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Will PCSK9 inhibitors stand up to statins till the end?

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Low-density lipoprotein cholesterol (LDL-C) level is the most potent modifiable risk factor for cardiovascular disease. Indeed, LDL-C levels can be lowered with statin treatment, and this effect translates into a reduced incidence of cardiovascular events.[1] However, not all patients on statin therapy achieve guideline-recommended LDL-C levels; thus, an additional and/or alternative lipid-lowering therapy may sometimes be required. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent an emerging class of nonstatin therapy. PCSK9 is a circulating serine protease that binds to the LDL receptor (LDL-R) in the liver or in the systemic circulation and enhances intracellular LDL-R degradation. This effect reduces the ability of the cells to take up and degrade additional LDL-C and results in hypercholesterolemia. Following mutations involving the LDL-R and apolipoprotein B genes, a gain-of-function mutation in the PCSK9 gene is the third most common form of autosomal-dominant familial hypercolesterolemia (FH).[2] Conversely, a loss-of-function mutation in the PCSK9 gene is associated with reduced LDL-C levels and rates of cardiovascular events.[3] Therefore, the PCSK9 gene and its downstream products are promising therapeutic targets. Since 2003, a number of strategies—including monoclonal antibodies, small interfering ribonucleic acid (siRNA), and antisense oligonucleotides (ASOs)—have been developed and have already been tested in phase 1-3 clinical trials.

Monoclonal antibodies (eg, evolocumab, alirocumab, and bococizumab) bind to the region of PCSK9 that is required for interaction with the LDL-R, thus inhibiting the interaction between PCSK9 and LDL-R and consequent LDL-R degradation.[4] Single-stranded siRNAs bind to the messenger RNA and inhibit PCSK9 function, thereby reducing circulating PCSK9 and LDL-C levels.[5] Similarly, ASOs bind to and inhibit messenger RNA, causing a decrease in PCSK9 and LDL-C concentrations.[6] More recently, a vaccine that targets circulating PCSK9 has also been developed and appears to significantly reduce total cholesterol, free cholesterol, phospholipids, and triglycerides in animal models, although this will need further clinical evaluation.[7]

Taken together, available evidence suggests that PCSK9 inhibitors can reduce LDL-C levels by 50% to 70%. This effect appears to be dose-dependent and not affected by baseline LDL-C concentrations, age, gender, or ongoing statin treatment.[8] In addition, PCSK9 inhibitors can reduce lipoprotein(a) levels by up to 30%,[9] with a more modest effect on serum triglyceride and high-density lipoprotein cholesterol (HDL-C) levels. Hence, PCSK9 inhibition is associated with a lipid profile that is at least as good as the one obtained with statin treatment. Furthermore, these drugs appear to have a very favorable safety profile, with no significant adverse side effects. In line with these considerations, the US Food and Drug Administration (FDA) recently approved the use of two monoclonal antibodies, alirocumab (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm) and evolocumab (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm460082.htm). Nonetheless, route of administration (by injection, received monthly or once every two weeks), exorbitant costs, and inadequate out-

Abbreviations

ASO: antisense oligonucleotide; **FH:** familial hypercholesterolemia; **FOURIER:** Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; **HDL-C:** high-density lipoprotein cholesterol; **LDL-C:** low-density lipoprotein cholesterol; **LDL-R:** low-density lipoprotein receptor; **PCSK9:** proprotein convertase subtilisin/kexin type 9; **siRNA:** small interfering ribonucleic acid

comes data could represent significant limitations for PCSK9-inhibitor therapy. Moreover, there is a final, but very important, question that remains to be answered: Will laboratory results showing cholesterol reduction translate into clinical benefits? In fact, except for ezetimibe,[10] nonstatin therapies have not been shown to confer additional cardiovascular benefits when added to statins.[11] Although a linear relationship between LDL-C and cardiovascular event rates was initially proposed for statins, the clinical utility of "surrogate end points," such as LDL-C levels, has not been proven. Indeed, further evidence has suggested that, besides lowering LDL-C levels, statins have a series of positive effects on plaque stabilization and endothelial homeostasis (eg, anti-inflammatory, antioxidant, antiproliferative, and immunomodulatory effects), globally called "pleiotropic effects," that could explain all of the beneficial clinical outcomes.[12]

PCSK9 inhibitors are also expected to significantly improve cardiovascular outcomes. These results are eagerly awaited since they could newly challenge our understanding of the relationship between cholesterol levels and cardiovascular outcomes. However, results from the first trial testing for clinical benefits—the FOURIER trial (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk; https://clinicaltrials.gov/ct2/show/NCT01764633)—will not be available until 2018. Until then, PCSK9 inhibitors can be considered for use in patients who are intolerant to statins or who do not achieve target levels despite statin therapy, both in those with FH and those with nonfamilial forms of hypercholesterolemia. ■

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