A novel therapeutic approach to dyslipidemia

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The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines call for more aggressive lowering of low-density lipoprotein cholesterol (LDL-C) and will substantially increase the number of patients eligible for lipid-lowering therapy. Statins, the current treatment standard, have proven to be highly efficacious in lowering LDL-C and reducing coronary heart disease (CHD) risk. Because some patients are unable to tolerate 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) or they are not candidates for statin therapy, however, other cholesterol-lowering modes of therapy are needed.

Currently available nonstatin drugs often do not reliably reduce LDL-C to a desired extent or are limited in their safety and tolerability. Ezetimibe, a novel lipid-lowering agent until recently in phase III development, is the first in a new class of selective cholesterol absorption inhibitors and offers a promising new approach to the treatment of dyslipidemia.

This article reviews the cholesterol metabolic pathways and the mechanism of action of the currently available lipid-modifying agents and introduces ezetimibe, the first selective cholesterol absorption inhibitor. (Key words: cholesterol, combination therapy, dyslipidemia, ezetimibe, monotherapy)

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The link between abnormal lipid levels and the development of coronary heart disease (CHD) is well established. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) emphasis on earlier and more aggressive treatment contributes to the growing need both to treat lipid abnormalities and to stimulate the development of more efficacious and better-tolerated agents. The development of new drugs that can favorably alter the lipid profile by mechanisms that differ from currently available drugs is of great interest.

Currently, several lipid-modifying agents are available (Figure), including plant stanols and sterols, fibrates, nicotinic acids, bile acid sequestrants, and the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins). Statins remain the therapy of choice for reducing cholesterol, but agents that target novel pathways of cholesterol metabolism may enable a greater number of patients to attain the low-density lipoprotein cholesterol (LDL-C) target levels recommended in the ATP III guidelines.

Ezetimibe, approved by the Food and Drug Administration (FDA) in October 2002, is the first in a novel class of agents. Ezetimibe is a selective cholesterol absorption inhibitor. These agents block cholesterol and bile acid absorption from the intestine, resulting in up to an 18% reduction in LDL-C with once-daily dosing and a safety profile no different from that of placebo. When 10 mg of ezetimibe is combined with a low-dose statin, the complementary mechanisms of action between the two agents produces LDL-C reductions typically seen only with high-dose statin therapy.

Cholesterol pathways

Developing clinically effective modes of therapy requires an understanding of the basic principles of cholesterol balance and how they relate to the regulation of plasma concentrations of LDL-C. Cholesterol is produced endogenously (900 mg/d) and is obtained from dietary or exogenous (300 mg/d) sources. Endogenous cholesterol synthesis is the product of numerous enzymatically mediated reactions, the most important of which is the conversion of HMG CoA to mevalonic acid. This step is regulated by the enzyme HMG CoA reductase that in turn is tightly controlled by the flow of intestinal cholesterol to the liver.

Newly synthesized cholesterol is released from the liver into the circulation as triglyceride-rich, very low-density lipoprotein cholesterol (VLDL-C). As VLDL-C circulates through the body, the triglyceride component is removed, resulting in the formation of remnant particles called intermediate-density lipoproteins (IDL). The IDL are depleted of triglycerides, but rich in cholesterol, and have two possible fates: they are either taken up by receptors on the liver or converted to LDL-C. The LDL-C produced from IDL can be either removed from the circulation by hepatic LDL-C receptors, or
it penetrates the arterial walls to develop atheromas.

The exogenous pathway processes cholesterol of dietary or biliary origin. Through a poorly understood mechanism, intestinal cholesterol is absorbed from the intestine into the enterocytes that line the intestinal lumen. In the enterocyte, cholesterol is ultimately packaged into a triglyceride-rich particle called a chylomicron. Chylomicrons are released from the enterocyte and enter the circulation where they are gradually reduced in size as the triglyceride component is stripped away in much the same way the VLDL particle is degraded. The resulting chylomicron remnants are cholesterol-rich particles that are removed from the circulation by remnant receptors found on the surface of the liver. In the liver, exogenously derived cholesterol is mixed with the endogenous cholesterol and used to form bile acids or incorporated into VLDL-C and return to the circulation.

Cholesterol balance is regulated by feedback mechanisms between the endogenous and exogenous pathways. Reduced delivery of intestinal cholesterol to the liver increases HMG CoA reductase activity and enhances cholesterol synthesis. Contrarily, high intestinal uptake of cholesterol inhibits HMG CoA activity, reduces hepatic synthesis, decreases LDL-C uptake, and increases plasma LDL-C.

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The liver and intestine are likely targets for cholesterol-modification modes of therapy because of their central role in the regulation of the cholesterol balance. The liver is the primary target for therapeutic modalities designed to reduce cholesterol synthesis (eg, statins), whereas the intestine is the target of modes of therapy designed to limit cholesterol uptake (eg, the novel cholesterol absorption inhibitor ezetimibe).

**Mechanism of action of currently available drugs**

- **Statins**—Statins have their effect largely by inhibiting the activity of the HMG CoA reductase enzyme. Reduced enzyme activity decreases the amount of free hepatic cholesterol and stimulates an upregulation of LDL receptors located on the surface of the hepatocytes to

Figure. Currently available lipid-modifying drugs and summary of their mechanism of action.
increase cholesterol uptake (principally LDL-C) from the circulation. Statins have both direct and indirect effects on cholesterol metabolism that results in a decline of LDL-C: they directly decrease cholesterol synthesis that in turn stimulates an increased uptake of cholesterol from the blood, thereby increasing the removal of cholesterol from the circulation. Statins also effect moderate high-density lipoprotein cholesterol (HDL-C) raising and triglyceride (TG) lowering.

**Bile acid sequestrants**—A decline in LDL-C levels can also be achieved by directly increasing cholesterol loss from the body. Augmentation of cholesterol loss has been achieved for many years with the use of bile acid sequestrants. A significant portion of the cholesterol entering the liver is eventually converted into bile acids. Bile acids are secreted into the lumen of the small intestine and are responsible for the absorption of fat-soluble vitamins and essential fatty acids.

Bile acids are recycled for future use by transporters in the intestine that return them to the liver. Bile acid sequestrants prevent this recycling by interfering with the ability of the transporter to move bile acids back to the gall bladder. Consequently, the bile is trapped in the intestine and is removed from the body with the feces. This process effectively removes cholesterol from the body because bile acids are synthesized from cholesterol. The effectiveness of this approach, however, is limited because the liver has a remarkable capacity to upregulate its own rate of cholesterol synthesis in order to produce more bile in the face of a deficit. This compensatory increase in cholesterol synthesis by the liver consequently blunts the cholesterol-lowering action of the sequestrant, limiting its ability to lower plasma LDL-C levels.

**Fibrates**—Fibrates have limited capacity to lower LDL-C levels. These agents are most useful in the treatment of isolated hypertriglyceridemia and combined hypercholesterolemia with elevated triglyceride concentrations. Fibrates primarily lower the triglyceride concentration and raise the HDL-C levels. Fibrates have their effect by stimulating fatty acid oxidation in muscle and the liver. In the liver, increased oxidative metabolism of fatty acids is associated with increases in lipoprotein lipase activity, the enzyme essential to fatty acid metabolism and in the uptake of fatty acids by skeletal muscle.

**Nicotinic acid**—Nicotinic acid is used primarily to treat hypercholesterolemia, but it also lowers the triglyceride concentration and increases the HDL-C level. Nicotinic acid works primarily by inhibiting the transport of free fatty acids from the peripheral tissues to the liver. This action reduces both the hepatic synthesis of triglycerides and the hepatic secretion of VLDL-C. Nicotinic acid may also limit the conversion of VLDL-C to LDL-C and initiate a shift in LDL from the small, dense atherogenic type to the large, buoyant, less-atherogenic particles.

**Plant stanols and sterols**—Plant stanols and sterols, currently available as food supplements and in some margarines, block cholesterol absorption from the intestinal lumen by interfering with the production and transport of micelles and ultimately, the formation of lipid-rich chylomicrons and chylomicron remnants. Although relatively effective in reducing LDL-C, these agents must be taken three times daily to be effective.

Given the limitations of currently available lipid-lowering approaches, a therapy or combination of therapeutic modalities that is tolerable, offers safe, convenient dosing, and removes cholesterol from the body without triggering compensatory hepatic mechanisms, may achieve superior LDL-C reductions.

**The novel cholesterol absorption inhibitor ezetimibe**

Approximately 50% of the total cholesterol found in the gut after a meal is absorbed by the intestinal enterocyte and passes into the circulation in the form of a triglyceride-rich chylomicron. The unabsorbed cholesterol is eliminated with the feces. Low-cholesterol diets can reduce the pool of cholesterol available for intestinal absorption, but such diets appear to have only a minor impact on plasma cholesterol levels. Blocking the absorption of cholesterol from the intestinal lumen may have a greater effect on the amount of cholesterol absorbed than would dietary restriction alone. The search for an effective, convenient, safe, and better-tolerated drug for the reduction of cholesterol and prevention of CHD has led to the development of a novel class of lipid-reducing agents, the selective cholesterol absorption inhibitors.

Ezetimibe, the first in a new class of selective cholesterol absorption inhibitors, reduces plasma cholesterol by selectively inhibiting the absorption of dietary and biliary cholesterol from the intestine. Early studies in animals show that ezetimibe lowers both serum and liver cholesterol concentrations in a dose-dependent manner. Ezetimibe is rapidly glucuronidated in the gut and liver, and the glucuronidated derivative is the active, more potent form of the drug. Both ezetimibe and its glucuronide derivative undergo extensive enterohepatic circulation and are ultimately secreted into the bile. Glucuronidated ezetimibe is returned to the intestinal lumen when bile is secreted in response to a high fat meal and localizes to the brush border membrane of the intestinal mucosal cell. Glucuronidated ezetimibe appears to specifically inhibit free cholesterol uptake into the enterocyte by interacting with a cholesterol transporter; however, its exact mechanism of action remains to be elucidated.

Because this article was prepared before FDA approval and while ezetimibe was undergoing phase III testing, content here is based on many of the results of the phase II development program. The goals of the phase II trials were to describe the dose-response relationship of ezetimibe, to investigate the existence of any food interactions, to determine if differences existed between morning and evening dosing, and to determine dosing regimens for phase III trials. The phase II trials also investigated the pharmacokinetic and pharmacodynamic interaction between ezetimibe and several statins, as well as the magnitude of LDL-C reduction when the drug was given in combination with statins.

Patients included in phase II trials are representative of those seen by primary care physicians. Total cholesterol and LDL-C levels at randomization were greater than 250 mg/dL and greater than 130 mg/dL, respectively, and triglyceride concentrations were less than 300 mg/dL. Patients with diabetes were excluded.
The first phase II trials were small, placebo-controlled trials that randomly assigned patients into groups that received ezetimibe at doses between 1 mg and 40 mg for approximately 8 weeks. One group received 40 mg of lovastatin as a benchmark against which to assess the lipid-lowering actions of ezetimibe. The results of these studies indicated a small, dose-dependent effect for ezetimibe, with the maximal LDL-C reduction achieved at once-daily dosing of 10 mg to 20 mg. Tolerability, side effects, and biochemical abnormalities were no different from those seen with placebo. This small pilot trial was followed by a 12-week, placebo-controlled, dose-ranging study. Approximately 50 patients were randomly assigned to each study arm using a dose range of 1 mg to 10 mg of ezetimibe per day. The results confirmed the findings of the smaller dose-ranging trial and demonstrated a peak LDL-C reduction of 18% from baseline at a dose of 10 mg/d.

To determine if the timing of dosing or the presence of food had an impact on LDL-C reduction, another phase II study evaluated the lipid-lowering effects of 5 mg and 10 mg of ezetimibe per day administered in morning and evening doses with and without food to approximately 189 patients. These studies found no significant differences between morning and evening dosing with 10 mg of ezetimibe, achieving LDL-C reductions of 17.5% and 18.2%, for morning and evening dosing respectively. Reductions in LDL-C were also unaffected by the presence (or absence) of food.

In total, the phase II monotherapy studies included 124 patients who received 5 mg of ezetimibe, 118 who received 10 mg, and 87 who received placebo. Pooling the data reveals a consistent dose-response effect, with a peak LDL-C reduction of 18.5% at 10 mg/d. Ezetimibe showed essentially no effect on triglyceride concentrations and a small, but statistically significant, increase of 3.5% in HDL-C levels.

A second arm of the phase II program was designed to test the effectiveness, tolerability, and safety of ezetimibe in combination with currently available agents. Each trial included 32 patients with elevated LDL-C and tested the cholesterol-lowering effect of ezetimibe, 10 mg/d, as monotherapy, and in combination with atorvastatin calcium, 10 mg/d; fluvastatin sodium, 20 mg/d; and fenofibrate, 200 mg/d. Ezetimibe monotherapy reduced LDL-C cholesterol by 22.7% from baseline compared with 40% with atorvastatin. Combination therapy with atorvastatin decreased LDL-C by 55%. Ezetimibe, when compared with fluvastatin, reduced LDL-C by 20.2% versus 12.8% for fluvastatin. When taken together, the combination achieved a reduction of 32.0% from baseline.

The trial that compared ezetimibe with fenofibrate demonstrated that ezetimibe decreased LDL-C by 22.3% from baseline versus 13.5% with the fibrate. The two drugs in combination produced a 36.3% reduction in LDL-C.

From the results of these small but well-designed studies, it can be concluded that ezetimibe, when used as monotherapy, produces clinically significant reductions in LDL-C compared with a low dose of either atorvastatin or fluvastatin. In addition, these trials suggest that combination therapy of ezetimibe with atorvastatin, fluvastatin, or fenofibrate leads to LDL-C reductions greater than those observed when the agents are administered alone.

The overall results of the phase II-development program indicate that the selective cholesterol absorption inhibitor ezetimibe is effective both as monotherapy and in combination with several statins. The coadministration trials also found that the combination of ezetimibe with statins or fenofibrate was safe and that ezetimibe did not alter the pharmacokinetics of the other agents or vice versa. The phase II trials established that ezetimibe achieved maximal cholesterol lowering at doses between 10 mg/d and 20 mg/d. These studies also demonstrated that ezetimibe was well tolerated, with a side effect profile no different from that of placebo.

After the completion of the phase II trials, the LDL-C-lowering effect of ezetimibe was tested in larger and longer trials. The third phase of the development program was designed to determine whether ezetimibe could provide consistent and predictable reductions in LDL-C when used as monotherapy, to evaluate the drug’s efficacy as an adjunct to dietary therapy, to determine whether ezetimibe could provide consistent LDL-C lowering when coadministered with a statin at any dose, and to further describe its safety and tolerability profile.

The purpose of the first phase III study was to evaluate the efficacy of ezetimibe versus placebo. This double-blind, randomized, parallel-group trial included 820 patients with LDL-C levels between 130 mg/dL and 250 mg/dL and triglyceride concentrations less than 350 mg/dL. Before randomization, all patients completed 6 to 12 weeks of drug washout and diet, followed by 3:1 randomization and 12 weeks of active treatment. The primary efficacy endpoint was the percentage reduction in LDL-C from baseline, with changes in total cholesterol, triglyceride, and HDL-C levels as secondary endpoints. Ezetimibe treatment reduced LDL-C by 18%, with a 12% decrease in total cholesterol, a 4.1% decrease in triglycerides, and a 1% increase in HDL-C.

The safety profile of ezetimibe was similar to that of placebo, with no clinically significant changes in creatine kinase or hepatic transaminase levels, and with no effect on the absorption of fat-soluble vitamins A, D, E, α-carotene, and β-carotene. The most common side effects in both the active treatment and placebo groups were headache, upper respiratory tract infections, and back pain not believed to be related to either ezetimibe or placebo.

At the conclusion of the 12-week study, all patients were enrolled in an open-label extension trial designed to provide confirmatory data of the stability of the lipid response and to assess long-term safety. In this extension study, the investigators will consider adding a statin to ezetimibe monotherapy in those patients not achieving the LDL-C target levels recommended in the ATP III guidelines.

A series of randomized, double-blind, placebo-controlled, factorial-design phase III trials investigating the coadministration of ezetimibe, 10 mg, with most available doses of simvastatin, lovastatin, pravastatin sodium, and atorvastatin is ongoing.
In addition to confirming the efficacy and safety of using ezetimibe, 10 mg, in combination with currently available statins, these studies are designed to assess whether a three-step statin titration—from 10 mg to 20 mg, 20 mg to 40 mg, and 40 mg to 80 mg—is better than, as good as, or not as good as a one-step administration of a low-dose statin and 10 mg of ezetimibe in patients classified by ATP III as having a 10-year risk of CHD greater than 10% with LDL-C level greater than 130 mg/dL despite low-dose statin monotherapy.

Comment
The actual number of patients requiring LDL-C reduction will increase as more patients become eligible for cholesterol-lowering therapy with ATP III. Ezetimibe monotherapy at 10 mg/d offers an excellent alternative for patients who cannot tolerate statins or those requiring moderate LDL-C reductions. Coadministration of ezetimibe and a statin offers an LDL-C reduction in addition to that achieved with statin therapy alone and is associated with an excellent tolerability and safety profile and ease of use.

Taken as a whole, the phase II and III studies indicate that ezetimibe, the first in a new class of selective cholesterol absorption inhibitors, is effective as monotherapy and complements the LDL-C–lowering effects of statins. Monotherapy with ezetimibe at a once-daily dose of 10 mg lowers LDL-C levels by 18% to 20%. When coadministered with a low-dose statin, ezetimibe produces LDL-C reductions usually observed only with high doses of statins. Furthermore, the ezetimibe–low-dose statin combination maximizes LDL-C reductions with a safety profile similar to that of placebo.

References
The purpose of this quiz is to provide a convenient means of self-assessment of your reading of the scientific content of this Supplement to the January 2003 issue of JAOA. Indicate your answers in the spaces provided so that you can easily check them with the answers that will be published in the April 2003 issue of JAOA.

1. A 50-year-old man is seen in routine checkup. He has no history of cardiovascular disease and denies a history of hypertension and diabetes. His mother is 77 years old and has type 2 diabetes mellitus, and his father died at age 70 years of colon cancer; neither parent had a history of heart disease. The patient had smoked a pack of cigarettes a day into his mid-20s but has not smoked since.

   Vital signs were blood pressure, 136/82 mm Hg; pulse, 80 beats/min; height, 70 inches; weight, 192 pounds; waist, 41 inches. Findings at physical examination were unremarkable. His fasting lipid profile revealed the following values: total cholesterol, 215 mg/dL; triglyceride concentration, 119 mg/dL; high-density lipoprotein cholesterol, 38 mg/dL. His fasting blood glucose level was 108 mg/dL.

   Which of the following would be considered a major risk factor for coronary heart disease (CHD) in this individual?
   - (a) his age of 50 years
   - (b) blood pressure of 136/82 mm Hg
   - (c) triglyceride concentration of 119 mg/dL
   - (d) fasting glucose level of 108 mg/dL
   - (e) family history of type 2 diabetes mellitus

2. The patient’s LDL-C level is calculated to be 153 mg/dL. His 10-year Framingham risk of CHD is determined to be 10%. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, what LDL-C goal would you recommend for this patient?
   - (a) less than 80 mg/dL
   - (b) less than 100 mg/dL
   - (c) less than 130 mg/dL
   - (d) less than 160 mg/dL
   - (e) less than 190 mg/dL

3. According to the NCEP ATP III guidelines, what initial therapy would you recommend to attain the LDL-C goal?
   - (a) therapeutic lifestyle changes
   - (b) a statin
   - (c) a bile acid sequestrant
   - (d) a fibric acid derivative
   - (e) a thiazolidinedione

4. Which of the following would not be considered a CHD risk equivalent according to the NCEP ATP III guidelines?
   - (a) peripheral vascular disease
   - (b) type 2 diabetes mellitus
   - (c) 10-year Framingham CHD risk score of 25%
   - (d) deep venous thrombosis
   - (e) symptomatic carotid artery disease

5. A statin is prescribed for a patient with a high LDL-C level. A complete lipid profile is obtained 6 weeks later, and the patient is not at goal. If the dose of the statin is doubled, one would expect the LDL-C level to decrease by what additional percentage?
   - (a) 2%
   - (b) 6%
   - (c) 10%
   - (d) 25%
   - (e) 50%

6. A patient with type 2 diabetes mellitus achieved tight control of blood pressure and glucose level. With glycemic control, the triglyceride concentration normalized, but the LDL-C remained elevated. Atorvastatin was prescribed and titrated to the maximum dose. Subsequent lipid analysis showed the LDL-C level to be 145 mg/dL. Which of the following would be the next step?
   - (a) Change to a different statin.
   - (b) Discontinue atorvastatin and begin a bile acid resin.
   - (c) Add fenofibrate to the drug regimen.
   - (d) Add another statin.
   - (e) Add a cholesterol absorption inhibitor or niacin.

7. Reduction in coronary heart disease (CHD) events has been clearly demonstrated by lowering LDL-C in both primary (West of Scotland Coronary Prevention Study [WOSCOPS], Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/Texas CAPS]) and secondary (Scandinavian Simvastatin Survival Study [4S], Cardiac and Recurrent Events [CARE]) disease prevention trials.
   - (a) True
   - (b) False

8. A patient with CHD or its risk equivalents should attain an LDL-C level of less than:
   - (a) 100 mg/dL
   - (b) 130 mg/dL
   - (c) 150 mg/dL
   - (d) 160 mg/dL
   - (e) 190 mg/dL

9. Which of the following best describes the mode of action of ezetimibe?
   - (a) potent inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A reductase enzyme
   - (b) stimulation of fatty acid oxidation in the liver with associated increase in lipoprotein lipase activity
   - (c) sequestrant of bile acids within the ileum
   - (d) inhibition of cholesterol absorption in the proximal small bowel
   - (e) interference with production and transport of micelles

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