

New Therapies on the Horizon

Based on a presentation by W. Virgil Brown, MD

Presentation Summary

Statins have proved to be potent drugs for reducing low-density lipoprotein cholesterol (LDL-C) levels. However, because the response to current statin therapy regimens is not always sufficient to reach defined goal levels, additional drugs to lower LDL-C are needed. New drugs may soon be available to lower LDL-C levels by mechanisms that differ from those of the statins. Among these new agents are a bile acid binding resin, inhibitors of bile acid transport, inhibitors of cholesterol transport, inhibitors of cholesterol esterification, and triglyceride-lowering agents.

The statins have proved to be potent and effective drugs for reducing low-density lipoprotein cholesterol (LDL-C) levels. However, not all patients sufficiently reach defined LDL-C goal levels with currently available statins. Some patients have low levels of high-density lipoprotein cholesterol (HDL-C) and/or high levels of triglycerides that respond only partially, or not at all, to statin therapy. Thus, the need for more effective drugs to normalize cholesterol levels is clear.

Two new and more effective statins are currently in Phase 3 trials and several other drugs are in development, which lower LDL-C by mechanisms that differ from those of the statins (Table).

More Effective Statins

Two new statins are now being evaluated in Phase 3 trials. One of them, rosu-

vastatin, is described in greater detail in the report based on Dr. Olsson's presentation beginning on page S152 of this publication.¹ The other drug, NK104, is also in clinical trials in the United States and other countries, but no published data on efficacy or safety are available at this printing.

Both statins are expected to offer more efficacy for a given dose and a much more impressive reduction at the first dose than do previous statins. Like other statins, rosuvastatin has demonstrated a fairly consistent reduction in LDL-C of an additional 4% to 6% with each doubling of the dose.

Inhibitors of Bile Acid Transport

Inhibitors of bile acid transport (IBATs) include resins as well as specific IBATs, one of which is cholestyramine. The rationale for bile acid transport inhibition is based on the fact that human beings have 2 to 5 g of bile acid that is continuously cycled from the liver to the gut, with only a small portion of that amount (about 300 to 600 mg) lost each day. Thus, completely blocking the bile reuptake process should greatly increase the loss of bile acid to about 1 g/day in certain individuals. That would have a tremendous effect because it would deplete the liver cell of its cholesterol and increase the number of LDL-C receptors.

Interest in the use of IBATs was generated by the Lipid Research Clinics Coronary Primary Prevention Trial,

which investigated the effects of cholestyramine in patients with elevated cholesterol levels.² Data from that trial—specifically, a 19% reduction in risk for a first myocardial infarction or coronary death in treated patients—were impressive enough to initiate the first National Cholesterol Education Program effort.

Despite the 19% reduction in risk,³ many physicians found cholestyramine to be less effective in practice because of the adverse gastrointestinal effects and the inconvenience of preparation.² The result has been poor patient adherence to the regimen. The 15% to 20% reduction in LDL-C with lower doses and the value of their use in combination with statins and other drugs have caused a rebirth in interest. This has stimulated some re-engineering of resin-based inhibitors of bile acid transport: Efficacy has been increased, and the agents encapsulation can be made with greater ease allowing physically smaller and more convenient dosing. These changes are expected to obviate at least some of the compliance issues associated with the older preparations.

One of these, colesevelam, was approved in the American market by the US Food and Drug Administration for the treatment of hypercholesterolemia in October 2000.³

The IBATs inhibit bile acid transport by entering the cell and inhibiting the active transport of bile acid rather than by competing for it in the intestinal lumen. Phase 3 clinical trials currently under way should soon provide the efficacy and safety data to determine the potential value of the first of these in clinical practice.

Inhibitors of Cholesterol Absorption

Intestinal absorption of lipids directly provides cholesterol for the liver through the clearance of chylomicron remnants, which contain most of the absorbed sterol. Intestinal cholesterol is derived from both dietary sources and from that which is delivered from the liver through the bile. Dietary modification to reduce cholesterol intake is often the first step in atherosclerosis management. Dietary

modification also complements the beneficial effects of statins and other cholesterol-lowering agents. Typically, American men still ingest about 350 mg of cholesterol per day. By comparison, American women typically ingest less than 300 mg of cholesterol per day, a level that is within the National Cholesterol Education Program guidelines. There is an even larger component of cholesterol delivered with bile (1 g or more each day), providing an enhanced opportunity to reduce hepatic cholesterol by inhibiting absorption of perhaps 800 to 1500 mg when both hepatic excretion and dietary cholesterol are considered.

One agent that directly inhibits liver and dietary cholesterol is ezetimibe,^{4,6} which is now being evaluated in clinical trials. Data from preclinical studies in animal models indicate that this drug works at the luminal pole of the enterocyte where it inhibits the intake of cholesterol by this cell.⁴ Ezetimibe is absorbed and glucuronidated in the intestinal cells. It is rapidly cleared from the blood by the liver and undergoes repeated enterohepatic recycling. Because the glucuronide is also a potent inhibitor of cholesterol absorption, the result is a biological half-life of approximately 1 day. Recent trials with ezetimibe in humans have shown average reductions in LDL-C levels from 16% to 23% with a

Table. New Lipid-Modifying Drugs in Clinical Trials or Development

- More efficacious statins (rosuvastatin, NK104)
- New bile acid binding resin (colesevelam)*
- Inhibitors of bile acid transport (resins)
- Specific inhibitors of bile acid transport
- Inhibitors of cholesterol transport
- Inhibitors of cholesterol esterification
- Triglyceride-reducing agents

*Approved for use, October 2000.

dose of 10 mg daily.^{5,6} These reductions have also been shown to be additive when the drug is used in combination with statin therapy.⁶

Inhibition of Cholesterol Esterification

A new area of cholesterol modification is the inhibition of cholesterol esterification. Here, the net result is not so much a lowering of cholesterol levels as it is a lowering of the accumulation of cholesterol in the arterial wall. Esterification of cholesterol in the macrophage leads to cholesterol storage and the development of foam cells. At present, one drug that inhibits the esterification of cholesterol (avasimibe) is being evaluated in Phase 2 trials; others are in development.

When cholesterol is taken up as part of lipoproteins in macrophages and smooth muscle cells in the arterial wall, it is stored as the ester of oleic acid in membrane-bound droplets. The formation of cholesterol oleate, however, depends on the enzyme acyl-coenzyme A cholesterol acyl-transferase (ACAT-1), which is present in virtually all cells. A second enzyme, ACAT-2, is present in cells that manufacture lipoprotein and secrete cholesterol ester in lipoproteins. ACAT-2 is less specific than ACAT-1, using a variety of fatty acids to form cholesterol esters and providing for insertion into very low LDL-C as it leaves the liver, and into chylomicrons as they leave the intestine.

Avasimibe inhibits both ACAT-1 and ACAT-2 and appears to have systemic effects.⁷ Because it may reduce the efflux of cholesterol from the gut in the chylomicrons and from liver in very low LDL-C,⁸ it may lower cholesterol levels in the blood. By preventing cholesterol ester storage in the liver, it also appears to stimulate bile acid synthesis through activating the enzyme cholesterol 7 alpha-hydroxylase.⁹ Although avasimibe does not lower cholesterol levels dramatically but instead acts on the arterial walls, this therapy necessitates careful assessment of arterial lesions to determine the right dose for beneficial effects on arteriosclerosis.

Summary

Clinical trials are now under way to evaluate 2 new and more effective statins. In addition, efforts are proceeding to evaluate newer agents that reduce cholesterol levels and cardiovascular risk by mechanisms that differ from those of statins. These newer agents include inhibitors of bile acid transport, inhibitors of cholesterol transport, and inhibitors of cholesterol esterification.

QUESTION-AND-ANSWER SESSION

Question from the Audience: In your opinion, which class of new agents might be used efficaciously in combination with statins without compromising safety?

Dr. Brown: That is certainly one of the exciting things about these new drugs and their mechanisms of action. In theory, each drug should be additive, at least to statin therapy, and perhaps all 3 of these new types of agents can be added to statins in very difficult cases.

Question from the Audience: What is your opinion regarding antioxidants and how do lipid-lowering agents affect the lipophilic vitamins A, D, E, and K?

Dr. Brown: We have an elegant theory about how atherosclerosis develops that I believe is an operative theory. Damaging lipoproteins by the LDL-C oxidative mechanism is an important aspect of atherosclerosis development. For that reason, it has been very disappointing to see results from the trials that have been done with antioxidant therapy. Several trials evaluating beta-carotene and vitamin E have failed to show any real benefit, as have trials evaluating vitamin C.

To date, no antioxidant therapy has proven to be beneficial in humans, including the most potent antioxidant that I am aware of that can be given to humans (probulcol).

Question from the Audience: Do you want to comment on trials of apo-A1 Milano infusion?

Dr. Brown: This variant version of the HDL-C protein apo-AI that has been found in Italian families by researchers in Milano has been proposed to be protective because the families seem to suffer no ill consequences from the associated low HDL-C. The infusion of the recombinant version of this protein is hypothesized to remove cholesterol from the artery wall. The real benefit of that experiment is it heightens our interest in how HDL-C actually works. The HDL-C transport system is complex. We need to know more about that before we can design a truly rational therapy to change HDL-C. I am waiting to see if it can be shown that apo-A1 Milano infusion will provide a benefit in patients with acute coronary syndromes, perhaps by stabilizing vulnerable lesions.

It is a difficult concept to accept: That the infusion of a peptide can be an acute treatment for atherosclerosis. We believe that you would need to remove significant amounts of cholesterol from the arterial cells over an extended period to provide significant impact on this disease. I await the results with great interest. I will be surprised if we see a dramatic reduction, but I have been surprised before.

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