Therapies on the Horizon for Cholesterol Reduction

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Summary: Statins are powerful agents for the reduction of low-density lipoprotein cholesterol (LDL-C) and reduction of cardiovascular risk. Newly developed statins with increased potency, such as rosuvastatin (Crestor™) and NK-104 (in earlier clinical development), are capable of achieving marked LDL-C reductions. Cholesterol-lowering agents with mechanisms of action distinct from those of the statins are in active development. These include bile transport inhibitors, such as improved bile acid-absorbing resins and specific inhibitors of the ileal Na+/ bile acid cotransporter. There are also specific inhibitors of cholesterol absorption, such as ezetimibe, which may provide cholesterol lowering that is additive to that achieved with statin treatment. Another approach is to reduce cardiovascular risk by modifying atherosclerotic processes within the arterial wall, as represented by the acyl CoA:cholesterol acyltransferase (ACAT) inhibitor avasimibe; ACAT inhibitors may reduce atherosclerotic lesions by inhibiting macrophage cholesterol storage.

Key words: rosuvastatin, NK-104, bile transport inhibitors, ezetimibe, avasimibe

Introduction

Statins have proven to be very powerful pharmacologic agents for the reduction of low-density lipoprotein cholesterol (LDL-C), and their documented benefits in clinical trials have led to a very large and growing market for these drugs. However, despite widespread use of statins in clinical practice, a large majority of patients with coronary heart disease (CHD) or significant risk factors have LDL-C levels higher than those recommended by the National Cholesterol Education Program (NCEP) or European Joint Task Force guidelines. Other patients may have low levels of high-density lipoprotein cholesterol (HDL-C) and elevated triglyceride levels that may not respond to statin therapy. Within the next few years, the clinician can expect to see a number of new therapeutic options, including more potent statins, agents that reduce LDL-C by different mechanisms (including new bile acid-binding resins and specific inhibitors of bile acid transport and cholesterol transport), and agents that inhibit cholesterol esterification within the arterial wall.

New Statins

Rosuvastatin (Crestor™) is a new, highly efficacious statin, which soon will be the seventh drug in this class to reach the market. The characteristics of this agent, which include the ability to reduce LDL-C by 65%, are reviewed in detail elsewhere in this supplement (see page III-18). The new statin NK-104, which is currently in phase III trials, has been shown to lower LDL-C by 55%. In general, both of these new agents appear to have greater efficacy than that reported for other statins at a given mg dose, while still exhibiting the characteristic statin dose–response curve, in which an additional 5 to 7% reduction in LDL-C is seen with each doubling of drug dose.

Bile Acid Transport Inhibitors

Inhibitors of bile acid transport include both the bile acid-binding resins and the specific inhibitors of bile acid transport known as ileal Na+/ bile acid cotransporter (IBAT) inhibitors. Bile acid absorption with the resin cholestyramine proved to be a clinically effective method for reducing cardiovascular risk in early lipid-lowering studies, but treatment with these older resins was cumbersome for both physicians and patients. As a result, these effective drugs are not well accepted and compliance with prescribed regimens is frequently poor. The rationale for inhibiting bile acid absorption lies in the fact that approximately 2 to 5 g of bile acid is constantly cycled from the liver to the gut, with a relatively small amount excreted in...
the stool (Fig. 1). Blocking the reuptake process in the liver with bile acid-sequestering agents can substantially increase the amount of bile acid that is lost as fecal bile acid. Because replenishment of this supply by the liver occurs by conversion of cholesterol to bile acid, the end result is depletion of liver cell cholesterol supply and upregulation of LDL receptors.

A new bile acid sequestrant, colesevelam (WelChoP), has recently been released for prescription use. It is effective at lower doses and is given in 625 mg capsules (6 times/day for monotherapy, 4–6 times/day for combination therapy). It is too early to report on any improvement in acceptance by patients or physicians. The IBAT inhibitors, such as S-8921, appear to inhibit the specific transport systems responsible for uptake of bile acids by the intestinal epithelium. Inhibition of intestinal uptake results in more complete blockade of reuptake of the bile acids in the biliary tract. Such agents have greater potential efficacy than the older bile acid-absorbing resins that work through competitive inhibition. If they are minimally absorbed, they may be of particular value in the treatment of hypercholesterolemic children, in whom systemic treatment often is avoided because of safety concerns. Both IBAT inhibitors and new bile acid-absorbing resins, in combination with low-dose statin therapy, have the potential to significantly augment LDL-C reduction.

**Cholesterol Absorption Inhibitors**

Benefits similar to those achieved by blocking bile acid uptake by the liver can theoretically accrue from drugs that interact directly with specific transport systems for cholesterol. The combined delivery of cholesterol to the bile from endogenous synthesis and from the diet usually amounts to 0.5 to 1.0 g/day; preventing absorption of this amount of cholesterol could produce a 15 to 20% reduction in LDL-C levels, which would be additive to the reduction achieved with statin treatment. Ezetimibe is a new, potent, and selective inhibitor of cholesterol absorption that has been shown to be active at or near the enterocyte brush border membrane, with the potential to block uptake of both dietary cholesterol entering the liver and the larger amount of cholesterol that is generally deposited in the intestine as fecal sterols after exiting the liver (Fig. 1). The drug is conjugated in the liver, secreted in the bile, and reabsorbed in the gut, undergoing rapid enterohepatic recycling.

Data from a cholesterol-fed hamster model indicated that ezetimibe doses of 1 mg/kg reduced plasma cholesterol levels by approximately 50%, with even larger reductions in liver cholesterol observed at smaller doses. In a dose-ranging study in humans, LDL-C reductions of approximately 10 to 19% have been observed with doses of 0.25 to 10 mg. Overall experience indicates that the maximal effect is achieved at a dose of 10 mg, which is associated with an approximately 19% reduction in LDL-C. A pooled analysis of data from two phase II, 12-week studies of 329 patients showed an LDL-C reduction > 15% in 68% of subjects receiving ezetimibe 10 mg and 54% of those receiving ezetimibe 5 mg (Fig. 2); 22 and 15% of subjects receiving ezetimibe 10 and 5 mg, respectively, achieved an LDL-C reduction > 25%.

Fig. 1: Effect of blocking bile acid absorption. Fecal bile acid (BA) is increased, with subsequent increase in BA production in the liver, depletion of liver cholesterol (C), and upregulation of low-density lipoprotein (LDL) receptors. VLDL = very-low-density lipoprotein. II: Effect of blocking cholesterol absorption. Elimination of fecal sterols is increased, resulting in sequence of events similar to that observed with inhibition of bile acid absorption.

Fig. 2: Ezetimibe pooled phase II data: Mean percent change from baseline in lipid parameters at 12 weeks. LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol. □ = placebo (n = 87), ■ = ezetimibe 5 mg (n = 124), ● = ezetimibe 10 mg (n = 118). Data from Ref. No. 18.
Acyl CoA:Cholesterol Acyltransferase Inhibition

The attempt to develop acyl CoA:cholesterol acyltransferase (ACAT) inhibitors represents an approach to cardiovascular disease reduction based on directly preventing the accumulation of cholesterol ester in macrophages and smooth muscle cells of the arterial wall. The ultimate objective of this strategy is to block the development of macrophage foam cells, which are central to the pathophysiologic sequence in atherosclerosis.

Macrophage foam cells develop as the rate of lipoprotein cholesterol influx exceeds the rate of efflux. The cholesterol ester in the lipoproteins is hydrolyzed within the macrophage and re-esterified with oleate derived from coenzyme A fatty acyl esters. The formation of this cholesterol oleate is mediated by the enzyme ACAT-1.\(^1\)\(^2\)\(^3\) ACAT-1 is present in all cells in the body; the related ACAT-2, found in the liver and intestine, facilitates incorporation of intracellular cholesterol into chylomicrons exiting the intestine and very-low-density lipoproteins exiting the liver.\(^4\)

Several agents have been developed to inhibit ACAT activity and thus reduce macrophage cholesterol storage. Most of the ACAT inhibitors that have been developed to date are not absorbed adequately and delivered in sufficient amounts to affect arterial cells. Avasimibe is one of the agents that has been shown to achieve systemic effects,\(^5\) and it is currently in phase II trials. In tissue culture studies, avasimibe has been shown to increase cholesterol efflux from human macrophages and to increase macrophage binding of acyl-LDL. In studies in apoE3-Leiden mice and cholesterol-fed rabbits, orally administered avasimibe reduced lipoprotein concentrations and reduced the size and extent of foam cell-containing arterial lesions.\(^6\) The reduction in lipoprotein concentrations observed in these models is believed to result from inhibition of ACAT-2 by avasimibe, whereas the reduction in arteriosclerosis is probably due to reduction in cholesterol ester storage in macrophages as a result of inhibiting ACAT-1. Another ACAT inhibitor currently in preclinical evaluation is TS-962;\(^7\) this agent has been found to have a potential effect on intimal lesion formation and the composition of advanced aortic lesions.

Conclusion

Statin therapy has proven remarkably effective in reducing LDL-C levels and cardiovascular disease risk, and the addition of more potent statins to current treatment options is likely to have a significant impact on LDL-C-lowering treatment. At the same time, a number of drugs that reduce LDL-C by mechanisms different from those of the statins are in development. Improved bile acid-absorbing resins, IBAT inhibitors, and cholesterol transport inhibitors have the potential to provide cholesterol reduction additive to that achieved by statin treatment, suggesting the potential for potent combination therapy. Agents that target atherosclerotic processes in the arterial wall, such as the ACAT inhibitors, may ultimately provide an additional strategy for reducing cardiovascular risk.

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