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EDITORIAL COMMENT

PCSK9 Inhibition

The Next Statin?*

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Statins have been approved for the treatment of dyslipidemia for 25 years. This class has demonstrated substantial and consistent reduction of cardiovascular events with an acceptable safety profile. Despite the widespread use of statins, patients continue to experience residual risk. To date, attempts to reduce that risk with additional lipid therapies have failed. Trials of niacin (AIM-HIGH [Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health] trial) and fenofibrate (ACCORD [Action to Control Cardiovascular Risk in Diabetes] trial) in subjects already on statins have recently shown no further risk reduction (1,2). Is statin therapy as good as it gets in treating dyslipidemia? If not, what will be the next lipid modifier with clinical benefit incremental to that of statins? The answer may lie in understanding how statins work. By inhibiting the rate-limiting step in hepatic cholesterol synthesis, statins decrease intracellular cholesterol, resulting in increased expression of hepatic low-density lipoprotein (LDL) receptors and increased hepatic clearance of circulating atherogenic particles including LDL. After delivering their cargo of atherogenic lipoproteins for intracellular degradation, most LDL receptors are recycled to the cell surface.

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Less well recognized is that statins increase the expression of proprotein convertase subtilisin kexin 9 (PCSK9). PCSK9 promotes hepatic LDL receptor degradation, thereby reducing LDL receptor density and clearance of LDL particles. This negative feedback response attenuates statins' lipid effects. Conversely, blocking PCSK9 might be expected to increase the clearance of atherogenic lipoproteins and enhance the efficacy of statins. Thus, PCSK9 offers a novel approach to lipid management.

PCSK9's role in lipid metabolism was suggested by 3 observations. Abifadel et al. (3) first reported that a specific heterozygous PCSK9 missense mutation caused autosomal dominant hypercholesterolemia. Because loss of a single allele is usually functionally inconsequential, a gain-of-function mechanism was hypothesized. The second link was that PCSK9 messenger ribonucleic acid levels were found to be responsive to intracellular cholesterol (4). In the hepatocyte, PCSK9 undergoes obligatory autocatalytic cleavage, but its catalytic activity is independent of its affinity for the LDL receptor (5). This spatial and functional separation has important pharmacological implications. PCSK9 binds to the receptor and channels it internally toward the lysosomal compartment for degradation. In doing so, it inhibits the normal recycling of the LDL receptor back to the hepatic cell surface. A third and perhaps most important clue was that nonsense mutations in PCSK9 were associated with 15% to 30% reductions in LDL cholesterol, with significant reductions in cardiovascular risk (6). These experiments of nature provide plausibility to the hypothesis that pharmacologic interference with PCSK9 can provide clinical benefit.

In this issue of the *Journal*, McKenney et al. (7) report the results of a phase 2 trial of REGN727/SAR236553, a human monoclonal antibody to PCSK9 in subjects with LDL cholesterol ≥100 mg/dl on stable atorvastatin (10 to 40 mg) therapy. This trial randomized 183 subjects to 1 of 3 antibody doses or placebo administered subcutaneously every 2 weeks or higher doses every 4 weeks for a total treatment of 12 weeks. Both 2- and 4-week dosing resulted in 40% to 72% and 43% to 48% reductions in LDL cholesterol, respectively. Up to 9% increases in high-density lipoprotein (HDL) cholesterol, 19% decreases in triglycerides, and 29% decreases in lipoprotein(a) were observed. Mild injection-site reactions were the most common adverse events and 1 subject experienced leukocytoclastic vasculitis, which was successfully treated with drug discontinuation and steroid therapy.

This is a significant study, both because of the magnitude of LDL reduction achieved and the novel pathway (PCSK9 inhibition) utilized. Important questions remain. *What is the extent of the unmet need for LDL reduction, not fulfilled by optimal statin therapy?* The few patients who are truly statin intolerant might benefit from an alternative approach to LDL reduction. However, PCSK9 inhibition probably would be used as an adjunct to statin therapy. Maximum doses of effective statins reduce LDL cholesterol up to about 60%, resulting in average serum levels of 70 to 80 mg/dl. Existing statin studies suggest that cardiovascular risk continues to decrease with more intensive therapy, resulting in lower LDL cholesterol levels (8). Because maximal statin doses are infrequently prescribed, one might argue that there is a greater need for clinicians to use higher, evidence-based statin doses, especially for high-risk patients (9), than to seek add-on therapy. However, neither goal is mutually exclusive.

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Is a combination of PCSK9 plus statin therapy safe? We do not know whether immune responses to fully humanized PCSK9 antibody will develop after prolonged treatment. The leukocytoclastic vasculitis observed in 1 subject may or may not have been a consequence of therapy, as this condition commonly occurs without drug initiation. Larger, phase 3 trials are certainly needed. *Equally important, what are the consequences of very low LDL cholesterol that could be achieved with combination therapy?* We currently have no clear safety concern for very low LDL cholesterol other than possibly an increase in hemorrhagic stroke (10). It has, however, taken 25 years of statin therapy to recognize their association with memory loss and new onset diabetes, recently acknowledged by the Food and Drug Administration (11).

Will patients be compliant with every 2- to 4-week administration of a subcutaneously administered drug, especially for an asymptomatic condition? About 50% of patients discontinue statin therapy within the first year. As mentioned previously, the affinity of PCSK9 for the LDL receptor is not dependent on its enzymatic activity, making oral administration of a small inhibitory molecule difficult. *What orally administered drugs under investigation might supplant the need for PCSK9 inhibition?* At present, anacetrapib, a cholesterol ester transfer protein inhibitor, has been shown to reduce LDL and increase HDL cholesterol by 40% and 138%, respectively (12). Even if its HDL effect has little clinical consequence, it may prove to be an effective LDL cholesterol–lowering agent.

What are the theoretical advantages and disadvantages of PCSK9 inhibition compared with statins? Statins have myriad pleiotropic effects, including reducing inflammation, coagulation, and oxidation, all important antiatherogenic factors (13). There is considerable debate about the extent to which these effects contribute to the efficacy of statins, but they probably play some role. PCSK9 inhibition probably will not share these effects. Conversely, maximally increasing LDL receptors may have synergistic advantages. By reversing statin-induced PCSK9 up-regulation, PCSK9 inhibition increases the statin's effectiveness on LDL cholesterol lowering. Moreover, LDL receptors contribute to the clearance of atherogenic lipoproteins other than LDL, such as intermediate-density lipoproteins and remnant particles, the latter via apolipoprotein E affinity. Increased intermediate-density lipoproteins and remnant particle clearance may have real therapeutic benefit beyond that provided by LDL reduction.

Brown and Goldstein won a Nobel Prize for their identification of the LDL receptor in 1985 while they were studying familial hypercholesterolemia. The therapeutic triumph of statins logically follows their pioneering efforts. So may PCSK9 inhibition (14).

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REFERENCES

1. The AIM-HIGH Investigators. AIM-HIGH: niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255–67.
2. Tonkin AM, Chen L. Effects of combination lipid therapy in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Circulation 2010;122:850–2.
3. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34:154–6.
4. Maxwell KN, Soccio RE, Duncan EM, Sehayek E, Breslow JL. Novel putative SREBP and LXR target genes identified by microarray analysis in liver of cholesterol-fed mice. J Lipid Res 2003;44:2109–19.
5. Akram ON, Bernier A, Petrides F, Wong G, Lambert G. Beyond LDL cholesterol, a new role for PCSK9. Arterioscler Thromb Vasc Biol 2010;30:1279–81.
6. Cohen JC, Boerwinkle E, Mosley TH Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264–72.
7. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand A-C, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kenexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J Am Coll Cardiol 2012;59:2344–53.
8. Martin SS, Blumenthal RS, Miller M. LDL cholesterol: the lower the better. Med Clin North Am 2012;96:13–26.
9. LaRosa JC. How much statin is enough? J Am Coll Cardiol 2011;58:1672–3.
10. Wiviott SD, Cannon CP. The safety and efficacy of achieving very low LDL-cholesterol concentrations with high dose statin therapy. Curr Opin Lipidol 2006;17:628–30.
11. Burton TM, Winslow R. FDA Warns on Statin Drugs: Labels on Popular Cholesterol Medicines Must Cite Risk of Diabetes, Memory Loss. Available at: http://online.wsj.com/article/SB10001424052970203833004577251392001194250.html. Accessed February 29, 2012.
12. Cannon CP, Shah S, Dansky HM, Davidson M, Brinton EA, Gotto AM Jr., et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med 2010;363:2406–15.
13. Liao JK, Lauf U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 2005;45:89–118.
14. Goldstein JL, Brown MS. History of discovery of the LDL receptor. Arterioscler Thromb Vasc Biol 2009;29:431–8.

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