Coadministration of Multidrug Therapy to Achieve Lipid Goals

Margo A. Denke, MD

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the drug of first choice for lowering low-density lipoprotein cholesterol (LDL-C) levels and reducing risk of coronary heart disease (CHD). Current therapeutic use of statins, however, has resulted in only a small percentage of patients reaching their LDL-C treatment goal. Despite the clinical trial data supporting early aggressive use of statins, prescribing physicians are more likely to use lower doses of statins, leaving many patients at high risk of CHD short of goals. The barrier to achieving cholesterol treatment goals does not appear to be the decision to initiate statin therapy, but the failure of prescribers to titrate statin therapy to a dose sufficient to achieve goals.

An alternative to statin monotherapy is coadministration of a statin and a second agent that has a different mechanism of action. This approach can increase the likelihood of achieving target lipid levels and may be more acceptable to physicians. The coadministration of ezetimibe and simvastatin reduces cholesterol derived from both endogenous and exogenous sources. Simvastatin reduces the hepatic production of cholesterol, and ezetimibe decreases the intestinal absorption of dietary and biliary free cholesterol. The coadministration of low doses of these agents has been proved to be as effective as high-dose statin therapy in reducing LDL-C levels and assisting patients achieve their treatment goals.

According to the Adult Treatment Panel III (ATP III) treatment guidelines, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) should be used as first-line therapy for lowering low-density lipoprotein cholesterol (LDL-C) levels. Because of their proven ability to lower LDL-C levels and reduce cardiovascular events, statins remain the preferred treatment for most patients with dyslipidemia.2 Despite the overwhelming evidence supporting the efficacy of statin therapy, clinical practices outside of clinical trials find that a high percentage of patients do not reach their ATP III target LDL-C goals.3 Among the many possible reasons for this trend are underidentification of patients at high risk of coronary heart disease (CHD), insufficient dosing of statins, and side effects associated with high-dose statin use.3

When target LDL-C levels are not achieved, especially in the patients at high risk, clinicians face treatment options, including increasing the statin dose, changing to another statin of higher potency, and adding a complementary drug to statin therapy.4 In clinical practice, these options are not effectively used, leaving patients short of goal. An additional treatment option is the use of coadministered drug therapy.2,5

Coadministration of two lipid-lowering agents is a valid therapeutic option for those patients with severe dyslipidemia, those who cannot achieve LDL-C target levels on monotherapy, and those patients in whom intolerance to higher doses of medications develops.5 Because statins are proved to be effective in lowering LDL-C levels, coadministration therapy should include a statin unless use of a statin is contraindicated.5 The choice of the other drug in the coadministration therapy is broad. Each class of lipid-lowering drugs has a distinct mechanism of action that has different effects on lipids (Figure).7

Coadministration therapy uses two or more drugs, each with different, and likely complementary, mechanisms of action, making it possible to tailor therapy to the specific lipid-lowering needs of the patient and the patient’s ability to tolerate drugs.7 The coadministration of multiple drugs should, at a minimum, provide sufficient LDL-C lowering to achieve target; it may, in addition, provide triglyceride lowering and increases in high-density lipoprotein (HDL-C). Although doubling the dose of a statin usually achieves a 6% reduction in LDL-C levels, at least a 10% additional reduction in LDL-C levels can be achieved with coadministration therapy.5

Commonly Used Modes of Lipid-lowering Coadministration Therapy

Bile Acid Sequestrants and Statins

A bile acid sequestrant coadministered with statin therapy has been shown to reduce LDL-C levels by an additional 20% to 30%.8 In their study, Knapp and colleagues9 observed a 42% mean reduction in LDL-C levels in patients who were treated with coadministration of a bile acid sequestrant (colesevelam hydrochloride) and a statin (simvastatin) compared

Supported by an unrestricted educational grant from Merck/Schering-Plough Pharmaceuticals

Dr Denke is on the advisory board of Merck/Schering-Plough Pharmaceuticals and on the speakers bureau for Merck & Co and Merck/Schering-Plough Pharmaceuticals. She also is an adviser and a coauthor on the Ezetimibe Add-on to Statin for Effectiveness (EASE) trial. Address correspondence to Margo A. Denke, MD, FACE, FACP, FACE, Clinical Professor, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr, San Antonio, TX 78284. Email: mdenke@ktc.com

Figure S17
with a 34% reduction in patients who were treated with simvastatin alone.

Although bile acid sequestrants are associated with few serious adverse events, large doses may be needed for efficacy. As the dose is increased, patient nonadherence also increases because of multiple daily dosing and gastrointestinal discomfort. In addition, triglyceride levels have been shown to be increased by the use of bile acid sequestrants; therefore, these drugs should not be used in patients with the metabolic syndrome.

**Fibrates and Statins**

The coadministration of low-dose statins and fibrates has been shown to have complementary effects on triglyceride and LDL-C levels, and this therapy may be useful in those patients who have mixed hyperlipidemia characterized by elevated triglyceride and LDL-C concentrations. In a study by Liamis et al to determine the safety and efficacy of coadministration of fibrates (fenofibrate [200 mg/d] or ciprofibrate [100 mg/d]) and small doses of atorvastatin calcium (5 mg/d), fibrate therapy resulted in a significant decrease in total cholesterol and LDL-C levels. Fibrate-statins had a further decrease, and it was well tolerated.

Clinical studies have shown that coadministration of statins and fibrates significantly reduces both LDL-C and triglyceride levels, but a number of safety concerns have been identified with this approach. This coadministration is associated with an increased risk of rhabdomyolysis and myopathy beyond that normally observed with either drug class alone; therefore, cautious consideration of the risks versus the benefits must be carefully weighed before coadministering these agents.

**Niacin and Statins**

Clinical trial data demonstrate that coadministration of a statin and niacin reduces LDL-C levels by an additional 16% comple-
pared with statin therapy alone.11 This course of therapy, however, may be associated with serious side effects as concomitant use of niacin and statin is associated with an increased risk of myopathy. Additionally, niacin used either in monotherapy or coadministration therapy is associated with vasodilatory side effects that are intolerable to some patients.5 This flushing has been shown to lead to discontinuation of therapy in up to 10% of patients taking niacin.12 Niacin has been shown to worsen glycemic control in patients with diabetes mellitus and may exacerbate gout.57

**New Treatment Option in Coadministration Therapy**

The recent development of the cholesterol absorption inhibitor ezetimibe provides an additional option in the treatment of lipoprotein disorders.6 Ezetimibe is the first drug that specifically blocks absorption of intestinal cholesterol. This action effectively reduces plasma LDL-C levels, because intestinal absorption may account for up to 50% of the cholesterol found in the circulating lipoproteins.13 Ezetimibe inhibits as much as 54% of all intestinal cholesterol absorption without affecting uptake of triglycerides or lipidsoluble vitamins.13 The mechanism of action of the statin-ezetimibe coadministration is attractive: the site of action and its alteration of lipid metabolism for both drugs are well characterized. Coadministration of ezetimibe and a statin reduces both intestinal cholesterol absorption and hepatic cholesterol synthesis, resulting in a significant reduction of the plasma LDL-C level.5

Lipid lowering with ezetimibe coadministered with low-dose statins is similar to that of high-dose statin monotherapy as LDL-C reductions up to 55% to 60% have been demonstrated.13 Ezetimibe (10 mg/d) plus simvastatin (10 mg/d) improved lipid profiles as effectively as simvastatin (80 mg/d). This coadministration therapy obviates the need for high statin doses.34,15 Davidson et al14 demonstrated that coadministration of ezetimibe and simvastatin resulted in significantly greater reductions in LDL-C (13.8%) than simvastatin alone (P<.01). Similarly, Goldberg et al15 noted that coadministration of ezetimibe and simvastatin was more effective than simvastatin (10 mg/d, 20 mg/d, 40 mg/d, or 80 mg/d) alone in reducing LDL-C levels (~53.1% vs ~38.3%). In addition, 82.4% of patients in whom the two agents were coadministered achieved an LDL-C target level less than or equal to 100 mg/dL, compared with 42.9% of patients receiving simvastatin monotherapy.15

Further evidence supporting the ability of ezetimibe and simvastatin in helping patients to achieve their National Cholesterol Education Program (NCEP) target levels comes from a study of 769 patients who failed to achieve goal despite ongoing statin therapy.16 The addition of ezetimibe to statin therapy resulted in an additional 21.4% reduction in LDL-C (P<.001 vs statin). The greater LDL-C reduction elicited by coadministration of ezetimibe and statin allowed 71.5% of patients to achieve their LDL-C goal compared with 18.9% of those who received statin plus placebo.16 Two recent trials confirmed this finding.17,18 The Ezetimibe Add-on to Statin for Effectiveness (EASE) trial17 demonstrated that coadministration of the two agents provided a 25% greater reduction in LDL-C than statin plus placebo for all CHD risk categories. The combination also significantly increased the percentage of patients reaching ATP III target levels compared with statin alone (Table 1). Similarly, Feldman and colleagues18 reported that coadministration of ezetimibe (10 mg) and any dose of simvastatin produced greater reductions in LDL-C and allowed more patients at high risk to achieve their ATP III target goal (<100 mg/dL) after 5 weeks of therapy (P<.001) than monotherapy with simvastatin (20 mg).

The safety profile for ezetimibe coadministered with a statin is similar to that of statin monotherapy (Table 2), but in some patients, hypersensitivity reactions, including angioedema and rash, were reported in postmarketing experience.19 **Patients Who May Benefit From Coadministration of Ezetimibe and a Statin**

Patients who may benefit from coadministration of ezetimibe and a statin include those who are intolerant to high-dose statin monotherapy and are thus unable to achieve their LDL-C treatment goal. Additionally, ezetimibe–statin therapy may increase the number of patients—particularly patients with diabetes mellitus, existing CHD, and the metabolic syndrome—reaching their NCEP lipid goals. Also, aggressive lipid lowering can be challenging in patients with type 2 diabetes mellitus who are taking multiple drugs to regulate glucose metabolism. In diabetic patients currently receiving thiazolidinediones, ezetimibe (10 mg/d) added to simvastatin (20 mg/d) reduced LDL-C levels by 21% compared with diabetic patients monotherapy with simvastatin (20 mg/d).19

The following case presentation illustrates the decision-making process in the development of a lipid-lowering treatment strategy for a typical patient seen in primary care practice.

**Illustrative Case Presentation**

A 51-year-old male construction worker sees a primary care physician in the office for a physical examination. Currently, he smokes half a pack of cigarettes daily, down from the four packs he used to smoke each day. He has a positive family history for CHD (father died of myocardial infarction in his late 40s) but no history of hypertension in the family. His blood pressure is 135/90 mm Hg, his body mass index is 32, his self-reported waist circumference is 32 inches, and his fasting blood glucose level is 115 mg/dL.

A risk-factor analysis reveals that he has four categorical risk factors, including hypertension, family history, smoking, and low HDL-C level, and his 10-year risk for a CHD event is 25%. His waist circumference, high triglyceride concentrations, low HDL-C level, hypertension, and impaired fasting glucose indicate that he also has the metabolic syndrome.

His fasting lipid levels before any intervention were as follows:
- Total cholesterol, 254 mg/dL;
- LDL-C, 156 mg/dL;
- HDL-C, 32 mg/dL;
- Triglyceride concentration, 195 mg/dL; and
- Non–HDL-C, 222 mg/dL.

After reviewing his risk factors and fasting lipid profile, his physician...
develops a treatment strategy to reduce the patient’s risk by initiating therapeutic lifestyle changes (TLC) and drug therapy. Treatment goals for this patient include achieving an LDL-C level of less than 100 mg/dL and a non–HDL-C level of less than 130 mg/dL.

Recommended lifestyle changes include a diet that obtains less than 7% of calories from saturated fat and an intake of dietary cholesterol of less than 200 mg/d. The caloric restriction should be designed to help him lose weight, but minimally, the patient should be encouraged not to gain more weight. In addition, a realistic physical activity program should be designed and implemented.

**Intermediate Outcomes**

The patient lost 10 pounds in the 3 months since initiation of TLC and statin therapy.

Three months posttreatment, his lipid levels were as follows:
- Total cholesterol, 220 mg/dL (13% reduction);
- LDL-C, 134 mg/dL (14% reduction);
- HDL-C, 34 mg/dL (6% increase);
- Triglyceride concentration, 175 mg/dL (10% reduction); and
- Non–HDL-C, 186 mg/dL (16% reduction).

Is more aggressive drug therapy indicated? What should this therapy include?

The estimated benefits of next-dose statin or combination therapy are as follows:

**Increase statin dose:**
- Total cholesterol, 191 mg/dL (25% reduction from baseline);
- Triglyceride concentration, 160 mg/dL (9% reduction from baseline);
- LDL-C, 124 mg/dL (7% reduction from baseline);
- HDL-C, 35 mg/dL (3% increase over baseline);
- Non–HDL-C, 156 mg/dL (30% reduction from baseline); and
- Glucose, 115 mg/dL (baseline).

**Statin plus ezetimibe:**
- Total cholesterol, 168 mg/dL (25% reduction from baseline);
- Triglyceride concentration, 145 mg/dL (17% reduction from baseline);
- LDL-C, 104 mg/dL (17% reduction from baseline);
- HDL-C, 35 mg/dL (3% increase over baseline);
- Non–HDL-C, 133 mg/dL (40% reduction from baseline); and
- Glucose, 115 mg/dL (baseline).

Thus, the combination of ezetimibe and a statin would achieve the greatest reductions in the triglyceride concentration and the LDL-C and non–HDL-C levels. A statin plus niacin is estimated to achieve the greatest reduction in triglyceride concentration and greatest increase in HDL-C level and an increase in blood glucose level.

**Comment**

Coadministration of a statin and another agent can provide greater LDL-C lowering than with either agent used as monotherapy. Despite this advantage, acceptance of coadministration therapy has been appropriately slowed owing to safety concerns and inconvenience, particularly when niacin, bile acid sequestrants, and fibrates were the drugs to consider for coadministration with a statin.

The advent of ezetimibe has changed the outlook on coadministration therapy for lipid lowering. The coadministration of ezetimibe (10 mg/d) and simvastatin (10 mg/d) has been shown to reduce LDL-C as effectively as monotherapy with simvastatin (80 mg/d) and has been well tolerated. These data suggest that this combination is a safe and effective addition to the choices of lipid-modifying modes of therapy.

---

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Receiving Placebo Plus Statin, %</th>
<th>Patients Receiving Ezetimibe Plus Statin, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>20.6</td>
<td>71.0</td>
</tr>
<tr>
<td>CHD or CHD Risk Equivalent</td>
<td>17.3</td>
<td>69.5</td>
</tr>
<tr>
<td>≥2 Risk Factors</td>
<td>32.2</td>
<td>75.1</td>
</tr>
<tr>
<td>≤2 Risk Factors</td>
<td>52.4</td>
<td>90.7</td>
</tr>
</tbody>
</table>

*Coadministration of ezetimibe with statin versus coadministration of placebo and statin (n=4888). All patients not at goal at baseline. Statis used: atorvastatin calcium, 40%; simvastatin, 31%; pravastatin sodium, 24%; fluvastatin sodium, 7%; lovastatin, 4%. (Source: Pearson T, et al. Ezetimibe added to statin therapy reduces LDL-C and improves goal attainment in patients with hypercholesterolemia. Abstract presented at: 2004 Scientific Session of the American College of Cardiology, March 7-10, 2004; New Orleans, La.)*


References


Table 2
Safety of Ezetimibe Plus Simvastatin Versus Statin Monotherapy*

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=259)</th>
<th>Ezetimibe, 10 mg (n=262)</th>
<th>All Statins* (n=936)</th>
<th>Ezetimibe, 10 mg, Plus All Statins (n=925)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Body as a Whole:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ General Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Chest pain, %</td>
<td>1.2</td>
<td>3.4</td>
<td>2.0</td>
<td>1.8</td>
</tr>
<tr>
<td>□ Dizziness, %</td>
<td>1.2</td>
<td>2.7</td>
<td>1.4</td>
<td>1.8</td>
</tr>
<tr>
<td>□ Fatigue, %</td>
<td>1.9</td>
<td>1.9</td>
<td>1.4</td>
<td>2.8</td>
</tr>
<tr>
<td>□ Headache, %</td>
<td>5.4</td>
<td>8.0</td>
<td>7.3</td>
<td>6.3</td>
</tr>
<tr>
<td>□ Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Abdominal pain, %</td>
<td>2.3</td>
<td>2.7</td>
<td>3.1</td>
<td>3.5</td>
</tr>
<tr>
<td>□ Diarrhea, %</td>
<td>1.5</td>
<td>3.4</td>
<td>2.9</td>
<td>2.8</td>
</tr>
<tr>
<td>□ Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Pharyngitis, %</td>
<td>1.9</td>
<td>3.1</td>
<td>2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>□ Sinusitis, %</td>
<td>1.9</td>
<td>4.6</td>
<td>3.6</td>
<td>3.5</td>
</tr>
<tr>
<td>□ Upper Respiratory Tract Infection, %</td>
<td>10.8</td>
<td>13.0</td>
<td>13.6</td>
<td>11.8</td>
</tr>
<tr>
<td>□ Musculoskeletal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Arthralgia, %</td>
<td>2.3</td>
<td>3.8</td>
<td>4.3</td>
<td>3.4</td>
</tr>
<tr>
<td>□ Back pain, %</td>
<td>3.5</td>
<td>3.4</td>
<td>3.7</td>
<td>4.3</td>
</tr>
<tr>
<td>□ Myalgia, %</td>
<td>4.6</td>
<td>5.0</td>
<td>4.5</td>
<td>4.5</td>
</tr>
</tbody>
</table>


Supplements to the Journal are a source of CME

The new 3-year continuing medical education cycle of the American Osteopathic Association (AOA) began January 1, 2004. One way to earn CME credit for this CME cycle is through the reading of AOA publications.

Nearly every issue of JAOA—the Journal of the American Osteopathic Association and all supplements to the JAOA carry CME quizzes. AOA members can earn 2 hours of Category 1-B CME credit for each quiz they complete and submit to the AOA Division of Continuing Medical Education. AOA members can complete these quizzes electronically on DO-Online, which is located at www.do-online.org AOA members can also fill in the quiz answers directly on the forms located inside the JAOA and its supplements. They should then mail the completed quiz forms to the Division of Continuing Medical Education, American Osteopathic Association, 142 E Ontario St, Chicago, IL 60611-2864.

AOA members who do not complete the quizzes can still obtain one-half hour of Category 2-B credit for each issue of the JAOA and each supplement by informing the AOA Division of Continuing Medical Education of the issues they read. Members can obtain the same credit for reading The DO, The Whole Patient, and other medical publications.

For more information on earning CME credit by reading medical journals, AOA members can call (800) 621-1773, Ext 8262, or (312) 202-8262; they can send e-mail to drodgers@aoa-net.org; or they can fax questions to (312) 202-8200. In addition, AOA members can write to the AOA Division of Continuing Medical Education.