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MANAGEMENT OF ACUTE CORONARY SYNDROMES (H JNEID, SECTION EDITOR)

The New Face of Hyperlipidemia and the Role of PCSK9 Inhibitors

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Abstract

Purpose of Review To review the clinical rationale for use of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors in clinical practice.

Recent Findings Despite widespread use of statins for lipid lowering, many patients at high cardiovascular risk continue to demonstrate unsatisfactory cholesterol levels and experience clinical events. This highlights the ongoing need to develop additional strategies to achieve more effective risk reduction in a greater number of patients. Proprotein convertase subtilisin kexin type 9 (PCSK9) plays an important role in the regulation of low-density lipoprotein metabolism. Inhibitory approaches that reduce PCSK9 activity have been demonstrated to produce substantive reductions in LDL cholesterol levels, when administered as either monotherapy or in addition to statin therapy. More recently, PCSK9 monoclonal antibodies have been reported to reduce cardiovascular event rates in large scale clinical trials.

Summary Increasing evidence suggests that PCSK9 inhibitors can produce effective lipid lowering in high risk patients. Ongoing work will identify those patients most likely to derive cost effective risk reduction with their use.

Keywords Lipids · Cardiovascular risk · Clinical trials · PCSK9

Introduction

On the basis of population studies demonstrating a curvilinear relationship between levels of low-density lipoprotein (LDL) cholesterol and cardiovascular risk, increasing attention focused on efforts to treat dyslipidemia [1]. A large number of randomized controlled trials unequivocally found that LDL cholesterol lowering with statins produced cardiovascular benefit in both the primary and secondary prevention setting [2]. More recently, additional, albeit modest, clinical benefit has been observed with the longer term use of ezetimibe, in statin-treated patients [3]. Despite their widespread use and clinical benefits, many patients fail to achieve effective LDL cholesterol lowering [4], while others continue to experience cardiovascular events [5]. Increasing recognition of statin intolerance has the potential to further amplify these clinical challenges [6]. Accordingly, there is an ongoing need to develop additional strategies for effective LDL cholesterol lowering.

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PCSK9 and Lipid Metabolism

Proprotein convertase subtilisin kexin type 9 (PCSK9) plays an important role in the homeostatic metabolism of LDL particles [7]. Physiologic uptake of circulating LDL particles by hepatocytes is facilitated by interaction with the LDL receptor. Within the hepatocyte, the LDL receptor dissociates from the particle, permitting shuttling of the receptor back to the cell surface to continue to remove excess LDL particles. The LDL particle and its cholesterol content are then broken down within lysosomes. Binding of PCSK9 within the circulation to LDL particles prevents intracellular dissociation from the LDL receptor and shuttling to the cell surface. As a result, greater PCSK9 activity associates with higher circulating levels of LDL cholesterol. Additional studies have demonstrated that PCSK9 activity associates with higher levels of lipoprotein (a) (Lp(a)), although the specific mechanism underlying this phenomenon remains to be fully elucidated. [7]

Genetic studies have further clarified the association between PCSK9, LDL cholesterol and cardiovascular risk. Early reports identified gain of function PCSK9 mutations

associated with higher LDL cholesterol levels, establishing PCSK9 as the third locus for autosomal dominant familial hypercholesterolemia, in addition to mutations involving the LDL receptor and apolipoprotein B [8]. A range of polymorphisms have been identified resulting in less PCSK9 activity, with large cohort studies demonstrating lower LDL cholesterol levels and risk of developing coronary heart disease [9, 10]. The proportionally greater reduction in cardiovascular risk per unit of LDL cholesterol supports the concept of lower exposure of the vessel wall to dyslipidemia throughout the life course. Mendelian randomization studies have similarly demonstrated that polymorphisms resulting in less PCSK9 associate with lower rates of cardiovascular risk, when in isolation and in combination with polymorphisms resulting in less hydroxy-methyl-glutaryl coenzyme A reductase, suggesting likely benefit from therapeutic PCSK9 inhibition, whether administered as monotherapy or in combination with statin therapy [11].

PCSK9 Monoclonal Antibodies

The elucidation of the role of PCSK9 function and genetics occurred during a time in which there were technological advances in monoclonal antibody production. This permitted the ability to target factors with great specificity, but also with considerably reduced immunogenicity as technology enabled a transition from mouse to fully human antibody administration. This led to the development of a number of humanized and fully human PCSK9 monoclonal antibodies, requiring administration by subcutaneous injection either every 2 weeks or monthly.

PCSK9 Inhibitors and Plasma Lipids

The emergence of several PCSK9 inhibitory monoclonal antibodies led to the conduct of a number of clinical trials, evaluating the impact of these agents on plasma lipid parameters. These agents, by virtue of their ability to increase hepatocyte LDL receptor expression, regulate LDL-C levels by reducing their systemic concentration, as opposed to limiting cholesterol absorption. Whether administered as monotherapy or in combination with statins, PCSK9 inhibitors produced dose-dependent reductions in LDL cholesterol by up to 60%. This was associated with modest reductions in triglycerides and elevations in high-density lipoprotein (HDL) cholesterol. In addition to their effects on conventional lipid parameters, PCSK9 inhibition treatment resulted in a decrease in Lp(a) by up to 30% [12–17].

This produced LDL cholesterol lowering in a range of clinically important scenarios. The ability to lower LDL cholesterol by 60% in addition to intensive statin therapy permits the opportunity to achieve levels below 40 mg/dL in patients at a high risk of experiencing a cardiovascular event. Patients with familial hypercholesterolemia typically have refractory high LDL cholesterol levels, despite treatment with statins and ezetimibe. Administration of PCSK9 inhibitory monoclonal antibodies produced similar reductions in LDL cholesterol (up to 60%) as observed in patients without genetic dyslipidemia [18, 19]. Reductions by up to 30% were reported in the setting of homozygous familial hypercholesterolemia, with the degree of LDL cholesterol lowering dependent on the presence of some residual LDL receptor activity [20]. This not only permits some degree of lipid lowering in patients who are typically refractory to standard therapy, but in those who require LDL apheresis, PCSK9 inhibition resulted in a reduction in either the overall use or frequency of this procedure.

An additional group who stand to benefit from use of these agents are those unable to tolerate statins. Increasing recognition of statin intolerance in clinical practice is supported by reports that at least 20% of high cardiovascular risk patients may stop therapy or take very low doses [6]. As a result, their LDL cholesterol levels remain unacceptably high for their level of cardiovascular risk. Evaluation in patients, who are demonstrated to have reproducible myalgia type symptoms, observed predictably more effective LDL cholesterol lowering than ezetimibe, with no excess in report of muscle symptoms [14]. This provides the opportunity to achieve more effective risk reduction in patients unable to tolerate statins.

PCSK9 Inhibitors and Atherosclerosis

Prior studies with arterial wall imaging have demonstrated favorable effects of lipid-lowering agents on atherosclerotic plaque burden and progression. A direct relationship was observed between achieved LDL cholesterol levels and disease progression, with evidence of regression with statins when levels decrease below 70 mg/dL [21]. One-third of patients who continue to demonstrate plaque progression with statins, despite achieving LDL cholesterol levels less than 70 mg/dL, have additional risk factors and increases in apolipoprotein B [22]. The later finding suggests that additional lipid lowering in these patients might be beneficial. Given the ability to lower LDL cholesterol to very low levels, PCSK9 inhibitors might produce even greater disease regression in patients already treated with a statin.

The GLAGOV study compared the impact of treatment with evolocumab 420 mg monthly and placebo on progression of coronary atherosclerosis, measured by serial intravascular ultrasound, in patients undergoing clinically indicated coronary angiography on stable statin therapy for at least 4 weeks. Achieving lower LDL cholesterol levels (36 vs 93 mg/dL) associated with a favorable impact on the change in percent atheroma volume (−0.95 vs + 0.05%). A greater proportion of patients treated with evolocumab demonstrated

any degree of plaque regression (64 vs 47%). A direct relationship continued to be observed between achieved LDL cholesterol levels and disease progression, with no evidence of loss of greater benefit at very low levels. Those patients with ongoing disease progression had additional cardiovascular risk factors, supporting findings from the statin literature. In those patients with LDL cholesterol levels less than 70 mg/dL at baseline, even greater regression was observed. Given their need to have additional risk factors for study entry at such low LDL cholesterol levels, it is likely that these patients had more modifiable disease [23••].

A virtual histology substudy within GLAGOV evaluated the impact of evolocumab on plaque components. Increases in plaque calcification were observed in both the group who continued statin monotherapy and in patients treated with the combination of evolocumab and statin therapy. An inverse relationship was observed between achieved LDL cholesterol levels and changes in plaque calcium. The evidence of this relationship with both statin and PCSK9 treatment, suggests that intensive lipid lowering produces plaque regression and calcification, which are likely to stabilize plaque and reduce cardiovascular events [23••].

PSCK9 Inhibitors and Cardiovascular Outcomes

The ultimate impact of these agents will be determined by evaluating their impact on cardiovascular events. A number of clinical trials have been reported since the beginning of 2017 that have demonstrated the cardiovascular benefits of PCSK9 inhibition. The FOURIER study [24••] compared the effects of treatment with evolocumab or placebo on cardiovascular events in patients with prior myocardial infarction, prior stroke or established peripheral arterial disease, treated with a stable dose of statin therapy for at least 4 weeks and evidence of ongoing dyslipidemia (LDL cholesterol > 70 mg/dL or non-HDL cholesterol > 100 mg/dL). Achieving lower LDL cholesterol levels (30 vs 90 mg/dL) was associated with a 15% reduction in the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, coronary revascularization or hospitalization for unstable angina with evolocumab with a median treatment exposure of 2.2 years. A 20% reduction was observed in the key secondary endpoint of cardiovascular death, myocardial infarction, or stroke. Furthermore, significant reductions were observed with analyses that measured both first and total cardiovascular events. This suggested that intensive lipid lowering might be particularly effective in patients at risk of having multiple clinical events. A delay in event curve separation of at least 6 months was observed, with prespecified landmark analyses suggesting greater benefit in patients treated for longer than 12 months. This observation, combined with the report of a direct relationship between LDL cholesterol and event rates to very low levels (including many patients below 10 mg/dL), suggests that treating to very low lipid levels for longer periods is likely to achieve the greatest benefit.

The clinical benefits of evolocumab were accompanied by the observation of no concerning safety findings [24••]. This included no excess in incidence of injection site reactions, no evidence of neutralizing antibodies and no signal of adverse events encountered in the statin literature (myalgia, cataracts, new onset diabetes, neurocognitive dysfunction). The last finding is important, given that an earlier report of pooled longer-term lipid studies suggested a potential signal of more neurocognitive adverse events with evolocumab [25]. This was further supported by a substudy within FOURIER which performed formal neurocognitive testing and reported no change with either evolocumab or in the setting of very low LDL cholesterol levels, including those below 10 mg/dL [26].

The ODYSSEY outcome study [27••] evaluated the impact of alirocumab compared with placebo in statin-treated patients with an acute coronary syndrome in the preceding 1–12 months and a LDL cholesterol greater than 70 mg/dL. The study protocol advised down titration of alirocumab in patients achieving very low LDL cholesterol levels (less than 15 mg/dL). As a result, the difference in achieved LDL cholesterol levels between the groups (53 vs 101 mg/dL) was less on formal intention-to-treat analysis (66 vs 103 mg/dL). This associated with a 15% reduction in the primary endpoint of coronary heart disease death, myocardial infarction, stroke or hospitalization for unstable angina with a median treatment of 2.8 years. An exploratory finding observed a 15% reduction in all-cause mortality. The greatest benefit was observed in those patients with baseline LDL cholesterol levels greater than 100 mg/dL. These benefits were accompanied by no safety concerns.

A third program involving the humanized PCSK9 monoclonal antibody, bococizumab, was terminated due to the incidence of neutralizing antibodies and loss of LDL cholesterol lowering in up to one-third of patients [28, 29]. While the two large cardiovascular outcomes trials were stopped early, the findings of SPIRE-2 are important. In this trial, patients at high cardiovascular risk had to have a LDL cholesterol greater than 100 mg/dL at baseline (mean 130 mg/dL) and demonstrated a significant reduction in events with bococizumab, despite only having accrued 400 clinical events. This suggested that the greatest benefit is likely to be derived in those patients with the highest LDL cholesterol levels.

A number of subgroup analyses from FOURIER and ODYSSEY outcomes have identified patient cohorts with higher event rates, greater absolute risk reductions and therefore potentially smaller numbers needed to be treated to derive clinical benefit. This included patients with diabetes, high risk myocardial infarction (recent event, multiple infarcts, multivessel disease), peripheral arterial disease and elevated

levels of both inflammatory markers and Lp(a) [30–34]. The peripheral arterial disease cohort was noteworthy also for a significant reduction in major adverse limb events (amputation, revascularization), supporting the polyvascular benefits of intensive lipid lowering [34]. The limitation of all of these studies involves their length of follow-up. At best, individual patients were treated for 4–5 years. The impact of PCSK9 inhibitors on both efficacy and safety over much longer periods of time will require observations from long-term follow-up that is occurring in both of these major clinical trials.

Practical Use of PCSK9 Inhibitors in the Clinic

A major challenge with these agents in clinical practice involves their cost, which is often the case encountered with novel biologic therapies. Early projections have suggested that widespread use of these agents at their current costs are unlikely to be cost-effective [35, 36]. As a result, there is a need to find a balance between lower cost of agent and identifying patient cohorts who are more likely to derive clinical benefit. In addition to the setting of familial hypercholesterolemia, where a strong economic argument can be made for their use, the subgroup findings of the outcome trials suggest a number of groups, in which they may be more cost-effective. Whether this requires simply meeting those criteria or the development of specific risk algorithms remains unknown. It is also possible that arterial imaging may be of use in identifying patients who are likely to derive the most benefit, although this has not been evaluated to date. Whether short-term administration of these agents, followed by monotherapy with intensive statin therapy, would be of long-term benefit has not been tested. Although, the finding that more extensive treatment is required in the non-acute setting may provide an argument against this concept. These agents have not been formally evaluated in the acute coronary syndrome setting. It is important to note that it was only in that setting that statin administration resulted in early event curve separation. Accordingly, this presents a clinical setting in which PCSK9 inhibitors should be evaluated.

Additional Approaches to PCSK9 Inhibition

Intensive efforts continue to investigate alternative strategies to achieve PCSK9 inhibition by reducing its synthesis. This intracellular approach is in contrast to the circulatory site of action of targeting existing PCSK9 with monoclonal antibodies. The most advanced intervention to date involves hepatic-targeted RNA synthesis inhibition, with early studies in humans demonstrating LDL cholesterol lowering up to 53% with inclisiran. The most striking effects of this approach lies in the durability of its LDL cholesterol, creating a scenario in which injections might only be required two to three times per year [37]. Larger, long-term studies are required to evaluate the impact of this therapy on cardiovascular outcomes and safety.

Conclusion

PCSK9 inhibition has evolved as an effective strategy for lowering LDL cholesterol, whether administered as monotherapy or in combination with statins. This has the potential to achieve greater reductions in cardiovascular risk. The challenge will be how to identify the most cost-effective scenarios for their clinical use.

Compliance with Ethical Standards

Conflict of Interest Stephen J. Nicholls has received research support from AstraZeneca, Amgen, Anthera, Athernova, CSL Behring, Cerenis, Eli Lilly, Esperion, Resverlogix, Novartis, InfraReDx and Sanofi-Regeneron; and is a consultant for Amgen, AstraZeneca, Boehringer-Ingelheim, CSL Behring, Eli Lilly, Esperion, Kowa, Merck, Omthera, Roche, Takeda, Pfizer, Sanofi-Regeneron and Novo Nordisk.

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