

Retargeting the management of hypercholesterolemia – focus on evolocumab

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Abstract: Hypercholesterolemia is one of the main risk factors for atherosclerosis and cardiovascular diseases. The treatment is based on the modification of the diet and lifestyle and if necessary on a pharmacological therapy. The most widely used drugs are the inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (statins); nevertheless, many patients do not reach optimal levels of low-density lipoprotein-cholesterol (LDL-C) even with maximal dosage of statins (eventually associated to ezetimibe) or present side effects, which do not allow them to continue the treatment. Inhibitors of PCSK9 represent a new therapeutic approach for lowering LDL-C. Evolocumab and alirocumab are human monoclonal antibodies, which bind to extracellular PCSK9 and thus interfere with the degradation of low-density lipoprotein receptor. Evolocumab use is approved for the treatment of patients with heterozygous familial hypercholesterolemia (FH) and homozygous FH as an adjunct to diet and maximally tolerated statin therapy or for subjects with clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C. Phase III clinical trials have demonstrated the effectiveness of evolocumab (140 mg/every 2 weeks or 420 mg/month, via subcutaneous injection) in monotherapy and in combination with statins, in the treatment of patients intolerant to statins or with FH. In monotherapy, it reduces LDL-C by 55%, and its association with statins leads to a reduction of LDL-C by up to 63%–75%. Evolocumab has been demonstrated to be safe and well tolerated. Ongoing clinical trials are assessing the long-term effects of evolocumab on the incidence of cardiovascular risk, safety, and tolerability. This review resumes the available clinical evidence on the efficacy and safety of evolocumab, for which a relatively large amount of clinical data are currently available, and discusses the retargeting of cholesterol-lowering therapy in clinical practice.

Keywords: PCSK9, hyperlipidemia, evolocumab, LDL-C, familial hypercholesterolemia

Introduction

Current guidelines highlight the importance of maintaining adequate levels of low-density lipoprotein-cholesterol (LDL-C), nonhigh-density lipoprotein-cholesterol (nonHDL-C), and apolipoprotein B100 (ApoB) for the prevention of atherosclerosis and of cardiovascular events,^{1,2} even if the American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not have a target-focused approach.¹ A number of approaches to lower LDL-C have been well studied: these include lifestyle interventions, drugs, and lipid apheresis.

The first recommendation is the lifestyle improvement,² eventually supported by some effective lipid-lowering nutraceuticals.³ Then, statins are the first drugs suggested,² and it has been estimated that statins are able to reduce atherosclerotic cardiovascular disease (ASCVD) risk by 15%–37%, but residual 60%–80% risk still remains and a significant part of this risk is probably related to an insufficient reduction of LDL-C.⁴

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The principle causes of the failure of the treatment are high baseline LDL-C levels, poor compliance, and statin-related side effects, such as muscle symptoms, which concern approximately 5%–29% of patients in clinical practice;^{5,6} moreover, some subjects present a subtherapeutic response to statins or genetic forms of hypercholesterolemia, as familial hypercholesterolemia (FH). This is a major concern because people with FH, which do not have an adequate and effective therapy, have an estimated 13-fold increased risk of cardiovascular events.⁷ Consequently, new therapies are needed to improve the health and the prospect of life of these patients.

Bile acid-binding resins, fibrates, niacin, and ezetimibe have been approved as nonstatin agents for treating dyslipidemia.⁸ However, only ezetimibe has shown a significant decrease of cardiovascular events in hypercholesterolemic subjects, when associated to statins,⁹ as demonstrated by the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), in subjects with high cardiovascular risk and acute coronary syndrome.¹⁰ Other pharmacological treatments have been recently approved: lomitapide, which is a microsomal triglyceride (TG) transport protein inhibitor, and mipomersen, the antisense oligonucleotide against ApoB, have been demonstrated to lower LDL-C and are already approved for treating patients with homozygous FH (HoFH). Nevertheless, there is concern about these drugs because of the increased hepatic fat accumulation due to the inhibition of hepatic very low-density lipoprotein secretion.¹¹

Consequently, researchers have focused their attention on new therapeutic approaches to safely reach optimal cholesterol levels and to reduce cardiovascular events in subjects at high risk of cardiovascular disease.

In the past decade, the PCSK9 gene has been identified as a potential target to lower LDL-C levels;^{12,13} it encodes for PCSK9, which is a serine protease that is expressed prevalently in the liver and is enzymatically inactive following autocatalytic cleavage.¹⁴ When it binds the low-density lipoprotein receptor (LDL-R) extracellularly, the complex PCSK9-LDL-R enters the hepatocyte and is degraded by lysosomes, not permitting the recycling of the receptor; therefore, lower concentrations of PCSK9 lead to increased levels of LDL-Rs on hepatocyte surface and a greater clearance of low-density lipoprotein (LDL) from the circulation. Mutations of PCSK9 with a gain of function decrease the number of LDL-Rs at the hepatocyte surface, causing FH.¹⁵

A promising therapeutic approach is represented by PCSK9 inhibitors, in particular monoclonal antibodies, which

have a great potential due to their ability to bind a selected target with high specificity.¹⁶

Evolocumab is a fully human monoclonal immunoglobulin G2, created through recombinant DNA technology with a structure that binds specifically to PCSK9 in the plasma and interferes with its binding to the LDL-R.¹⁷

Currently, the Food and Drug Administration and the European Medicine Agency have approved evolocumab (Repatha; Amgen Inc., Thousand Oaks, CA, USA) for the treatment of hypercholesterolemia,¹⁸ indicating the treatment in adjunct to diet and maximally tolerated statin therapy in patients with heterozygous FH (HeFH) or HoFH or clinical ASCVD, which require additional lowering of LDL-C.¹⁹

This review discusses the clinical evidence on the evolocumab efficacy and safety, suggesting a possible retargeting of cholesterol-lowering therapy in the clinical practice. The aim is to provide a patient-specific therapy, minimizing side effects and reaching the optimal LDL-C levels in subjects with high cardiovascular risk, besides statin therapy.

Evolocumab: from pharmacokinetic data to Phase III clinical trials

In nonhuman primates, the injection of evolocumab leads to a dose-dependent reduction of LDL-C which is already significant after 3 days and maximal after 10 days from the first dose, with a parallel reduction in ApoB levels.¹³ Its absorption follows nonlinear pharmacokinetics at a dose of 140 mg and linear pharmacokinetics at a dose of 420 mg. After 4 hours from the evolocumab administration, the maximal suppression of unbound plasma PCSK9 can be observed. The evolocumab metabolism follows the immunoglobulin clearance pathways, being degraded to small peptides and individual amino acids.²⁰

The approved doses of evolocumab are subcutaneous (SC) 140 mg every 2 weeks or SC 420 mg once monthly.¹⁸

Phase I clinical studies have shown evolocumab monotherapy to reduce LDL-C by up to 64% in healthy subjects and by up to 81% in hypercholesterolemic patients receiving low-to-moderate doses of statins. Phase II trials have confirmed these results, demonstrating reduction of LDL-C by 40%–80%.²¹ Moreover, significant reductions have also been shown in ApoB, nonHDL-C, TGs, and lipoprotein (a) (Lp[a]), with increases in HDL-C.²²

The lipid-lowering effectiveness of the treatment with evolocumab in addition to statin therapy has been tested in subjects who have not had managed to achieve acceptable LDL levels despite maximum statin therapy. This combination has a great potential because statin therapy contributes

itself to the increase of the expression of PCSK9 gene through the nuclear transcription factor SREBP-2, so the association of a PCSK9 inhibitor as evolocumab and statins may be particularly indicated in clinical practice.²³

The Phase III of LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy (LAPLACE-2) double-blind randomized study has evaluated the effects of evolocumab in association with statin therapy.²⁴ In particular, 1,899 patients with moderate–severe hypercholesterolemia and/or mixed dyslipidemia, after receiving a statin treatment for 4 weeks (statin choices based on cholesterol levels: moderate intensity or high intensity), were randomized into different groups: evolocumab + placebo, ezetimibe + placebo, and placebo only, all in addition to the treatment with statins. At a mean of weeks 10 and 12, evolocumab reduced LDL-C levels by 63%–75% compared to placebo group. Evolocumab also lowered the concentrations of nonHDL-C, ApoB, Lp(a), and TGs ($P < 0.001$ for all). The cases where the side effects have not allowed a continuous treatment with evolocumab were $< 2\%$.²⁴

Phase III of Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2 (MENDEL-2) double-blind randomized trial has evaluated the effects of evolocumab monotherapy in comparison with ezetimibe or placebo. This phase included 614 participants with hypercholesterolemia (LDL-C ≥ 100 and ≤ 190 mg/dL and Framingham risk scores $\leq 10\%$) divided into six groups and treated with SC injection of evolocumab 140 mg biweekly or 420 mg monthly or placebo and ezetimibe.

The reduction of the LDL-C at 12 weeks obtained by the mono-/bi-monthly treatment of evolocumab has been similar ($-55\%/57\%$ in comparison to the placebo group), and has been 38%–40% greater than that observed in the ezetimibe group ($P < 0.001$ for all compared data). A significant reduction ($P < 0.001$) has also been observed in the values of total cholesterol, ApoB, nonHDL-C, ApoB/apolipoprotein A1, Lp(a), and total cholesterol/HDL-C, compared to both placebo and ezetimibe groups.²⁵

Evolocumab effects on patients affected by FH

Evolocumab has also been tested in patients with FH, a relatively frequent genetic disorder based on low plasma LDL clearance.²⁶ Genetic mutations may be present at levels of ApoB, PCSK9, or LDL-R; the majority of subjects with these genetic mutations suffer from HeFH, characterized by markedly increased cardiovascular disease risk.²⁶

Patients with HoFH present more severe hypercholesterolemia (typically 500 mg/dL of LDL-C in untreated subjects) and an extreme risk of premature cardiovascular disease and death;²⁷ in these subjects, the treatment with statins is able to reduce LDL-C by only 25%, due to the impairment of LDL-R function.^{28,29}

The effectiveness of evolocumab has been tested in HeFH patients. The Reduction of LDL-C With PCSK9 Inhibition in HeFH Disorder Study (RUTHERFORD)-2 study involved 331 subjects with HeFH who, after a month of therapeutic statin stabilization, were randomized into four groups in a ratio of 2:2:1:1 (evolocumab 140 mg once every 2 weeks, evolocumab 420 mg monthly, placebo every 2 weeks, and placebo monthly, respectively). The results at 12 weeks showed that patients treated with evolocumab have reached a reduction of serum cholesterol (63%–68% managed to achieve LDL-C < 70 mg/dL), which could not be obtained only with statin therapy (in the placebo group, only 2% of patients had LDL-C < 70 mg/dL). The mean percentage reduction of cholesterol in the evolocumab group was 60% ($P < 0.001$) compared with the levels at baseline. This is very relevant considering that the most part of the enrolled patients had already been treated with maximal statin dose associated with ezetimibe and that the observed effect seems not to be affected by the nature of the patient's LDL-R mutation.³⁰

The Trial Evaluating PCSK9 Antibody in Subjects With LDL-R Abnormalities (TESLA Part B) has evaluated the efficacy of evolocumab in 50 patients with HoFH, as well. After 4 weeks of statin therapy stabilization, patients were randomized into two groups in a 2:1 ratio (evolocumab 420 mg monthly and placebo, respectively). At 12 weeks, patients treated with evolocumab showed a 30.9% reduction of LDL-C (95% confidence interval [CI] -43.9% to -18.0% ; $P < 0.0001$) compared to placebo. In TESLA B, the LDL-C reduction under evolocumab treatment has been proportional to the residual LDL-R function; where there had been a relevant loss of function, the drug efficacy appeared to be less than in all other conditions where it had been tested.³¹

Statins-intolerant patients

Phase III clinical trials have evaluated the potential efficacy and tolerability of evolocumab in monotherapy in patients unable to tolerate statins due to muscle-related or other side effects.^{32,33}

The Phase III Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS-2) double-blind randomized trial has evaluated the effects of

evolocumab monotherapy in comparison with ezetimibe. This study involved 307 participants who had experienced in the past intolerance to at least two or more types of statins.

Patients treated with evolocumab (140 mg every 2 weeks or 420 mg monthly) at the end of 12 weeks showed a reduction of LDL-C by 53%–56%, corresponding to treatment differences, vs 37%–39% reduction by ezetimibe ($P < 0.001$). At 12 weeks, the treatment was completed by 96% of patients with evolocumab and 86% with ezetimibe; the subjects, who had not concluded the treatment, had for the most part side effects (six for evolocumab group and eleven for ezetimibe group). The most common side effect (muscle myalgia) had hit the 12% of the participants treated with evolocumab, a lower percentage than the 23% of patients treated with ezetimibe.³²

The Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS-3) is a two-stage randomized clinical trial including 511 adult patients with uncontrolled LDL-C levels and history of intolerance to two or more statins enrolled in 2013 and 2014 globally. Phase A used a 24-week crossover procedure with atorvastatin 20 mg or placebo to identify patients having symptoms only with atorvastatin but not placebo. In Phase B, after a 2-week washout, patients were randomized to ezetimibe 10 mg daily or evolocumab 420 mg monthly for 24 weeks. Of the 491 patients who entered Phase A, muscle symptoms occurred in 209 of 491 (42.6%) while taking atorvastatin but not while taking placebo. Of these, 199 entered Phase B, along with 19 who proceeded directly to Phase B due to elevated creatine kinase. LDL-C level at week 24 decreased with ezetimibe by -16.7% (95% CI -20.8% to -12.5%) and with evolocumab by -52.8% (95% CI -55.8% to -49.8%) with a between-group difference of -36.1% . Muscle symptoms were reported in 28.8% of ezetimibe-treated patients and 20.7% of evolocumab-treated patients. Active study drug was stopped due to muscle symptoms in five of 73 ezetimibe-treated patients (6.8%) and one of 145 evolocumab-treated patients (0.7%).³³

The main difficulty encountered in trials on statin-intolerant subjects has been the difficulty to correctly define statin intolerance in clinical practice and to define a “real” prevalence of statin intolerance in general population.^{34,35}

In this context, the GAUSS-3 trial has shown that, during the blinded statin–placebo phase, a large number of previously defined statin-intolerant subjects have been able to tolerate atorvastatin 20 mg, while a large number of placebo-treated subjects have claimed muscle-related adverse events. The very high tolerability of PCSK9 inhibitors in

“real” statin-intolerant patients is thus relevant, especially for high-risk patients who need to achieve ambitious LDL-C targets.

Evolocumab middle- and long-term effects on patients at high cardiovascular disease risk

The profile of efficacy, safety, and tolerability of evolocumab in the long term has been the subject of the studies Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES), Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER)-1 (for subjects who completed Phase II of a parent evolocumab trial), and OSLE-2 (for subjects who completed the Phase III). Another objective of these long-term studies has been to analyze the main cardiovascular outcomes and the incidence of cardiovascular events.

In the DESCARTES study, 905 subjects after a pretreatment (from 4 to 12 weeks) based on a dietetic change or a statin/statin and ezetimibe therapy (treatment assigned according to the risk categories delineated by ATP III of the National Cholesterol Education Program) were subjected (due to levels of LDL-C > 75 mg/dL) to a treatment with evolocumab (420 mg/month) or placebo in a 2:1 ratio.

At the end of 52 weeks, patients showed on average a 57% reduction in LDL-C levels ($P < 0.001$). In addition, there was a significant reduction in the levels of ApoB (44.2%), non-HDL-C (50.3%), Lp(a) (22.4%), and TGs (11.5%). HDL-C significantly increased by 5.4%.³⁶

In OSLE-1 and OSLE-2 open-label studies, the safety parameters and side effects of evolocumab have been primarily evaluated, followed by the effectiveness of this active ingredient in the long term. A total of 4,465 patients (from the parent Phase II–III trials) were included in the OSLE program (1,324 in OSLE-1 and 3,141 in OSLE-2) and randomized into two groups in the ratio of 1:2. The first group was treated with standard therapy, and the second with evolocumab plus standard therapy (140 mg every 2 weeks in OSLE-1 and on the basis of patient choice 420 mg/month or 140 mg/every 2 weeks in OSLE-2), and was followed for a median of 11.1 months.

The median LDL-C at baseline before randomization in the parent study was 120 mg/dL. At 12 weeks of OSLE study, evolocumab groups showed a reduction in LDL-C by 61% (median level of LDL-C: 48 mg/dL; $P < 0.0001$), which was similar in both OSLE-1 and OSLE-2 compared to the standard therapy groups. In addition, a significant reduction was observed in the levels of nonHDL-C (52%),

ApoB (47.3%), total cholesterol (36.1%), TGs (12.6%), and Lp(a) (25.5%) ($P < 0.0001$ for all comparisons).³⁷

Another ongoing large long-term study, the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, is involving patients at high cardiovascular risk in statin therapy to assess whether the inclusion of ongoing to standard therapy reduces cardiovascular risk and the number of events in patients with clinically evident vascular disease. The study includes 27,564 patients who have had a cardiovascular event (myocardial infarction, symptomatic peripheral artery, or an ischemic stroke) and who have not reached the target of LDL-C (< 70 mg/dL) and/or nonHDL-C (≤ 100 mg/dL) after > 2 weeks of optimized stable lipid-lowering therapy (at least atorvastatin 20 mg daily or equivalent with or without ezetimibe). The randomized double-blind, placebo-controlled trial (1:1 ongoing 140 mg/every 2 weeks or 420 mg/month vs placebo) will be completed by February 2018.³⁸

The available clinical data, included in the Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations (PROFICIO) project, are used for assessing the long-term effects of ongoing on the incidence of cardiovascular risk, safety, and tolerability. According to data reported by the European Society of Cardiology in August of 2015, on a subanalysis of 3,146 patients, the administration of project (140 mg/every 2 weeks or 420 mg/month) for 10 and 12 weeks has led to a reduction of LDL-C from 56.5% to 74.9% compared to placebo and from 36.9% to 44.9% compared to ezetimibe. A significant reduction ($P < 0.001$) has also been observed in the values of total cholesterol, ApoB, nonHDL-C, Lp(a), and TGs, compared to both placebo and ezetimibe groups. Side effects have been well tolerated and comparable in percentage to placebo.²²

Finally, the Global assessment of plaque regression with a PCSK9 antibody as measured by intravascular ultrasound (GLAGOV) study, a multicenter, randomized, double-blind, placebo-controlled trial, will be the first study to assess the impact of the evolocumab treatment on the coronary atheroma volume (through a serial coronary intravascular ultrasound). Nine hundred and sixty-eight patients with clinical indication for coronary catheterization, randomized 1:1 (into two groups), will receive evolocumab 420 mg/month or placebo for 78 weeks. The GLAGOV study will be important therefore to explore the regression of atherosclerotic plaque as well as to assess the safety profiles and tolerability of the therapy.³⁹

Tolerability and safety

PCSK9 inhibitors are overall well tolerated and safe. The most prevalent adverse events observed in evolocumab Phase II and III trials are resumed in Table 1. Reactions at the injection site were uniform and comparable to placebo (5% for each group).

Nasopharyngitis is usually the relatively most common adverse event observed during use of PCSK9 inhibitors but is usually not associated to an increased risk of treatment interruption. The cause of this phenomenon is yet not fully explained and will require further researches.

Middle- and long-term data from the above-cited trials suggest that incidence of muscular problems in PCSK9 inhibitors-treated patients is usually $< 5\%$ and comparable to the one observed in placebo-treated subjects. From a quantitative point of view, this is a clinically relevant result, considering that statin therapy is related with muscle problems in $\sim 10\%$ – 25% of patients treated.⁴⁰ The prevalence of muscle-related disorders increases when patients previously reporting statin-related side effects are treated with evolocumab but remained always significantly less than the one observed in ezetimibe-treated patients.^{32,33}

In the OSLER trials, side effects were observed in 69.2% of the evolocumab group and 64.8% of the standard therapy group. However, the same percentage of serious side effects was found (7.5%) in both groups. Only 2.4% of patients treated with evolocumab were noncompliant due to side effects. Significant, compared to standard group, neurocognitive events (including delirium confusion, attention and memory disorders, and disorders of thought and perception) were reported by 0.9% of subjects besides the injection-site reactions (4.3%). After 1 year of evolocumab treatment, the rate of cardiovascular events was reduced from 2.18% in the standard therapy group to 0.95% in the evolocumab group ($P = 0.003$).³⁷

Even if available evidence indicate that neurocognitive adverse events may occur more commonly in individuals receiving an antibody to PCSK9, these events are uncommon and have not been associated with on-treatment LDL-C levels. Moreover, it is unclear to what extent closer monitoring of trial participants allocated to PCSK9 inhibitors has led to an ascertainment bias.⁴¹ The specific concern about neurocognitive effects of evolocumab will be deeply investigated in a further large trial, Evaluating PCSK9 Binding antiBody Influence on coGnitive HeAlth in High cardiovascular Risk Subjects (EBBINGHAUS) ([ClinicalTrials.gov Identifier: NCT02207634](https://clinicaltrials.gov/ct2/show/study/NCT02207634)). Participants without dementia or mild cognitive impairment at baseline will be randomized

Table 1 Evolocumab: Phase III clinical trials

Study	Population	Duration of the study/number of participants	Groups	Dosage	Mean % LDL-C reduction	Adverse events
MENDEL-2 (Phase-III) ³⁴	Adult-elderly with Framingham risk score $\leq 10\%$ and LDL-C level ≥ 100 and < 190 mg/dL; statin-untreated patients	12 weeks N=614: 306 evolocumab, 154 ezetimibe, 154 placebo	Evolocumab biweekly + oral placebo, evolocumab monthly + oral placebo, ezetimibe + SC placebo, 10 mg/day SC placebo monthly + oral placebo, SC placebo biweekly + oral placebo	Evolocumab 140 mg biweekly, evolocumab 420 mg monthly, ezetimibe 10 mg/day	Evolocumab 420 mg monthly vs placebo: -57.1% (95% CI -61.1 to -53.1) Evolocumab 140 mg biweekly vs placebo: -54.8% (95% CI -58.5 to -51.1) Evolocumab 420 mg monthly vs ezetimibe: -39.3% (95% CI -43.3 to -35.3) Evolocumab 140 mg biweekly vs ezetimibe: -37.6% (95% CI -41.2 to -33.9)	Leading to discontinuation of study drug: 2.3% (3.2% with ezetimibe, 3.9% with placebo); potential injection-site reactions: 5.2% (4.5% with ezetimibe, 5.2% with placebo); headache: 3.3% (3.2% with ezetimibe; 2.6% with placebo); diarrhea: 2.9% (1.9% with ezetimibe, 3.9% with placebo); potential muscle events: 2.6% (3.2% with ezetimibe, 3.9% with placebo); nasopharyngitis: 2% (3.9% with ezetimibe, 1.9% with placebo)
GAUSS-2 (Phase-III) ³⁵	Adult-elderly on no or low dose-statin, with previous intolerance to two or more statins and 100 mg/dL $>$ LDL-C ≤ 190 mg/dL	12 weeks N=307: 205 evolocumab, 102 ezetimibe	Evolocumab monthly + oral placebo, evolocumab every 2 weeks + oral placebo, ezetimibe + SC placebo every 2 weeks, ezetimibe + SC placebo monthly	Evolocumab 140 mg biweekly, evolocumab 420 mg monthly, ezetimibe 10 mg/day placebo every 2 weeks, ezetimibe + SC placebo monthly	Evolocumab 420 mg monthly vs ezetimibe: -38.1% (95% CI -43.7 to -32.4) Evolocumab 140 mg biweekly vs ezetimibe: -37.6% (95% CI -42.2 to -32.9)	Leading to discontinuation of study drug: 8% (13% with ezetimibe); muscle-related adverse events: 12% (23% with ezetimibe); headache: 8% (9% with ezetimibe); pain in extremity: 7% (1% with ezetimibe); nausea and fatigue: 4% (16.7% with ezetimibe); nasopharyngitis: 3% (3% with ezetimibe); potential injection-site reactions: 3% (8% with ezetimibe); and diarrhea: 2% (7% with ezetimibe)
LAPLACE-2 (Phase-III) ³⁵	Adult-elderly with primary hypercholesterolemia or mixed dyslipidemia (taking statin therapy with or without ezetimibe)	12 weeks N=1,896: 1,117 evolocumab, 221 ezetimibe, 558 placebo	Evolocumab every 2 weeks + oral placebo, evolocumab monthly + oral placebo, SC placebo monthly + oral placebo, SC placebo every 2 weeks + oral placebo, ezetimibe + SC placebo every 2 weeks, 40 mg, rosuvastatin ezetimibe + SC placebo 5 or 40 mg monthly	Evolocumab 140 mg biweekly + atorvastatin 80 mg vs ezetimibe: -47.2% (95% CI -57.5 to -36.9) Evolocumab 140 mg biweekly + atorvastatin 80 mg vs placebo: -76.3% (95% CI -86.9 to -65.7) Evolocumab 140 mg biweekly + rosuvastatin 40 mg vs placebo: -68.3% (95% CI -77.0 to -59.6) Evolocumab 140 mg biweekly + atorvastatin 10 mg vs ezetimibe: -39.6% (95% CI -45.8 to -33.4) Evolocumab 140 mg biweekly + atorvastatin 10 mg vs placebo: -71.4% (95% CI -77.6 to -65.3) Evolocumab 140 mg biweekly + simvastatin 40 mg vs placebo: -70.6% (95% CI -76.7 to -64.4) Evolocumab 140 mg biweekly + rosuvastatin 5 mg vs placebo: -68.2% (95% CI -74.7 to -61.7) Evolocumab 420 mg monthly + atorvastatin 80 mg vs ezetimibe: -38.9% (95% CI -48.2 to -29.6) Evolocumab 240 mg monthly + atorvastatin 80 mg vs placebo: -70.5% (95% CI -79.8 to -61.2)	Leading to discontinuation of a study drug: 1.9% (1.8% with ezetimibe, 2.2% with placebo); serious adverse events: 2.1% (0.9% with ezetimibe, 3.2% with placebo); back pain: 1.8% (3.2% with ezetimibe, 2.5% with placebo); headache: 1.7% (2.3% with ezetimibe, 2.7% with placebo); arthralgia: 1.7% (1.8% with ezetimibe, 1.6% with placebo); muscle-related adverse events: 1.5% (2.7% with ezetimibe, 1.1% with placebo); pain in extremity: 1.5% (1.4% with ezetimibe, 1.3% with placebo); potential injection-site reactions: 1.3% (0.9% with ezetimibe, 1.4% with placebo)	

Table 1 (Continued)

Study	Population	Duration of the study/number of participants	Groups	Dosage	Mean % LDL-C reduction	Adverse events
TESLA (Part B) ³²	≥12 years of age and HoFH with LDL-C ≥132 mg/dL (3.4 mmol/L)	12 weeks N=49: 33 evolocumab, 16 placebo	Evolocumab monthly, placebo monthly	Evolocumab 420 mg biweekly	-32.1% (95% CI -45.1 to -19.2) vs placebo	Leading to discontinuation of a study drug: 0% (0% with placebo); upper respiratory tract infection: 9% (6% with placebo); influenza: 9% (0% with placebo); nasopharyngitis: 6% (0% with placebo); gastroenteritis: 6% (0% with placebo); generalized muscle pain: 3% (0% with placebo) Ongoing
FOURIER ³⁸	Adults with clinical CVD, high risk of recurrent CVD event, and LDL-C level ≥70 mg/dL or nonHDL-C ≥100mg/dL on optimized statin regimen N=27,564; ~13,750 evolocumab, ~13,750 placebo	The trial is planned to continue until at least 1,630 patients experience the secondary end point	Evolocumab every 2 weeks, evolocumab monthly placebo every 2 weeks, placebo monthly	Evolocumab 140 mg	Ongoing	Ongoing
GLAGOV ³⁹	Adult-elderly with coronary heart disease; clinical indication for coronary catheterization; and LDL-C level ≥80 mg/dL, or with additional risk factors, ≥60 and ≤80 mg/dL on statin treatment	78 weeks N=968: 484 evolocumab, 484 placebo	Evolocumab monthly, placebo monthly	Evolocumab 420 mg monthly	Ongoing	Ongoing
GAUSS-3	Adult-elderly with statin intolerance and not at LDL-C goal by NCEP ATP III risk category or with a documented CK elevation >10 ULN on statin experiencing muscle-related symptoms	3 years N=511: ~341 evolocumab, ~170 ezetimibe	Evolocumab + oral placebo, placebo SC + ezetimibe	Evolocumab 420 mg/month, oral placebo daily Placebo SC monthly, ezetimibe daily	Ongoing	Ongoing

EBBINGHAUS	Adult-elderly with clinical CVD, high risk of recurrent CVD event, and LDL-C level ≥ 70 mg/dL or nonHDL-C ≥ 100 mg/dL on optimized statin regimen and without dementia or MCI	4 years	Evolocumab biweekly + statin therapy, evolocumab monthly + statin therapy, placebo SC biweekly + statin therapy, placebo SC monthly + statin therapy	Evolocumab 140 mg biweekly Evolocumab 420 mg monthly Placebo SC monthly Placebo SC monthly Effective statin dose, defined as \geq atorvastatin 20 mg or an equivalent statin	Ongoing	Ongoing
		N=4,000: ~2,000 evolocumab, ~2,000 placebo				

Abbreviations: LDL-C, low-density lipoprotein-cholesterol; SC, subcutaneous; CI, confidence interval; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; CVD, cardiovascular disease; HDL-C, high-density lipoprotein-cholesterol; CK, creatine kinase; ULN, upper limit of normal; MCI, mild cognitive impairment.

in a double-blind, placebo-controlled, multicenter study to evaluate evolocumab + background statin therapy vs statin therapy alone. The primary outcome will be the Spatial Working Memory test, an assessment of executive function. Results are expected in September 2017 with an enrollment of 4,000 subjects.⁴²

Even if Phase III clinical trials have demonstrated the safety of the treatment with evolocumab and the great reduction of LDL-C levels, in particular the association, evolocumab–statins combination raises questions about the potential risk of very low-density lipoprotein-cholesterol concentrations, in particular vitamin E deficiency, hemorrhagic stroke, and impaired steroid hormone synthesis. DESCARTES and OSLER-1 trials evaluated this risk and demonstrated no cases of hemorrhagic stroke in subjects with LDL-C <40 or <25 mg/dL and no increased adverse events between subjects with LDL-C <50 or >50 mg/dL.^{43,44} Even if cholesterol is needed for steroidogenesis, despite the very low level of LDL-C achieved during evolocumab treatment, there have not been found changes in cortisol, estradiol, or testosterone concentrations after dramatic reduction in circulating LDL-C after treatment with evolocumab. Vitamin E levels instead decreased by a mean of 16% because of the involvement of lipoproteins in the transport of liposoluble vitamins; anyhow, when LDL-C concentrations were normalized, vitamin E raised to previous levels.⁴⁵ Moreover, from its discovery, we know that the human LDL-C receptor is saturated for plasma level >25 mg/dL;⁴⁶ this information further supports the safety of extreme LDL-C reduction in most patients.

Discussion

Despite the great success of statin therapy in the treatment of hypercholesterolemia and in prevention of cardiovascular events, some subjects need a different approach. First, a relatively large number of patients needing to reach ambitious LDL-C target such as <70 mg/dL (for instance, diabetics in secondary prevention for cardiovascular disease) are rarely able to reach them with conventional lipid-lowering treatments.⁴⁷ Then, some forms of hypercholesterolemia as HoFH or HeFH require alternative therapies in combination with standard therapy in order to achieve optimal levels of cholesterol goals and reduce the atherosclerotic cardiovascular risk.³¹ Thirdly, a relevant part of patients are intolerant to statin therapy (10%–15%), showing some typical side effects such as myopathy/myalgia and hepatotoxicity.^{48,49} For these subpopulations, it is possible to consider a new therapeutic approach through the PCSK9 inhibitors. However, while patients with myopathy/myalgia have been specifically studied as PCSK9 inhibitors target, the ones with statin-related

liver disorders have been excluded from the most part of the studies so that we have yet no direct safety data on them.

Data about the acceptance and adherence to the treatment with evolocumab are important. In particular, patients showed a good acceptance of the use of an injectable therapy: the 74% of the subjects eligible for the OSLER studies decided to join the treatment, while the 26% did not participate for other reasons than tolerability.³⁷ Moreover, the prolonged dosing intervals contributed to increase the adherence.

The treatment with evolocumab (both 420 mg/month and 140 mg/every 2 weeks) has reported in several scenarios a significant activity in reducing LDL-C (Table 1). In addition, the FOURIER study (ongoing) will give information about the relationship between the reduction of LDL-C levels and the cardiovascular risk. In addition, the FOURIER study (ongoing) will further clarify the relationship between the reduction of LDL-C levels and the cardiovascular risk. The final results of FOURIER study will probably support the known law “the lower is the better” applied to LDL-C reduction.³⁷

Data on safety of evolocumab require confirmations in the long term. To date, only one randomized double-blind study (DESCARTES) has lasted 52 weeks. Other clinical studies had a mean duration of 12 weeks. The use of evolocumab for 12 weeks has been demonstrated to be safe and well tolerated by most of the people involved in the studies; only a small percentage of subjects gave up the therapy. The most common side effects have been injection-site reactions, nasopharyngitis, urinary tract infections, back pain, arthralgia, and headache. Myalgia has been reported in only 2% of the patients and in 12% of subjects who suffered from statins-related myalgia.

The fact that the preliminary data on another fully human antibody against PCSK9, alirocumab, are quite similar both in terms of efficacy and safety supports the above-reported data on the advantage of this new class of drugs.⁵⁰

The effect of PCSK9 inhibitors on other lipid fractions has also to be taken into account. In fact, these drugs, while dramatically reducing LDL-C, are also able to significantly improve the levels of very low-density lipoprotein, TG, HDL-C, and Lp(a). The effect on Lp(a) is of particular interest since the plasma level of this proatherogenic and prothrombotic molecule is mainly genetically determined and resistant to the standard lipid-lowering therapies.⁵¹

The results of long-term trials will also give an answer to the debate about the possible development of neutralizing antidrug antibodies that may lead to a loss of the clinical response to the therapy. Current evidence has demonstrated that only 0.1% of the subjects treated with evolocumab

presented binding antidrug antibodies, but they did not lower the effectiveness.²⁰

It is important to emphasize that the entry of evolocumab in the market could redefine the strategies in current clinical practice. Possible target of evolocumab population are patients with FH, intolerant to statin therapy (to high side effects and/or poor compliance), or those at “high risk” who still need a further reduction of serum cholesterol not obtainable with only classical therapy.

The most important debate to redefine the current clinical practice will be to define classes of subjects with “high” cardiovascular risk, which then require further reduction of serum cholesterol and thus inhibitors of PCSK9 in combination with standard therapy (statin, statin + ezetimibe, or other combinations).

The results of the ongoing trials on the reduction of cardiovascular risk and improvement of the quality of life in the long term may provide further data to also evaluate the cost:benefit ratio. In fact, a great concern about evolocumab is the cost, much higher respect to other lipid-lowering therapies that may limit the use to a very limited group of subjects with restricted criteria for the treatment.⁵² However, a recent cost-effectiveness analysis carried out in the US shows that evolocumab treatment has been associated with both increased cost and improved quality-adjusted life years (QALY) (HeFH: incremental cost: US\$153,289, incremental QALY: 2.02, incremental cost-effectiveness ratio: US\$75,863/QALY; ASCVD: incremental cost: US\$158,307, incremental QALY: 1.12, incremental cost-effectiveness ratio: US\$141,699/QALY; and ASCVD with statin intolerance: incremental cost: US\$136,903, incremental QALY: 1.36, incremental cost-effectiveness ratio: US\$100,309/QALY). Evolocumab has met both the ACC/AHA and World Health Organization thresholds in each population evaluated. Thus, the use of evolocumab in these categories of patients has to be considered cost-effective.⁵³

The use of evolocumab associated with low-dose statins in order to reduce the risk of adverse events in subjects at high risk for adverse events is a possibility as well; however, its cost-effectiveness has yet to be evaluated.

Conclusion

In summary, it is possible to state that evolocumab therapy (both 420 mg/month and 140 mg/every 2 weeks), in monotherapy or associated to statins and/or ezetimibe, significantly reduces the levels of LDL-C (53%–75%) in a large range of patients at very high cardiovascular disease risk, including statin-intolerant subjects and FH patients. Moreover, it parallelly reduces the levels

of ApoB, Lp(a), total cholesterol, and nonHDL-C. Adverse events incidence was comparable to placebo. Its long-term safety with the efficacy on hard cardiovascular outcome reduction is under investigation in the ongoing FOURIER trial.

Disclosure

The authors report no conflicts of interest in this work.

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