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REVIEW ARTICLE

PCSK9 Inhibitors in Hyperlipidemia: Current Status and Clinical Outlook

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Abstract The clinical reality of residual risk despite statin (HMG-CoA reductase inhibitor) therapy and emergence of statin intolerance support the need to develop additional lipid-lowering strategies. Proprotein convertase subtilisin kexin type 9 (PCSK9) has received considerable attention by virtue of genetic and clinical studies that have revealed its pivotal role in the regulation of cholesterol homeostasis. Monoclonal antibodies have been developed targeting PCSK9, which have been demonstrated to produce profound low-density lipoprotein cholesterol (LDL-C) lowering when provided as monotherapy or in combination with statins. With the reports that the PCSK9 inhibitor evolocumab has a favorable impact on both plaque progression and cardiovascular outcomes, these findings begin to translate the benefits of PCSK9 inhibition from lipids to the vessel wall and ultimately to clinical outcomes. The clinical implications for the use of these agents are reviewed in this article.

Key Points

Proprotein convertase subtilisin kexin type 9 (PCSK9) regulates expression of the low-density lipoprotein (LDL) receptor.

Genetic and biochemical studies suggests that lowering PCSK9 activity will favorably decrease LDL cholesterol levels.

More recent trials have demonstrated that PCSK9 inhibitors promote regression of coronary atherosclerosis and reduce cardiovascular events.

1 Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are widely used in clinical practice on the basis of clinical trials that have consistently demonstrated that they reduce cardiovascular event rates in the primary and secondary prevention settings [1]. While the treatment guidelines increasingly emphasize the use of intensive statin therapy for patients at a high risk of cardiovascular events, a number of issues have limited their ability to eliminate cardiovascular risk. Many clinical events continue to occur despite use of intensive statin therapy, suggesting that these agents cannot exclusively eradicate cardiovascular disease [2]. Similarly, the findings that many patients cannot attain treatment goals despite statin treatment [3] and that statin intolerance has become increasingly recognized [4] further support the need for additional approaches to lowering atherogenic lipoprotein levels.

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2 Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) and Regulation of Cholesterol Metabolism

The finding that statins inhibit a key enzyme in the hepatic cholesterol synthesis pathway with consequent upregulation of hepatic expression of the low-density lipoprotein (LDL) receptor not only provides the mechanistic rationale underlying the lipid-lowering action of these agents but also reaffirmed the importance of the LDL receptor in lipid metabolism. This supports observations that familial hypercholesterolemia primarily involves genetic mutations involving LDL receptor expression and function. Initially identified as neural apoptosis regulated convertase-1 (NARC-1) within apoptotic neuronal cells, proprotein convertase subtilisin kexin type 9 (PCSK9) is a serine protease, which plays an important role in regulation of hepatic LDL receptor expression [5]. When the circulating LDL particle binds to the LDL receptor on the liver surface, the whole complex is internalized within the hepatocyte, after which the particle and its constituent cholesterol dissociates, enabling receptor recycling—as opposed to increased receptor synthesis—to the hepatocyte surface, where it can continue to remove LDL particles from the circulation [6]. PCSK9 inhibits this shuttling, thereby limiting surface receptor expression and ultimately removal of circulating LDL particles. While predominantly expressed within the liver and small intestine, PCSK9 has also been identified within the pancreas, adrenal glands, kidneys, and brain [7]. However, it is unknown why it is expressed in these organs and whether it possesses additional functional properties beyond influencing LDL receptor expression.

3 Genetic Evidence Implicating PCSK9 in Lipid Metabolism

A number of lines of evidence from genetic studies support a role of PCSK9 in the regulation of cholesterol levels and potentially cardiovascular risk. Gain-of-function *PCSK9* mutations were identified as the third genetic locus underscoring autosomal dominant familial hypercholesterolemia, in addition to mutations of the LDL receptor and apolipoprotein (apo) B, the major protein found on LDL particles [8]. A number of polymorphisms have been identified resulting in reduced PCSK9 activity [9, 10]. These associate with lower LDL cholesterol (LDL-C) levels and a substantially reduced rate of cardiovascular events [11]. This observation highlights the potential importance of having lower LDL-C levels throughout the life course. Two individuals have been identified with no PCSK9 and very low LDL-C levels, both having grown to adulthood with no evidence of health or fertility problems [12]. More recently, Mendelian randomization approaches have been applied to further delineate the association between *PCSK9* mutations, LDL-C levels, and cardiovascular events [13]. Using this approach, large numbers of individuals with and without *PCSK9* mutations are compared, analogous to a natural randomization to these groups, demonstrating that *PCSK9* mutations do associate with fewer cardiovascular events, with the degree of benefit proportional to the degree of LDL-C reduction. In a short period of time, the molecular biology, lipid biochemistry, and genetics have combined to provide a comprehensive picture suggesting that therapeutic approaches to lowering PCSK9 activity might be an attractive strategy for the development of novel lipid-lowering agents (Fig. 1).

4 Development of PCSK9 Inhibitors

Molecular biology approaches to inhibit the role of PCSK9 in lipid metabolism and atherosclerosis have employed various strategies including use of (1) antisense oligonucleotides [14]; (2) mimetic peptides that competitively inhibit binding of PCSK9 to the LDL receptor [15]; and (3) use of monoclonal antibodies [16]. As the technology of monoclonal antibody production has evolved, it is now possible to produce humanized or fully human antibodies, with much lower rates of immunogenicity than early mouse-based antibodies [17]. This has resulted in the ability to produce PCSK9 antibodies, which should in theory be well-tolerated from an immunological perspective. As a result, a number of clinical development programs have emerged evaluating the clinical effects of humanized (bococizumab, LY3015014) and fully human (alirocumab, evolocumab) PCSK9 antibodies in a range of dyslipidemic settings.

5 Effects of PCSK9 Inhibitors in Dyslipidemia

Each monoclonal antibody has been evaluated in studies administered as either monotherapy or in combination with statin therapy. All require subcutaneous injections, administered either 2-weekly (evolocumab 140 mg; alirocumab 75–150 mg) or monthly (evolocumab 420 mg), resulting in dose-dependent lowering of LDL-C by up to 70% compared with placebo treatment. Similar effects were observed in both monotherapy and statin background settings [18]. The observation that PCSK9 levels are elevated with statin therapy, likely due to lower cholesterol-stimulating sterol regulatory element binding protein (SREBP2), suggests the potential for additional LDL-C

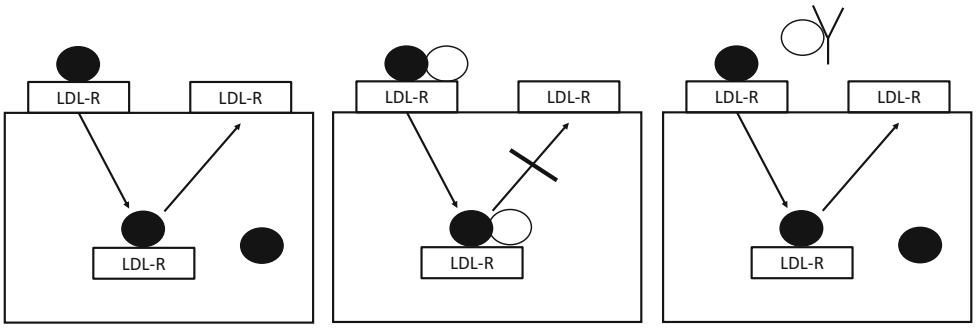

Fig. 1 Mechanistic impact of proprotein convertase subtilisin kexin type 9 (*PCSK9*) and inhibition on low-density lipoprotein (*LDL*) receptor (*LDL-R*) metabolism. *Left panel* the physiological function of the LDL-R is to bind circulating LDL particles (*black circles*). Within the hepatocyte, the LDL-R dissociates and is recycled to the cell surface to promote ongoing LDL uptake. *Middle panel* circulating PCSK9 (*white circle*) binds to the LDL-R/particle complex and is internalized into the hepatocyte, inhibiting dissociation of the LDL-R and recycling to the cell surface. *Right panel* monoclonal antibodies bind PCSK9, preventing their complex with the LDL-R and particle, permitting physiological recycling of the LDL-R to the cell surface and ongoing LDL uptake

lowering when PCSK9 inhibitors are used in combination [19]. It is interesting to note that the lipid effects appear to be additive, rather than synergistic. There appears to be no difference in lipid lowering according to the intensity of background statin therapy [20, 21]. This provides the opportunity for more than 90% of high-risk patients to achieve a treatment LDL-C goal of less than 1.8 mmol/L with a PCSK9 inhibitor in addition to statin therapy. While there is some suggestion of more saw tooth-like LDL-C response with monthly administration, there are currently no data to suggest that this would result in any attenuation of cardiovascular protection [22].

Reductions in apolipoprotein (apo) B, non-high-density lipoprotein cholesterol (HDL-C), and very low-density lipoproteins parallel the decrease observed in LDL-C levels, while variable reports of both modest triglyceride lowering and elevation in HDL-C and apoA-I levels have been demonstrated in some studies. In contrast to statin therapy, the LDL-C lowering with PCSK9 inhibitors is observed in the absence of any effect on circulating levels of C-reactive protein. Of particular interest, lipoprotein a [Lp(a)] levels are also reduced by up to 30% with variable reports that this reflects either a decrease in apo(a) production or increase in Lp(a) metabolism [23–26]. The relative contribution of Lp(a) to any cardiovascular benefit of PCSK9 inhibitors will be important to elucidate given that there is currently no effective Lp(a)-lowering agent in clinical practice that reduces cardiovascular events.

6 Effects of PCSK9 Inhibitors in Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a highly prevalent genetic form of dyslipidemia, with estimates that the heterozygous form is present in 1:250 individuals and the homozygous form in 1:250,000 [27, 28]. While the premature cardiovascular disease in FH could be prevented in many, lipid levels can be difficult to control with conventional therapy. Similar lipid lowering was observed in heterozygous FH patients compared with the studies performed in a more general dyslipidemic population. The RUTHERFORD-2 study, in patients with a baseline LDL-C of 4.1 mmol/L despite statin therapy, demonstrated that evolocumab produced LDL-C lowering by up to 61% over a 12-week treatment period, which enabled up to 68% to achieve a LDL-C goal below 1.8 mmol/L [29]. A similar lowering of LDL-C by up to 61% was observed with alirocumab in the larger ODYSSEY FH1 and FH2 trials, which evaluated treatment for 52 weeks [30].

The impact of PCSK9 inhibitors has also been evaluated in the setting of homozygous FH, where LDL-C levels often remain elevated despite conventional treatment and the risk of premature cardiovascular events is high. The TESLA Part B trial evaluated the impact of evolocumab compared with placebo in patients with a baseline LDL-C of 9.1 mmol/L, despite intensive statin therapy [31]. Treatment for 12 weeks demonstrated a 31% reduction in LDL-C with evolocumab. While such a benefit may seem counterintuitive, given the commonly held view of apparent lack of LDL receptors in homozygous FH, the findings of TESLA not only provide a useful therapeutic strategy for these patients, but also informs about LDL receptor status. Considerable heterogeneity exists amongst homozygous FH patients in terms of the number of expressed LDL receptors. While those expressing no receptors demonstrated no benefit with evolocumab, the presence of some receptors enabled some degree of LDL-C lowering to support its therapeutic use in these patients.

One specific benefit of administering PCSK9 inhibitors in FH patients may involve a potential reduction in use of LDL apheresis. This approach is variably used in some

countries to treat refractory LDL-C and Lp(a) levels in medically managed FH patients. In the ODYSSEY ESCAPE study, administration of alirocumab to heterozygous FH patients who were undergoing regular apheresis, demonstrated that the greater than 50% lowering of LDL-C resulted in a 75% additional reduction in the rate of apheresis treatment, with more than 90% avoiding at least half of the treatments [32]. Given that apheresis is administered every 1–2 weeks in patients, the ability to avoid a significant proportion, if not all, of further treatments has the potential for considerable benefits in terms of fewer complications, improved quality of life, and cost savings.

7 Effects of PCSK9 Inhibitors in Statin Intolerance

Despite the clinical benefits of statin therapy in patients at a high risk for cardiovascular events, many patients ultimately stop therapy [33–35]. While some of this voluntary cessation reflects difficulties adhering with lifelong medical therapy, many of these patients report a range of symptoms attributed to the statin that they are taking that ultimately limits their compliance. While a range of symptoms has been reported in association with statin therapy, the evidence base is strongest supporting an association with myalgia and, uncommonly, myopathy [36]. In fact, up to 20% of patients ultimately report being intolerant to even minimal doses of statins, which has important implications for their ability to effectively reduce their cardiovascular risk [4]. PCSK9 inhibitors have been extensively investigated in patients with documented statin intolerance (GAUSS [Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects] 1–3, ODYSSEY ALTERNATIVE) [37–40]. In these studies, administration of a PCSK9 inhibitor, predictably produced more effective lowering of LDL-C by up to 56% compared with ezetimibe, with no difference in drug discontinuation rates between treatment groups. ODYSSEY ALTERNATIVE, and GAUSS 3 incorporated run-in periods with blind treatment with either placebo or a statin to confirm true statin intolerance. Of particular interest, GAUSS 3, which incorporated a more comprehensive double-blind run-in period, demonstrated that muscle symptoms could be reproduced only with statin therapy in 43% of patients, further highlighting the complexity of managing these patients in clinical practice. While these findings suggest that PCSK9 inhibition may represent a useful strategy in the statin-intolerant patient, challenges limiting a consensus definition for intolerance must be overcome in order to make this a viable therapeutic option in these patients.

8 Effects of PCSK9 Inhibitors on Atherosclerotic Plaque

Advances in plaque imaging permit accurate measurement of plaque burden and composition, with these tools being increasingly employed in clinical trials to evaluate the impact of medical therapies. Studies with serial intravascular ultrasound have consistently demonstrated that LDL-C lowering with statins slows progression of coronary atherosclerosis, with evidence of regression at achieved LDL-C levels <1.8 mmol/L [41, 42]. However, the lowest LDL-C level in any of these studies was 1.5 mmol/L and it was unknown if there would be incremental benefits at much lower levels that could be achieved using the combination of a PCSK9 inhibitor and statin therapy. The GLAGOV (Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial evaluated the impact of adding evolocumab to at least moderate-intensity statin therapy in patients with angiographic coronary disease on plaque progression measured by serial intravascular ultrasound. Achieving an LDL-C level <1 mmol/L with evolocumab and statin therapy produced plaque regression, with evidence of a linear relationship with incremental benefit down to an achieved LDL-C level of 0.5 mmol/L [43]. This finding translates the benefits of PCSK9 inhibition from circulating lipid levels to the artery wall.

9 Effects of PCSK9 Inhibitors on Cardiovascular Events

The ultimate determinant of widespread use of these agents will come from their ability to lower cardiovascular event rates in large outcome trials. Analysis of the longer term lipid studies in lower risk patients demonstrated a substantial reduction in cardiovascular events with both alirocumab and evolocumab. Pooled analysis of the alirocumab studies demonstrated a 24% lower cardiovascular event rate for every 1 mmol/L reduction in LDL-C [44]. This is consistent with the lower rate of cardiovascular events (12.2 vs. 15.3%) with evolocumab in the GLAGOV trial [43].

The first cardiovascular outcomes trials evaluating the effects of PCSK9 inhibitors have been reported. FOURIER (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) is evaluated the impact of evolocumab compared with placebo in more than 27,500 patients with a history of myocardial infarction, stroke, or peripheral artery disease with an LDL-C level >1.8 mmol/L [45]. LDL-C lowering by 59% with evolocumab was associated with a 15% reduction in the primary

composite endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization. The hard ischemic endpoint of cardiovascular death, myocardial infarction, and stroke was reduced by 20% with evolocumab. While FOURIER incorporated a relatively short follow-up period (mean treatment 26 months), there was evidence that the event curves continued to separate with longer exposure [46].

While two additional outcomes trials were conducted (SPIRE [Studies of PCSK9 Inhibition and the Reduction of vascular Events] 1 and 2) in broad high-risk cohorts, these have been terminated on the basis of cessation of the bococizumab development program due to an apparent lack of lipid efficacy subsequent to development of neutralizing antibodies [47]. It is unknown whether the IgG isotype of the monoclonal antibody influences subsequent immunogenicity, given that these differ between individual agents. However, the findings provide further information with regard to the cardiovascular benefits of PCSK9 inhibitors. Both studies were stopped early, with a small number of cardiovascular events recorded. The finding that even in this scenario, SPIRE 2 (baseline LDL-C >100 mg/dL or non-HDL-C >130 mg/dL) demonstrated a significant reduction in cardiovascular events highlights the potential importance of PCSK9 inhibitors in atherosclerotic cardiovascular disease with unacceptably high LDL-C levels, despite use of maximally tolerated statin therapy [48]. The ODYSSEY Outcomes trial is evaluating the effect of alirocumab compared with placebo in more than 18,000 patients with an acute coronary syndrome in the prior 4–52 weeks and an LDL-C level >1.8 mmol/L, with expected completion in 2018 [49] (Table 1).

10 Safety Considerations

While the characterization of the impact of PCSK9 inhibitors on cardiovascular outcomes is critical for determination of how best to use these agents in clinical practice, a comprehensive safety evaluation is equally important. Given potential concerns regarding immunogenicity of monoclonal antibodies, particularly with the humanized forms, it is important to determine whether any of these agents evoke local infusion-site reactions or more systemic effects. Reassuringly, to date this has not proven to be the case. All programs are systematically measuring for the appearance of both binding and neutralizing antibodies, with this proving to be problematic only in the bococizumab program thus far.

These agents, in combination with statin therapy, will reduce LDL-C to much lower levels than previously observed in the lipid field. Post hoc analysis of the statin trials has failed to demonstrate any adverse effect associated with achieving LDL-C levels below 0.6 mmol/L, although this continues to be evaluated in the outcomes trials [50]. While the individuals with no PCSK9 activity are healthy and no overt health issues have been identified in association with *PCSK9* polymorphisms, it will be important to fully characterize safety and tolerability in the setting of therapeutic PCSK9 inhibition. It was therefore reassuring in FOURIER that no safety concerns were observed, particularly with regard to incidence of reports of muscular symptoms, cataracts, or new diagnoses of diabetes mellitus [46]. The most important side effect of interest appears to be neurocognitive function. Despite the finding of an increase in neurocognitive adverse events,

Table 1 Summary of effects of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors on outcome measures used in clinical trials to date

Outcome measure	Comments
Circulating biomarkers	Dose-dependent LDL-C lowering with all agents
	Some saw-tooth pattern in LDL-C lowering with less frequent administration; the clinical implications are uncertain
	Variable lowering of triglycerides
	Lowering of Lp(a)
	No discernible effect on CRP [20, 21]
Atherosclerotic plaque	GLAGOV demonstrated plaque regression with evolocumab added on top of background statin therapy, extending the relationship between LDL-C levels and disease progression/regression to lower levels than previously reported [43]
Cardiovascular events	FOURIER demonstrated reduction in the primary endpoint by 15% and hard ischemic endpoint (CV death, MI, stroke) by 20% with no effect on mortality [45]
	EBBINGHAUS substudy of FOURIER demonstrated no adverse impact on neurocognitive function with evolocumab [52]
	SPIRE 2 demonstrated significant reduction in CV events, despite early termination and low number of events accrued, reinforcing importance of LDL-C lowering in high LDL-C patients [48]
	ODYSSEY Outcomes study continues to evaluate the impact of alirocumab in patients with an acute coronary syndrome in preceding 4–52 weeks [49]

CRP C-reactive protein, *CV* cardiovascular, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein a, *MI* myocardial infarction

reported by investigators, in the longer-term evolocumab study, pooled analyses have failed to replicate this finding [51]. More specific evaluation of executive function using validated assays has been incorporated into the EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) substudy of the FOURIER trial, which demonstrated no impairment of cognitive function with evolocumab compared with placebo, on a background of statin therapy [52].

11 Clinical Perspectives

Over the course of the last 18 months, PCSK9 inhibitors have received regulatory approval in a number of countries. The indication for use consistently includes patients with either FH or atherosclerotic cardiovascular disease with unacceptably high LDL-C levels. Positive findings from the large outcomes trials would be expected to broadly increase their use, particularly if there was the additional finding of a reduction in mortality. While early reports have challenged the cost effectiveness of these agents, these projections have been made in the absence of outcome data and in the setting of high prices in the USA, which varies markedly from pricing in other countries [53]. As data emerge over the course of the next 2 years, the cost-effectiveness modeling is likely to be refined, which will help to more accurately inform how these agents are used in clinical practice. This will be particularly important as evidence from FOURIER suggests greater benefit of evolocumab with increasing duration of treatment.

12 Alternative Approaches

Additional approaches to reduce PCSK9 activity are undergoing development. Selective targeting of a PCSK9 RNA inhibitor directly to the hepatocyte, administered subcutaneously, provides the opportunity to inhibit PCSK9 synthesis, as opposed to the extracellular action of the monoclonal antibodies [54]. Early human studies with this agent confirm preclinical studies that demonstrated not only greater than 50% lowering of LDL-C but also evidence of durability of effect for more than 3 months following each injection [55]. This provides the opportunity for a therapeutic that might only be administered three to four times per year. Given the hepatic delivery of an RNA inhibitor, a comprehensive safety evaluation of this approach will be essential before it can come to the clinic. There continues to be interest in the development of orally ingestible, small-molecule PCSK9 inhibitors, and vaccines, although to date none have advanced to human evaluation.

13 Conclusion

While the statins have produced profound clinical benefit for more than 20 years, there has been an ongoing search for additional therapies to further lower cardiovascular risk. Early experience with PCSK9 inhibitors is promising, although the true efficacy and safety impact of these agents will be provided by the large outcome trials. Only then will we be able to know how best to cost-effectively use these in a broader selection of our patients at high risk for cardiovascular events.

Compliance with Ethical Standards

Conflicts of interest SJN has received research support from Amgen, Anthera, AstraZeneca, Cerenis, Eli Lilly, Novartis, Resverlogix, and Sanofi-Regeneron and is a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Merck, Pfizer, Takeda, Roche, Novartis, and Sanofi-Regeneron. BDB, DJS, AB and PJP have no relationships to be disclosed.

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