Proprotein Convertase Subtilisin Kexin 9 Inhibitors

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KEYWORDS

• PCSK9 • Monoclonal antibodies • Evolocumab • Alirocumab • LDL-C • Hypercholesterolemia • Cardiovascular disease • Proprotein convertase subtilisin kexin 9

KEY POINTS

- Low-density lipoprotein (LDL) is a major risk factor for cardiovascular disease.
- Patients at high or very high cardiovascular risk may benefit from large LDL-C reduction.
- Many patients often cannot achieve their LDL-C goals with the starting therapy.

INTRODUCTION

Low-density lipoprotein (LDL) is a major risk factor for cardiovascular disease (CVD), and a large number of epidemiologic studies have established the strong and direct relationship between high LDL-cholesterol (LDL-C) levels and coronary heart disease (CHD), and a wealth of clinical trials have shown that reducing LDL-C levels results in a reduced incidence of cardiovascular (CV) events. In fact, 12% reduction in all-cause mortality, 19% reduction in coronary mortality, and 17% reduction in any vascular cause of mortality per millimole per liter reduction in LDL-C have been observed,[1] and the higher the degree of reduction of LDL-C levels, the greater the benefit in terms of reduction of CV risk, as suggested by the comparison between more intensive and less intensive lipid-lowering therapies.[2] Thus, patients at high or very high CV risk may benefit from achieving the largest LDL-C reduction, as suggested by current guidelines,[3] which need to be maintained over time to gain a clinical benefit. However, many patients often cannot achieve their LDL-C goals with the starting therapy, which thus require adjustment based on the individual response to the lipid-lowering approach. Statins represent the first-line choice, and their efficacy in reducing CV morbidity and mortality in both primary and secondary prevention has been established in several clinical trials and meta-analyses.[1,2,4–9]

However, despite the efficacy of statins, many patients do not reach their LDL-C level goals due to several reasons, including the occurrence of statin-related adverse events (mainly muscle-related disorders) leading to therapy discontinuation.[10] In addition, a large proportion of patients with high or very high CV risk, including those with genetically determined forms of familial hypercholesterolemia (FH), does not achieve the recommended LDL-C level target even with maximally tolerated doses of drugs. Thus, there is the need of additional interventions that can efficiently reduce

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LDL-C levels below those achievable with the common cholesterol-lowering drugs.

PROPROTEIN CONVERTASE SUBTILISIN KEXIN 9

Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease that plays a key role in the regulation of hepatic low-density lipoprotein receptor (LDLR) function, which represents the key regulator of cellular LDL uptake and plasma cholesterol levels (Fig. 1). Following the binding to LDL particles, the complex LDLR/LDL particle is internalized within the cell where it dissociates allowing receptor recycling and lysosomal degradation of LDL particle. When circulating PCSK9 binds to the epidermal growth factor-like repeat domain of LDLR, a conformational change of LDLR occurs, making it more vulnerable to degradation within lysosomes.[11] The binding PCSK9/LDLR thus results in a reduced LDLR surface expression, reduced LDL uptake, and increased plasma levels of LDL-C.

The relevance of PCSK9 as main regulator of plasmatic cholesterol levels derives from the observations that genetic variants of PCSK9 associated with loss or gain of function of this protein resulted in lower or higher levels of LDL-C, respectively.[12,13] More importantly, an association with protection against cardiovascular disease (CVD) was observed in subjects carrying loss-of-function mutations in *PCSK9* gene,[13–17] whereas gain-of-function mutations are associated with an increased risk of premature CVD.[18–20] These findings suggested that PCSK9 may be a useful pharmacologic target for the control of hypercholesterolemia (Fig. 2) and led to the development of 2 fully human monoclonal antibodies (mAbs) against circulating PCSK9, evolocumab and alirocumab, which are now approved for the treatment of hypercholesterolemia. The development of a third mAb against PCSK9 (bococizumab) was recently halted because of a high titer of antidrug antibodies, which may significantly attenuate the LDL-C-lowering effect.[21] Another mAb to PCSK9, named LY3015014, the safety and efficacy of which have been so far tested in a phase 2 study, is still in development.[22] Recently, other approaches are being developed, such as RNA interfering drugs; inclisiran is a long-acting RNA interference drug that produces a specific and sustained inhibition of hepatic PCSK9 synthesis. Finally, an approach for long-term LDL-C management through PCSK9-specific active vaccines has been evaluated in preclinical models.[23–25]

It is worth noting that although PCSK9 targets mainly the LDLR in the liver, the protein is expressed also in extrahepatic tissues, including kidney, pancreas, and brain,[26] suggesting that pharmacologic inhibition of PCSK9 may lead to extrahepatic effects of PCSK9, which may raise concerns about this approach. To date, there is no evidence indicating a direct association between lipid-lowering therapy (LLT) with PCSK9 inhibitors with or without statins and the risk of cognitive disorders,[27] but specifically designed long-term clinical trials are awaited to clarify this aspect.

CLINICAL STUDIES ON EVOLOCUMAB AND ALIROCUMAB

Several clinical studies have evaluated the efficacy and safety of evolocumab and alirocumab in

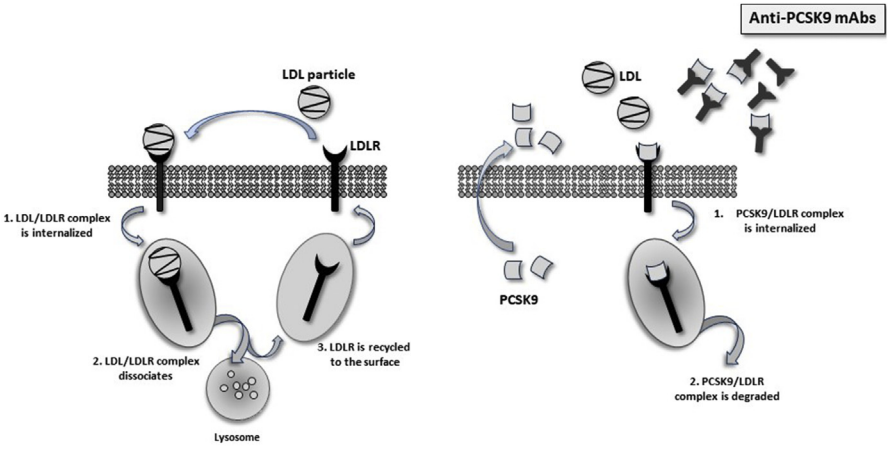

Fig. 1. Mechanism of action of PCSK9 and mAbs to PCSK9. In the absence of PCSK9, following the binding with LDL, LDLR is internalized and then recycled to the cell surface to restart the cycle. PCSK9 binds to LDLR and targets it to the degradation. MAbs to PCSK9 neutralize the circulating protein and block its binding to LDLR. (*Modified from* Pirillo A, Norata GD, Catapano AL. Advances in hypercholesterolemia. In: Chackalamannil S, editor. Comp Med Chem III. 3rd edition. Cambridge (MA): Elsevier; 2017. p. 669; with permission.)