Molecules of the Millennium

Torcetrapib: A new strategy to raise HDL cholesterol levels

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase. They reduce low-density lipoprotein (LDL) cholesterol levels and hence they are used to reduce the risk of coronary heart disease. However, many of the cardiovascular events are not prevented by statin therapy. There is therefore a great deal of interest in identifying therapies capable of further reducing the risk of coronary heart disease. One such potential therapeutic target is a low level of high-density lipoprotein (HDL) cholesterol which constitutes a common lipid abnormality in coronary heart disease patients.

Agents that increase the HDL cholesterol level are inhibitors of cholesteryl ester transfer protein (CETP) which simultaneously reduces LDL cholesterol and are in advanced stages of development. CETP is a plasma glycoprotein that facilitates the transfer of cholesteryl esters from HDL cholesterol to apolipoprotein-B containing lipoproteins. CETP mediates the exchange of cholesteryl ester for triglycerides between HDL and VLDL-LDL and may be proatherogenic if the CETP-mediated VLDL-LDL cholesteryl ester is taken up by arterial macrophages or may be antiatherogenic if this cholesteryl ester is returned to the liver through LDL receptor by means of the pathway of reverse cholesterol transport that is initiated by HDL.

Recently a novel CETP inhibitor torcetrapib has been assessed during clinical trial study for its effects on plasma lipoproteins in patients with a low level of HDL cholesterol (less than 40 mg per deciliter), when given either alone or in combination with atorvastatin. In this single-blind, placebo-controlled study, torcetrapib was found to significantly reduce CETP activity with both doses of 120 mg once daily and 120 mg twice daily which in turn led to marked increases in plasma HDL cholesterol levels. Also, torcetrapib raised HDL cholesterol levels effectively in subjects who also received atorvastatin. Torcetrapib also reduced LDL cholesterol and apolipoprotein B levels. The reduction in LDL levels was observed both in subjects who received atorvastatin and in those who had not. This finding is consistent with the fact that patients with homozygous defects in the CETP gene have reduced levels of LDL-cholesterol. The metabolic basis for the low levels of LDL - cholesterol in persons with CETP deficiency is an increase in the rate of clearance of LDL cholesterol from the plasma due to upregulation of the LDL receptor pathway in CETP deficiency. Torcetrapib, alone or in combination with atorvastatin resulted in no clinically significant changes in vital signs, biochemical values or hematological values. Most of the adverse events reported were mild in nature and included headache, dizziness, asthenia, pain, dyspepsia, sweating, Amnesia or abnormal thinking and herpes simplex, herpes zoster infections were reported in two to three patients receiving 120 mg torcetrapib twice daily. Thus, torcetrapib is a well tolerated and effective CETP inhibitor, that not only increased the levels of HDL cholesterol but also reduced the levels of LDL cholesterol and apolipoprotein B, both when given as monotherapy and when administered in combination with a statin.

Current data suggests that CETP inhibitors may hold great promise as a new class of drugs in the therapy of lipid disorders. The combined use of statins and CETP inhibitors has the potential for markedly improving the effectiveness of reducing cardiac events in high-risk patients with cardiovascular disease.

Sources

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