Therapies for Raising High-density Lipoprotein Cholesterol

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A low high-density lipoprotein cholesterol (HDL-C) level is one of the strongest predictors of coronary risk (1). The negative correlation between coronary artery disease (CAD) and plasma HDL-C has been attributed to the ability of HDL to take up cellular cholesterol from the periphery and to mediate the transport of excess cholesterol to the liver (reverse cholesterol transport, RCT) (2). In Japan, Satoh et al recently reported that a low level of HDL-C was a significant independent risk factor for CAD in young middle-aged men based on the results of a 10-year cohort study (3). Although HDL-C is a target in the treatment of atherosclerotic CAD, there are currently only a limited number of therapeutic options to increase HDL-C. However, several exciting therapeutic strategies have recently been developed and are currently the focus of intriguing research, such as reconstituted recombinant (r)HDL (4) and cholesterol ester transfer protein (CETP) inhibitors.

Effects of currently available drugs on HDL-C

Statins are competitive inhibitors of 3-hydroxy-2-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes the rate-limiting step in cholesterol synthesis. Although statins have long been known to suppress elevated LDL-C levels, they also raise HDL-C, but not drastically. In addition, peroxisome proliferator-activated receptor (PPAR)-\(\alpha\) agonists, fibrates, regulate the transcription genes involved in RCT, such as apolipoprotein (Apo)A-I, ApoA-II and scavenger receptor B1. Bezafibrate increased HDL-C by 6% with an increase in HDL\(_3\) in the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT). In patients with combined dyslipidemia, fenofibrate significantly increased HDL-C and improved flow-mediated dilation of the brachial artery (5). Another drug, nicotinic acid, inhibits hepatic diacylglycerol acyltransferase 2, which is involved in the synthesis of triglyceride (TG). The inhibition of TG synthesis indirectly raises HDL-C. These currently available HDL-C raising drugs are of limited efficacy due to their different mechanisms of action. Therefore, over the past decade, new agents have been studied to raise HDL-C.

CETP inhibitor

CETP facilitates the exchange of cholesterol esters from HDL for TG. The cholesterol esters can then be delivered either to the liver via the low-density lipoprotein (LDL) receptor or to the vasculature. JTT-705, an oral CETP inhibitor, leads to a significant increase in HDL-C (as much as 37%) in addition to a 4-8% decrease in LDL-C (10). In ad-
dition, torcetrapib another CETP inhibitor profoundly increases HDL-C by 91% and reduces LDL-C by 21-42% (11). Daily treatment with torcetrapib increased plasma concentrations of HDL-C by 61% and 46% when given with atorvastatin and non-atorvastatin, respectively (12). Torcetrapib also reduced LDL-C by 17% in combination with atorvastatin. In this way, CETP inhibitors markedly increase HDL-C and also decrease LDL-C when administered as monotherapy or when administered in combination with statins.

Conclusions

Although the value of the extensive lowering of LDL-C levels by drugs in preventing cardiovascular events has been well documented, two-thirds of such events are not prevented. The combination of the extensive lowering of LDL-C with an aggressive HDL-C raising strategy may dramatically improve our ability to prevent such events. Since currently available drugs can not adequately raise HDL-C, the use of rHDL or CETP inhibitors to markedly increase HDL function or HDL-C levels offers a potential method for preventing more cardiovascular events.

While this manuscript was in preparation, all clinical development of torcetrapib was halted because of a statistically significant imbalance in mortality between patients receiving torcetrapib/atorvastatin and those receiving atorvastatin alone.

References


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