PERSPECTIVES

New weapon in fighting atherosclerosis: Effective inhibition of circulating low density lipoprotein cholesterol

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Abstract: Last but not least a warning. Cholesterol is not only a pathogenic metabolite, it is an essential biological component. Indiscriminate cholesterol lowering may be inappropriate and harmful. The more effective is a weapon, the higher is the potential for a collateral damage (Fig. 1, Ref. 10). Text in PDF www.elis.sk.

Key words: atherosclerosis, low density lipoprotein cholesterol (LDL C), LDL receptor (LDL-R), PCSK9, AMG 145, statins.

Lowering low density lipoprotein cholesterol (LDL-C) is a cornerstone for the prevention of heart disease. The recent review published in BLL (1) described various methods of cholesterol management. Statins are the first line agents, being effective in reducing LDL-C. However, many patients are unable to achieve the optimal target lipid level despite an intensive statin therapy. This resulted in a strong impetus to develop novel pharmacological agents that would further decrease LDL-C in patients not adequately responding to statins.

Recent research, addressed in this review, revealed a novel pathways for reduction of LDL. Big step forward in the management of atherosclerosis is the discovery of an LDL receptor (LDL-R). This discovery was appropriately awarded a Nobel prize. LDL-R is a cell-surface mosaic protein that mediates the endocytosis of cholesterol-rich LDL. Activity of this receptor determines the level of circulating LDL-C.

The next essential step was the identification of a factor blocking the LDL-R, a proprotein convertase subtilisin-like type 9 (PCSK9) (2). This is an extracellular protein expressed primarily in the liver. A secreted form of PCSK9 binds directly to the LDL-R and results in lysosomal degradation of LDL-R (Fig. 1). This outcome interferes with recycling of LDL-R back to the cell surface. The result is a decline of LDL-R in cell membranes, with lower binding of LDL and with an unfavorably increased amount of circulating LDL in blood vessels. Importantly, inhibition of PCSK9 is followed by an uninterrupted recycling of LDL (Fig. 1 on the right).

Genetic studies mapped PCSK9 along with LDL-R to elucidate the cause of autosomal dominant hypercholesterolemia (3). Gain-of-function mutations increased plasma levels of LDL-C while loss-of-function mutations which interfere with folding or secretion of PCSK9, led to a reduction of plasma levels of LDL C, along with a decrease in the risk of atherosclerosis. Statins are reported to increase the level of circulating PCSK9 (4).

This suggested the possibility that inhibition or decrease of PCSK9 may potentiate the efficacy of cholesterol lowering medications. Intensive research aimed at inhibition of PCSK9 resulted in discovery of AMG 145 (5). This compound is a fully human monoclonal immunoglobulin G2 antibody that binds specifically to human PCSK9 and inhibits its interaction with the LDL-R (6). Clinical development programs for monoclonal antibodies against PCSK9 have advanced rapidly with AMG 145. They clearly demonstrated substantial reductions in LDL-C levels in patients on AMG 145, when receiving diet alone, when on low, moderate or high doses of statins and also both in heterozygous familial hypercholesterolemia and nonfamilial hypercholesterolemia subjects (7, 8). AMG 145 administered subcutaneously every 4 weeks yielded
rapid and substantial reductions in LDL-C in heterozygous familial hypercholesterolemia patients despite intensive statin use, with minimal adverse events and good tolerability. Larger and much longer trials are now in progress to assess the long-term tolerability, safety, and impact on cardiovascular disease events of these very effective LDL-C lowering compounds. The results to date indicate that the AMG 145 appears safe, well-tolerated, and profoundly lowers LDL-C levels. This new compound is expected to meet an important clinical need for patients unable to achieve adequate lowering of LDL-C when on currently available therapies.

Last but not least a warning. Cholesterol is not only a pathogenic metabolite, it is an essential biological component. Indiscriminate cholesterol lowering may be inappropriate and harmful (9, 10). The more effective is a weapon, the higher is the potential for a collateral damage.

References


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