was addressed in phase III trials of 52 weeks or longer^{23–28,35,39} which all demonstrated adherence as good as trials with statins, ezetimibe and other oral lipid altering agents.

Three trials in patients unable to tolerate statins have been published or presented, two with evolocumab (GAUSS and GAUSS-2) and one with alirocumab (ODYSSEY Alternative).^{23,31,34} In these studies, the majority of patients were at high or very high risk for CVD and had mean baseline LDL-C of >190 mg/dL emphasizing the significant unmet need for additional effective LDL-C lowering in these patients. In all three of these studies, despite significant reductions in LDL-C of 45 to 63%, muscle adverse effects were uncommon and no more frequent than those seen with ezetimibe.

Familial hypercholesterolemia

In phase I studies in heterozygous (He) FH, both alirocumab and evolocumab demonstrated LDL-C reductions of similar magnitude to that seen in nonFH subjects.^{18,19} This was confirmed in larger phase II trials in HeFH patients already on maximal statin, with or without ezetimibe.^{21,30} Reductions in LDL-C were 60±5% with alirocumab 150 mg once every two

weeks (Q2W) and evolocumab 140 mg Q2W or 420 mg once every four weeks (Q4W).³⁶ In the Rutherford-2 study mutation analysis causing FH was performed and showed similar LDL-C reductions irrespective of LDLR mutation.³⁶ The global phase III alirocumab HeFH trials increased the number of patients and diversity of genetic mutations along with longer duration of therapy and confirmed that the reductions in LDL-C are maintained in the long term.^{24,28,39}

Two trials with evolocumab in HoFH patients have been carried out; In TESLA part A, a small pilot proof-of-concept trial, 8 patients on maximal stable drug therapy were treated with evolocumab 420 mg Q4W for 12 weeks.³⁷ Six patients, with LDLR defective activity, experienced mean reductions in LDL-C of 19.3% while the two patients with LDLR negative activity had no response.³⁷ The definitive phase III randomized, placebo-controlled, double-blind trial, TESLA part B, randomized 50 patients, 12 years or older on maximal statin ± ezetimibe but not apheresis with mean baseline LDL-C of 348 mg/dL.³⁸ After 12 weeks LDL-C decreased by 31% compared to placebo, an absolute reduction in LDL-C of 93 mg/dL. This trial confirmed that the response was dependent on residual LDLR activity, with a 41% reduction seen in those with at least one LDLR defective mutation and a 46% reduction seen in those with two LDLR defective genes.³⁸ Based on these results evolocumab was approved by FDA and EMA for treatment of HoFH.^{11,12}

Effect on lipoprotein(a) and other lipids and lipoproteins

As expected PCSK9 mAbs reduce apolipoprotein B and related lipids and lipoproteins in parallel to LDL-C, along with small reductions in triglycerides and increases in high-density lipoprotein (HDL)-C.⁴² An unexpected effect has been a robust and consistent reduction in lipoprotein(a) (Lp[a]) of 25% to 30% seen with both alirocumab and evolocumab.⁴²

Safety, tolerability and cardiovascular Events

No specific or serious clinical or laboratory adverse events have been identified in the >10,000 patients who have been treated with PCSK9 mAbs for durations of 3+ years.^{20–39} Despite the need for SC injections, they have been well tolerated with few injection site reactions.^{20–39} No physical, psychological, endocrine or reproductive abnormalities or ‘off-target’ effects have been observed in these large trials. Careful examination, by the drug sponsors, and FDA regulators, of patients achieving very low LDL-C levels (<25 or <15 mg/dL) found no differences in adverse events compared to those with higher LDL-C, or those treated with placebo or standard of care.⁴³ However, as with statins, it may take decades of therapy in many thousands of patients to detect more subtle side effects not readily apparent in relatively short term trials.

A recently published predefined exploratory and a post hoc analysis assessing CVD events from two phase III trials with evolocumab and alirocumab respectively showed very similar 50% reductions in CVD events compared to standard of care or placebo.^{34,45} Although the number of events were small, both studies were statistically significant. While these early results are encouraging, definitive CVD outcome trials are already underway and will also address long term safety concerns.^{49–51} Results from the 27,500-patient Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER

NCT01764633), trial comparing evolocumab 150 mg Q2W or 420 mg Q4W added to statin versus statin alone, are expected in late 2016.^{28,39}

Approved indications and annual Cost

In the USA the approved indications (Table 1) are slightly more restrictive than that approved in Europe; both drugs are approved for use in adults with HeFH or clinical atherosclerotic CVD, on maximally tolerated statin therapy who require additional LDL-C lowering. In addition evolocumab is approved for HoFH patients aged 13 or older.^{10,11} The reported list price for alirocumab, 75 mg or 150 mg doses is \$14,600 per year, and for evolocumab 140 mg or 420 mg \$14,100.^{44,45} Actual costs to health insurance payers will likely be significantly less. Thus it is important that they be used only where appropriate, after implementation of maximal tolerable doses of the most efficacious statins, atorvastatin and rosuvastatin, plus ezetimibe.

Conclusion

The PCSK9 inhibitors have shown excellent LDL-C lowering efficacy, good safety and encouraging early CVD results resulting in regulatory approval of a new therapeutic class of drugs which have the potential to surpass the impact of statins. Large CVD outcome trials are due to be completed starting in 2016 and will likely provide impetus for more widespread use of these agents resulting in further reductions in the burden of CVD.^{46,47} ■

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