Ezetimibe (Zetia): a new type of lipid-lowering agent

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Coronary heart disease is the leading cause of death in adults in the USA. It has been associated with elevated levels of low-density lipoprotein (LDL) cholesterol and reduced levels of high-density lipoprotein (HDL) cholesterol. Premature coronary atherosclerosis is a major manifestation of hyperlipidemia. Because atherosclerosis is one of the major causes of coronary heart disease, controlling plasma lipid levels is essential. According to the National Health and Nutrition Examination Survey (1988–1994) and the National Cholesterol Education Program Adult Treatment Panel III, an estimated 100,870,000 American adults have total cholesterol levels ≥200 mg/dL and are at increased risk of developing coronary heart disease. Treatment should address both diet and pharmacological therapy regimens. It may be concluded that 7% of American adults are candidates for lipid-lowering agents, since dietary intervention alone reduces LDL cholesterol by only 10%. Modification of risk factors such as hyperlipidemia may be beneficial in slowing the atherosclerotic process and preventing cardiovascular mortality (1).

Therapeutic lifestyle changes include dietary changes, weight reduction, and increased physical activity. For those patients who are at high risk of coronary heart disease, LDL cholesterol–lowering drug therapy may be essential. Such drugs include hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), bile acid sequestrants, nicotinic acid, and fibric acids. Guidelines indicating the utilization of these agents have been set by the National Cholesterol Education Program Adult Treatment Panel III (1).

Ezetimibe (Zetia) is distinct from these agents because it does not inhibit cholesterol synthesis in the liver or increase bile acid excretion. It belongs to a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. Ezetimibe's pharmacological effect is complementary to that of the statins (1).

INDICATION

The Food and Drug Administration approved ezetimibe on October 25, 2002 (2). Ezetimibe is indicated as monotherapy for the treatment of primary hypercholesterolemia and homozygous sitosterolemia. Combination therapy with any of the statins is also indicated for the treatment of primary hypercholesterolemia. For the treatment of homozygous familial hypercholesterolemia, a combination of ezetimibe with atorvastatin or simvastatin is indicated (3).

PHARMACOLOGY

Ezetimibe's mechanism of action involves reducing blood cholesterol by inhibiting the absorption of cholesterol in the small intestine. Unlike other cholesterol-reducing agents, ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This leads to a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe has been demonstrated to have no significant effect on the plasma concentrations of the fat-soluble vitamins A, D, and E (3).

PHARMACOKINETICS

Ezetimibe, which is water insoluble, is absorbed and extensively conjugated to an active phenolic glucuronide (ezetimibe-glucuronide) after oral intake. After a single dose, mean ezetimibe peak plasma concentrations (C_{max}) of 3.4 to 5.5 ng/mL were obtained within 4 to 12 hours (T_{max}). The extent of ezetimibe absorption is not affected by taking it with high-fat or nonfat meals. However, the C_{max} value of ezetimibe is increased by 38% when taken with a high-fat meal. Overall, ezetimibe may be taken with or without food (3).

Both ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins. Ezetimibe is metabolized mainly in the small intestine and liver via glucuronide conjugation, with subsequent biliary and renal excretion. There has been minimal evidence of oxidative metabolism or phase I reaction in all species involved. Ezetimibe is rapidly metabolized to ezetimibe-glucuronide in humans. Both ezetimibe and its conjugate are the major drug-derived compounds detected in plasma, making up 10% to 20% and 80% to 90% of the total drug in plasma, respectively. Both forms have a long half-life of about 22 hours, accounting for their slow elimination from plasma. Also, multiple peaks are seen on plasma concentration-time profiles, implying enterohepatic recycling. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while its conjugate was the major component in urine and accounted for 9% of the administered dose (3).

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CLINICAL TRIALS

All of the clinical studies that have been performed are limited to primary hypercholesterolemia. Primary hypercholesterolemia is due to a genetic defect in cholesterol metabolism, whereas secondary hypercholesterolemia is due to secondary factors such as obesity, diabetes mellitus, physical inactivity, and/or nutrition. Unfortunately, there are no data to support the use of ezetimibe in patients with secondary hypercholesterolemia. Therefore, the findings of these trials, some of which are summarized here, apply only to those patients with primary hypercholesterolemia.

Ezetimibe vs placebo

Dujovne et al performed a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of ezetimibe 10 mg in 892 patients with primary hypercholesterolemia. These patients had previously been treated with lipid-lowering agents (bile acid sequestrants, nicotinic acid, fibrates, and/or statins). Ezetimibe 10 mg or placebo was administered daily for a period of 12 weeks. The primary efficacy endpoint was the percentage reduction in direct plasma LDL cholesterol from baseline. Secondary endpoints included changes and percentage changes from baseline in LDL cholesterol calculated by the Friedewald equation, total cholesterol, triglyceride, and HDL cholesterol levels over time and at endpoint, and changes from baseline in HDL cholesterol subfractions HDL_2 cholesterol and HDL_3 cholesterol, apolipoprotein A-I, apolipoprotein B, and lipoprotein (a) at endpoint (4).

The study consisted of the following 3 phases: a 2- to 12-week initial screening/drug washout phase during which there was no treatment, a 4- to 8-week single-blind, placebo run-in phase, and a 12-week double-blind treatment phase. The washout period was 12 weeks for those patients receiving fibric acid derivatives and 6 weeks for those patients on statins and other agents or supplements. Patients were randomized in a 3:1 ratio to receive ezetimibe 10 mg or placebo (4).

A mean percentage reduction in the plasma concentration of LDL cholesterol of about 17% was observed in the treatment group. On the other hand, the placebo group had an increase of 0.4% in LDL cholesterol ($P < 0.01$). Also, 60% of the treated patients had a >15% reduction in direct LDL cholesterol from baseline to endpoint, as opposed to 10% of placebo recipients. Early onset (within 2 weeks) and maintenance of LDL cholesterol reduction was seen in the treatment group throughout the 12 weeks. Effects of ezetimibe were similar among the various subgroups analyzed, regardless of risk factor status, race, sex, age, or baseline lipid profile. Overall, ezetimibe significantly decreased calculated LDL cholesterol, apolipoprotein B, total cholesterol, and triglyceride levels and significantly increased HDL cholesterol as well as HDL_3 cholesterol levels ($P < 0.01$) (4).

Adverse events were reported in 64% of patients: 66% of the placebo group and 63% of the treatment group. Upper respiratory tract events (11% of the placebo group vs 9% of the treatment group) and headaches (8% in both groups) were the most common events. Thirty-five patients had to stop treatment because of adverse events (6 patients in the placebo group vs 29 patients in the treatment group) (4).

One of the limitations of this study was that the statistical power was not indicated. Thus, it may not be assumed that a sufficient number of patients was enrolled to detect a difference between treatments. Also, the study report failed to mention the specific caloric intake of the patients. This factor could have had a positive or negative effect on the results of the trial.

Ezetimibe coadministered with atorvastatin or simvastatin vs statin monotherapy

This multicenter double-blind, parallel-group study was done to evaluate the efficacy, tolerability, and safety of ezetimibe as an adjunct to diet and statins (atorvastatin or simvastatin) with or without LDL cholesterol apheresis. LDL cholesterol apheresis is repeated plasmapheresis in which apo B–containing lipoproteins are removed from blood as it passes extracorporeally through a column that binds apo B. This process is performed in patients with primary hypercholesterolemia because lifestyle changes, such as diet and exercise, and often pharmacotherapy, will not have much influence on LDL cholesterol reduction.

The study consisted of 2 phases: a 6- to 14-week open-label, nonrandomized statin (atorvastatin 40 mg or simvastatin 40 mg) lead-in phase and a 12-week study phase during which patients were randomized to receive 1 of 3 once-daily double-blind treatments: statin 80 mg, ezetimibe 10 mg plus statin 40 mg, or ezetimibe 10 mg plus statin 80 mg. Atorvastatin and simvastatin were selected for this study because they are the only statins that are approved by the Food and Drug Administration for the treatment of homozygous familial hypercholesterolemia. Patients continued a prescribed diet and the statin that they received during the open-label phase. The primary efficacy variable was the percentage change of LDL cholesterol from baseline to endpoint. A total of 50 patients were randomized (5).

The 2 groups that received ezetimibe plus a statin exhibited a greater direct LDL cholesterol reduction from baseline to endpoint than the group that received statin monotherapy (–20.7% vs –6.7%, $P = 0.007$). The LDL cholesterol–lowering benefits of ezetimibe plus statin were observed as early as 2 weeks following ezetimibe initiation and were maintained throughout the 12-week study. Only 18% of patients in the statin monotherapy group experienced a >15% reduction in LDL cholesterol level, as opposed to 58% of patients who received ezetimibe plus statin ($P = 0.001$). These results were consistent in both statin groups. The reduction in LDL cholesterol in the ezetimibe plus statin 80 mg group was 27.5%, while it was 7% in the statin monotherapy group ($P = 0.0001$). Differences in mean percentage change in total cholesterol from baseline to endpoint between the ezetimibe plus statin group and the statin monotherapy group were statistically significant (–18.7% vs –5.3%; $P < 0.01$). No significant difference between the study groups was found in effect on mean HDL cholesterol, triglyceride, or apolipoproteins B or A-I concentrations (5).

One limitation of this study was the small number of subjects enrolled (50 patients). The probable reason for the small number of patients is the low prevalence of homozygous familial hypercholesterolemia. Also, the study failed to mention LDL cholesterol reduction percentages for the different doses of simvastatin and atorvastatin used. The study combined the results for the 40-mg and 80-mg doses.

Another limitation of the study was the fact that subjects were not stratified according to whether they underwent LDL cholesterol apheresis. This could have led to uneven distributions of patients who did or did not undergo LDL cholesterol apheresis in the active and placebo groups. Patients who underwent LDL cholesterol apheresis may have had an additive effect on LDL cholesterol reduction when compared with patients who did not undergo LDL cholesterol apheresis.

One other potential problem with this study was that the results were reported by using standard error of the mean instead of standard deviation. Standard error of the mean is an estimate of the true mean of the population from the mean of the sample, whereas standard deviation is a measurement of the range of data values around the mean. Thus, readers may misinterpret the results of the study.

Also, it is important to note that the utilization of statins would not be that advantageous in patients with homozygous familial hypercholesterolemia. This is because statins affect cholesterol synthesis and have no effect on the clearance of LDL cholesterol from plasma. Patients with homozygous familial hypercholesterolemia have a genetic deficiency of LDL cholesterol receptors, impairing their ability to clear LDL cholesterol from the blood. Thus, the utilization of statins will not increase LDL cholesterol receptors but just delay the process of cholesterol synthesis.

Efficacy and safety of ezetimibe when added to ongoing statin therapy

This randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy and safety of adding ezetimibe to ongoing statin therapy in patients with primary hypercholesterolemia. The study group consisted of 769 adults with primary hypercholesterolemia who had not achieved National Cholesterol Education Program Adult Treatment Panel II goals with dietary alteration and statin monotherapy. Patients who received a stable dose of a statin for at least 6 weeks were randomized to receive concurrent treatment with placebo (n = 390) or ezetimibe 10 mg/day (n = 379), in addition to continuous open-label statin, for 8 weeks. The primary efficacy endpoint was the percentage change in LDL cholesterol from baseline (i.e., with statin monotherapy) to endpoint after intervention. Secondary endpoints consisted of changes in HDL cholesterol and triglyceride levels (6).

After adding ezetimibe 10 mg/day to ongoing statin monotherapy, an additional mean LDL cholesterol reduction of 25.1% was seen, while addition of placebo reduced the LDL cholesterol level by 3.7% ($P < 0.001$). Maximal effect was seen at week 2 and was maintained throughout the 8-week treatment period. Over the course of the study, 75.5% of the subjects in the statin plus ezetimibe group achieved target LDL cholesterol levels set by the National Cholesterol Education Program Adult Treatment Panel II at endpoint, while 27.3% of the subjects in the statin plus placebo group achieved these levels ($P < 0.001$). Among those patients who had LDL cholesterol levels greater than Adult Treatment Panel II target levels at baseline, 71.5% of the statin plus ezetimibe group and 18.9% of the statin plus placebo group achieved the target levels at endpoint ($P < 0.001$). The HDL cholesterol level increased by 2.7% after the addition of ezetimibe to ongoing statin monotherapy and by 1.0% when placebo was added ($P < 0.05$). Triglyceride levels were reduced by 14.0% when ezetimibe was added to ongoing statin monotherapy and by 2.9% when placebo was added ($P < 0.001$). Total cholesterol, non–HDL cholesterol, and apolipoprotein B levels and the LDL cholesterol: HDL cholesterol ratio were all significantly improved ($P < 0.001$) by coadministration of ezetimibe with statin compared with statin plus placebo (6).

One limitation of the study was that a power analysis was not performed. In addition, the duration of the subjects' statin therapy prior to the study was not noted. Duration of statin therapy prior to the addition of ezetimibe may have an effect on LDL cholesterol reduction. Also, the duration of the study could have been longer. Most studies have used a time period of at least 12 weeks to observe changes in LDL cholesterol reductions. However, this study was conducted for a period of only 8 weeks, which might not be long enough to reveal the full benefits of the drug.

Efficacy of ezetimibe coadministered with lovastatin

This multicenter, randomized, double-blind, placebo-controlled clinical study tested the hypothesis that coadministration of lovastatin and ezetimibe would provide significantly greater LDL cholesterol reduction than administration of lovastatin alone. Secondary objectives were to assess the change from baseline for a panel of lipid variables, such as total cholesterol, triglyceride, and HDL cholesterol levels. A total of 548 patients with an LDL cholesterol level >145 mg/dL and <250 mg/dL and a triglyceride level <350 mg/dL were enrolled. After dietary stabilization, a 2- to 12-week washout period, and a 4-week single-blind placebo lead-in period, patients were randomized to one of the following groups: ezetimibe 10 mg; lovastatin 10, 20, or 40 mg; ezetimibe 10 mg plus lovastatin 10, 20, or 40 mg; or placebo. Medications were administered daily for a period of 12 weeks (7).

The results indicated that coadministration of ezetimibe plus lovastatin (pooled doses) was significantly more efficacious than lovastatin alone (pooled doses) or ezetimibe alone in decreasing direct plasma levels of LDL cholesterol from baseline to endpoint. The mean percentage change was –39% for the coadministration group as opposed to –25% for the lovastatin monotherapy group ($P < 0.01$) and –19% for the ezetimibe monotherapy group ($P < 0.01$). Moreover, the mean percentage decrease in direct LDL cholesterol resulting from coadministration of ezetimibe with each dose of lovastatin was significantly greater than that obtained with the corresponding dose or the next higher dose of lovastatin monotherapy ($P < 0.01$). Efficacy of the addition of ezetimibe was noticed after 2 weeks and was maintained throughout the duration of the study. The additional reduction in LDL cholesterol seen with ezetimibe plus lovastatin was consistent across all patient subgroups (7).

Coadministration of ezetimibe plus lovastatin significantly decreased LDL cholesterol levels at all lovastatin doses ($P < 0.01$), increased HDL cholesterol levels at doses of 20 and 40 mg ($P < 0.01$ and $P < 0.02$), and decreased triglyceride levels at doses of 20 and 40 mg ($P < 0.01$). It is important to note that 23% of patients who received combination therapy had achieved a >50% decrease in direct LDL cholesterol at the study endpoint as opposed to only 2% of patients who received lovastatin monotherapy (7).

Table 1. Clinical adverse events occurring in >2% of patients treated with ezetimibe and at an incidence greater than placebo, regardless of causality*

Adverse event	Placebo (n = 795)	Ezetimibe 10 mg (n = 1691)
Back pain	3.9%	4.1%
Arthralgia	3.4%	3.8%
Diarrhea	3.0%	3.7%
Sinusitis	2.8%	3.6%
Abdominal pain	2.8%	3.0%
Pharyngitis	2.1%	2.3%
Coughing	2.1%	2.3%
Viral infection	1.8%	2.2%
Fatigue	1.8%	2.2%

*Adapted from reference 3.

Overall, there was an incremental mean percentage change in LDL cholesterol concentration of –14% in the combined therapy group relative to the lovastatin monotherapy group. Also, coadministration of 10 mg ezetimibe and lovastatin 10 mg had similar effects on LDL cholesterol reduction as lovastatin 40 mg alone (7).

From this study, it may be concluded that addition of ezetimibe has incremental effects on LDL cholesterol reduction. In patients with a high risk of hepatic insufficiency, the addition of ezetimibe to the lowest dose of lovastatin may be helpful in preventing adverse effects of high-dose lovastatin while gaining the full benefits of high-dose lovastatin. Also, the combination of ezetimibe and lovastatin has no greater adverse effects than lovastatin monotherapy (7).

A potential limitation of this study was the fact that patients were required to keep their own diaries, noting any missed doses. This may lead to incomplete or biased data. In addition, the study presented pooled instead of individual baseline results but individual endpoint results.

ADVERSE EFFECTS

The safety of ezetimibe has been evaluated in >4700 patients in clinical trials. Some of the common adverse effects of ezetimibe (greater than placebo) are listed in *Table 1* (3).

DOSING AND ADMINISTRATION

Ezetimibe has a long half-life that allows for once-daily dosing. It is available as a 10-mg tablet. Ezetimibe 10 mg daily may be given with or without food along with a standard cholesterol-lowering diet. To obtain a greater effect, ezetimibe may be given with a statin. Both agents may be given simultaneously for convenience. No dosage adjustment is needed in patients with mild hepatic insufficiency. Use is not recommended in patients with moderate to severe hepatic insufficiency because no studies have been conducted in this patient population. No dosage adjustment is needed in patients with mild renal insufficiency. In patients with severe renal insufficiency, the mean area under the curve for total ezetimibe after a single dose was increased by 1.5-fold (3).

Table 2. Monthly costs of ezetimibe and statins

Drug/strength/dose (once-daily dosing)	Monthly cost
Ezetimibe (Zetia) 10 mg	$54.86
Atorvastatin (Lipitor) 20 mg	$89.67
Fluvastatin (Lescol) 40 mg	$38.71
Lovastatin (Mevacor) 20 mg	$62.92
Lovastatin 20 mg	$17.62
Pravastatin (Pravachol) 20 mg	$72.22
Simvastatin (Zocor) 20 mg	$75.25

Ezetimibe is a pregnancy category C agent. There are no well-controlled studies of ezetimibe in pregnant women. Ezetimibe has been demonstrated to cross the placenta when given to pregnant rats and rabbits in multiple oral doses. So, ezetimibe is indicated in pregnant women only if the potential benefit outweighs the risk to the fetus. It is not known whether ezetimibe is excreted into human breast milk, so it should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant (3).

DRUG INTERACTIONS

Ezetimibe is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes, so metabolism of other agents is not affected. The mean area under the curve of total ezetimibe was reduced by approximately 55% when given concurrently with cholestyramine. The ezetimibe concentration was increased by about 1.5-fold when given with fenofibrate. Concurrent administration with gemfibrozil increases ezetimibe's concentration by approximately 1.7-fold. The level of ezetimibe was increased 12-fold in one renal transplant patient who was also taking cyclosporine (3).

ECONOMIC ISSUES

Table 2 compares the cost of ezetimibe with those of the statins. The costs are based on Baylor University Medical Center pharmacy acquisition costs. Even though ezetimibe is expensive, the benefits conferred by its addition of statin therapy outweigh the increased cost.

SUMMARY AND CRITICAL ISSUES

All of the clinical trials that have been conducted apply to patients with primary hypercholesterolemia. It is important to note that many more people have secondary hypercholesterolemia than primary hypercholesterolemia. Thus, more studies of ezetimibe in patients with secondary hypercholesterolemia would be beneficial. On the basis of the literature reviewed, it may be concluded that ezetimibe is efficacious in reducing LDL cholesterol. It is more beneficial when used as an adjunct to statins than as monotherapy. *Table 3* lists the mean percentage reductions of LDL cholesterol with each statin, with ezetimibe alone, and with ezetimibe/statin combinations. Based on the summary, ezetimibe should be added to statin monotherapy in patients with uncontrolled hyperlipidemia. This combination is

Table 3. Mean percentage reduction in LDL cholesterol with various regimens*

Regimen	Percentage reduction in LDL cholesterol
Ezetimibe 10 mg	17%
Ezetimibe 10 mg + statin	25.1%
Fluvastatin 10–80 mg	18.9%–35%
Lovastatin 10–80 mg	21%–40%
Pravastatin 10–40 mg	22%–34%
Simvastatin 10–80 mg	14%–47%

*Adapted from references 4–7.

associated with a greater mean reduction in LDL cholesterol than achieved by either drug alone.

Ezetimibe is one of the newer agents that have been approved for the treatment of hyperlipidemia. Unlike other cholesterol-lowering agents, ezetimibe works by selectively inhibiting the intestinal absorption of cholesterol and related phytosterols. Its mode of action has been found to be complementary to that of statins. A review of the clinical studies that have been done on ezetimibe indicates that it does have efficacy in reducing LDL cholesterol when used as monotherapy as well as when co-administered with statins. Because combination therapy with other cholesterol-reducing agents (e.g., bile acid sequestrants, nicotinic acid, and fibrates) has not been studied, the use of ezetimibe with these other drugs is not recommended. More studies evaluating ezetimibe's use with other agents, such as niacin, are needed to confirm the safety and benefits of these combinations in reducing LDL cholesterol. Further studies that compare ezetimibe as an add-on agent to other statins would also be beneficial.

Overall, ezetimibe appears to be effective in the treatment of hyperlipidemia. Due to once-daily dosing and limited side effects, compliance should not be a major concern. As with many drugs, ezetimibe is not indicated in women who are pregnant or breastfeeding because of the lack of clinical studies in these populations. Currently, ezetimibe should be considered as an add-on therapy to statins for patients who are not at their LDL cholesterol treatment goal. Also, it should be considered for patients who are intolerant of statins because of serious side effects.

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