Antibodies to PCSK9
A Superior Way to Lower LDL Cholesterol?

Kara N. Maxwell, Jan L. Breslow

Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol
Stein et al

Lowering of LDL cholesterol, predominantly accomplished clinically by statins, is one of the key components of both the prevention and medical management of coronary atherosclerosis; however, additional or alternative cholesterol lowering agents are needed for patients who fail to achieve goals or have adverse effects on statins. Owing to relatively rapid translation of basic science research on a novel regulatory pathway of the LDL receptor by PCSK9, a new class of such drugs with a different mode of action, and potentially better tolerance and less off-target effects may be just over the horizon.

Proprotein convertase subtilisin/kexin 9 (PCSK9) binds to LDL receptors, resulting in their accelerated degradation and increased LDL cholesterol levels. In a recent New England Journal of Medicine article, Stein et al reported the use of a monoclonal antibody (REGN727) to PCSK9 with the goal of lowering LDL cholesterol levels in 3 randomized double-blind placebo controlled phase I studies. The first 2 studies were single-dose escalation studies performed in healthy volunteers, 1 by the intravenous and the other by the subcutaneous route, and each led to dose-dependent reductions in LDL cholesterol levels (28%–65% and 32%–46%, respectively) that were rapid and prolonged. The third study was a multiple-dose escalation study, with drug delivered subcutaneously on days 1, 29, and 43, performed in patients with familial hypercholesterolemia (FH) and non-FH receiving atorvastatin and a small group of 10 patients with non-FH carriers appeared otherwise healthy.

The discovery of the PCSK9 gene and its role in LDL metabolism provides a clear example of the power of modern techniques in genetics and genomics and the current rapidity of translational science. Less than 10 years ago, 3 laboratories reported the identification of the PCSK9 gene using large-scale gene discovery techniques. Nabi Seidah’s laboratory cloned the PCSK9 gene (then called \( \text{Narcl} \)) as a result of a proteomics project, and, simultaneously, PCSK9 was identified as a gene involved in cholesterol metabolism in mice by large-scale gene expression studies in Jay Horton’s laboratory and our own.2–4 The key piece of translational data came that same year from studies of families with autosomal dominant hypercholesterolemia in which no mutation could be found in the LDL receptor or apolipoprotein B, the 2 known causative genes in this disease. By exon sequencing of genes in a narrowed locus interval in their French autosomal dominant hypercholesterolemia families, Catherine Boileau’s laboratory found a substitution in the PCSK9 gene.5 These were the sole 4 papers published on PCSK9 in 2003, but they firmly established that the gene has an important role in cholesterol metabolism.

Subsequent basic science data on the biology of PCSK9 made it clear that PCSK9 possesses many desirable attributes of a potential drug target. PCSK9 was shown in mice and cell culture to lead to the degradation of LDL receptors;6 therefore, inhibition of PCSK9 by relieving this degradation process would directly increase cellular LDL receptors and decrease LDL cholesterol levels (Figure). Moreover, although PCSK9 is secreted into the general circulation,7 published data suggest it preferentially degrades LDL receptors in the liver over other tissues.8 In contrast, statins work indirectly to increase LDL receptors via inhibition of cholesterol synthesis, a process that occurs in all tissues and the consequences of which may help explain the 5% to 20% rate of statin intolerance (mainly muscle and neurological effects).9 In this way, fewer off-target effects could favorably distinguish PCSK9 inhibitors from statins.

A second (and almost never present) desirable trait is afore knowledge that inhibition or loss of function of the target is likely to have the desired effect and be safe in humans. Early genetics work identified human subjects with nonsense mutations in PCSK9, and it was found that carriers not only had lower plasma LDL cholesterol levels but also a large reduction in the risk of coronary heart disease.10 Furthermore, adult carriers appeared otherwise healthy.

Given the widespread availability of various protease inhibitors, the fact that PCSK9 is a protease led to the notion

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that it might be straightforward to develop small molecule inhibitors. Unfortunately, basic science data showed that the ability of the protein to degrade the LDL receptor does not require its protease activity and instead relies on the extra-cellular interaction of secreted PCSK9 and the LDL receptor.\(^7,11\) Given that small molecule protease inhibitors are unlikely to be effective, attention has been turned to alternative means of preventing PCSK9 from interacting with LDL receptors, either by decreasing its production with antisense or RNA interference technologies or by inhibiting it with a monoclonal antibody.

Antisense technology is already gaining momentum in the field of novel lipid lowering agents as the apolipoprotein B synthesis inhibitor, mipomersen, has recently been shown to lower LDL cholesterol levels by approximately 50% in statin-intolerant patients as compared to placebo.\(^12\) Isis, Alnylam, and Santaris all published data in 2007 and 2008 using antisense or RNA interference technology to inhibit PCSK9 production in rodents and nonhuman primates.\(^13–15\) All these molecules lowered plasma LDL cholesterol levels; however, antisense technology is still an evolving field as only one antisense drug has been FDA approved (fomivirsen for CMV retinitis). In comparison, monoclonal antibodies have been firmly established as an important drug class with over 30 FDA approved monoclonal antibodies in clinical use. Given preclinical data showing that antibodies can disrupt the binding of PCSK9 to the LDLR and lead to increased LDLR expression, it is not surprising that the development of a monoclonal antibody to PCSK9 seemed like a logical next step.

Figure. Lowering plasma LDL cholesterol levels by increasing cellular LDL receptors. A, Statins act by inhibiting HMG CoA reductase and thus inhibiting cellular synthesis of cholesterol. Low sterol conditions turn on the activity of the SREBP transcription factor, which upregulates transcription of the LDL receptor and increases uptake of LDL from the plasma effectively lowering LDL cholesterol levels. The SREBP transcription factor also upregulates transcription of PCSK9, which leads to post-translational degradation of the LDLR. B, Addition of a drug to inhibit PCSK9, such as the monoclonal antibody REGN727, will lead to increased cellular LDL receptors, enhanced uptake of LDL, and further lowering of LDL cholesterol levels. This class of drug would be predicted to lower LDL cholesterol levels alone and in combination with statins.

The monoclonal antibody REGN727 clearly accomplishes the goal of significant LDL cholesterol lowering in humans. In the Stein et al study, the antibody effectively decreased concentrations of free PCSK9 in serum on the first day of treatment and levels remained below baseline for at least 1 month. This translated into a 28% to 65% reduction in LDL cholesterol levels depending on dose and route of administration as measured on day 57 after treatment on days 1, 29, and 43. Thus, REGN727 appears to lower LDL cholesterol levels to a similar degree as statins, and it does so in the presence or absence of statins. Furthermore, a single subcutaneous injection remained effective for a prolonged period of time. This has been confirmed in a subsequent study showing that subcutaneous injections every 2 to 4 weeks effectively lowered plasma LDL levels.\(^17\) Besides Regeneron/Sanofi’s REGN727 antibody, Amgen, Merck and Pfizer reported reductions in LDL cholesterol in rodents and nonhuman primates with their own PCSK9 antibodies.\(^18–20\)

Although these studies are promising, many questions remain. Clearly one important issue is whether the results of Stein et al’s phase I study will hold up in subsequent larger phase II and III studies and in actual clinical practice in terms of safety. The phase I studies of the CETP inhibitor torcetrapib for raising HDL cholesterol levels were equally as exciting as this phase I trial, but torcetrapib was quickly taken off the table when phase III studies showed it caused hypertension and excess mortality. Phase III trials are only the first pass and long-term use in real-life patient populations can reveal unexpected adverse events, as has been the case with statins. In preventive cardiology, any new drug that is to be given for years or decades to asymptomatic persons in the hope of forestalling disease many years in the future (if ever) must truly be safe. PCSK9 inhibition has potential for harm because PCSK9 has been postulated to play roles in such widespread pathways as neuronal apoptosis, regulation of sodium channels, pancreatic islet cell function, and nervous system development. It is reassuring, however, that human carriers of PCSK9 null alleles and PCSK9-deficient mice do not appear to have any other deficits.

Another important issue is whether PCSK9 inhibitors will prove effective in altering a relevant disease outcome (ie, cardiovascular disease events) and not just affecting a surrogate measure of that outcome (ie, LDL cholesterol levels). Phase III trials of the cholesterol absorption inhibitor ezetimibe showed clear reductions in LDL cholesterol both alone and in combination with a statin, leading to FDA approval of the drug. However, the efficacy of the drug is now being questioned as the ENHANCE trial failed to show a reduction in atherosclerotic plaque burden as represented by carotid artery intima-media thickness when ezetimibe was added to a statin, although carotid artery intima-media thickness is also a surrogate measure and the trial did not investigate actual cardiovascular disease events.\(^21\) PCSK9...
clearly modulates atherosclerotic plaque burden in genetically modified mice. In addition, besides the data on low cardiovascular risk in carriers of PCSK9 null alleles, a recent genome wide association study identified a polymorphism in the PCSK9 locus associated with early onset myocardial infarction. Additional work is needed to delineate the relationship between this SNP, PCSK9 function, LDL levels, and ischemic heart disease; however, it is encouraging that genetics data supports the hypothesis that PCSK9 inhibition will lead to reduced atherosclerosis.

A final major concern with REGN727 is the fact that it is a monoclonal antibody. Whereas monoclonal antibodies have increased target specificity and longer half lives than small molecule inhibitors, these are injectable drugs with potentially serious side effects such as infusion reactions. The vast majority of monoclonal antibody drugs in clinical practice are used in oncology or rheumatologic diseases where existing treatments are either toxic or ineffective. In this setting, these concerns are tolerated given the lack of good alternatives. It is difficult to apply this argument to a risk-factor modifying drug such as REGN727 and therefore one wonders how applicable the drug will be for use by the general population. That said, millions of people inject insulin up to 4 times a day for diabetes; therefore if REGN727 proves to be effective in a subcutaneous form that can be given monthly, this may be acceptable to patients and physicians.

Clearly the next step for REGN727 is further large-scale phase II and III trials; however, this is not as straightforward as it sounds. Because statins have proven mortality benefit in secondary prevention trials and proven decreased incidence of cardiovascular events in primary prevention trials, they have become the standard-of-care and new agents altering the plasma lipoprotein profile are being tested in addition to statins and not as stand-alone drugs in a noninferiority design. This is most unfortunate, because the new agents are therefore being asked to show benefit on top of the cholesterol-lowering effects of statins, which is a tall order when in some studies LDL cholesterol levels have already been lowered to 70 mg/dL or less by a statin. This has at least 3 potential problems. First, it precludes understanding the potential stand-alone benefits of these drugs. Second, it does not address the important question of the appropriate agent for patients intolerant of statins. Finally, as shown by the study design of the IMPROVE-IT trial, the sample size required to demonstrate cardiovascular disease benefits on top of statins alone balloons to a very large number (18,000 in this case), which greatly drives up the cost of lipid-lowering clinical trials. Stein et al’s study was able to show REGN727 produced significant LDL cholesterol lowering in non-FH subjects on statin, but these patients had LDL cholesterol levels above goal at approximately 110 mg/dL. What if, as in other studies, REGN727 was tested on top of statins in patients treated to LDL cholesterol levels of 70 mg/dL or less? In future trials on top of statins might REGN727 fail either at LDL cholesterol lowering or in reducing cardiovascular disease end points and be relegated to the waste bin? Even more important was the demonstration by Stein et al in a small group of non-FH subjects treated with diet alone that REGN727 was effective. This makes it an especially important study. Given the theoretical benefits of the PCSK9 inhibition mechanism of action for LDL cholesterol lowering compared to statins, and the growing appreciation of statin intolerance as a clinical problem, it might be judicious to fully evaluate PCSK9 inhibition as a stand-alone therapy for LDL cholesterol lowering, perhaps in a noninferiority trial versus statins, or at the very least in the statin-intolerant subset of patients.

References


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