Perspectives in Cholesterol-Lowering Therapy
The Role of Ezetimibe, a New Selective Inhibitor of Intestinal Cholesterol Absorption

Eric Bruckert, MD; Philippe Giral, MD; Philippe Tellier, MD

Low-density lipoprotein cholesterol (LDL-C) reduction is a key factor in preventing coronary heart disease (CHD), particularly in high-risk patients. The greatest reductions in CHD mortality and morbidity have been achieved with the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, more commonly known as statins. Optimal LDL-C levels have been set at 100 mg/dL and 115 mg/dL for high-risk patients by US and European guidelines, respectively. To achieve these therapeutic target values for LDL-C, statins have become a mainstay in the treatment of hyperlipidemia. Nevertheless, in clinical practice, despite major improvement in lipid management, current strategies may have important limitations with regard to the reduction of LDL-C, as illustrated by the following case presentations.

Case Presentations

Case 1
A 51-year-old man showed evidence of an uncomplicated myocardial infarction. His body mass index was 25.5 kg/m². At baseline, his LDL-C level was 260 mg/dL. Dietary counseling had been strictly applied in combination with simvastatin (40 mg) during the 6 months after the coronary event. The patient had shown poor tolerance to bile acid sequestrants. Despite this strategy, fasting plasma concentrations of relevant metabolic variables (in mg/dL) were as follows: glucose 99, total cholesterol (TC) 220, LDL-C 160, high-density lipoprotein cholesterol (HDL-C) 40, and triglycerides (TG) 100.

To achieve therapeutic goals in such a clinical case, there are limited options. Doubling the daily dose of a statin up to 80 mg with either simvastatin or atorvastatin has little chance of decreasing LDL-C to the optimal target, and combination therapy with a fibrate may lead to myopathy, and bile acid sequestrants were poorly tolerated. Ten milligrams of ezetimibe was prescribed in combination with 40 mg of simvastatin. Three months later, fasting concentrations of TC, LDL-C, HDL-C, and TG were 175, 120, 55, and 95 mg/dL, respectively.

Case 2
R.C. was a 15-year-old boy with the homozygous form of familial hypercholesterolemia. He underwent cardiac surgery at the age of 10 (coronary artery bypass grafting and aortic valve replacement) and subsequently was treated with warfarin. Despite regular LDL apheresis (every 2 weeks) for 6 months and compliance with a low-fat diet combined with high dosages of atorvastatin (40 mg b.i.d), mean values of LDL-C remained high (220 mg/dL), whereas TC, HDL-C, and TG were 300, 80, and 65 mg/dL, respectively.

In this clinical case, therapeutic options were even more limited than in the previous one because increased frequency of LDL apheresis was refused by the patient and bile acid sequestrants that interfere with warfarin have little relevance in this clinical case. Ten milligrams of ezetimibe was started in combination with 80 mg of atorvastatin, and 3 months later LDL-C decreased to 180 mg/dL, whereas HDL-C and TG remained unchanged. The drug was well tolerated.

How Can Clinicians Achieve LDL-C Goals?
Despite serious improvements in treatment of lipid abnormalities, a European
survey of risk factor management with established CHD revealed that only half of those patients receiving lipid-lowering therapy had attained recommended lipid treatment goals. Moreover, another survey showed that the use of statins in clinical practice leads to observed reductions in LDL-C levels that are significantly less than those projected by package insert guidelines. Non-compliance is one reason for the disparity between treatment guidelines and real-life treatment patterns. In addition, potential, known, or perceived issues of tolerability and/or safety of current lipid-altering drugs may result in therapeutic challenges, especially at the higher doses. In particular, many physicians are reluctant to titrate up statin treatment. On the other hand, it is not uncommon that the highest dosage of such drugs lacks sufficient efficacy in the most severe dyslipidemias.

Although clinicians can help reduce the number of undertreated patients through improved lipid management, additional therapies are required to optimize prevention and treatment of cardiovascular diseases. This demand has directed research toward new mechanisms such as the inhibition of intestinal cholesterol absorption, which is the main mechanism of action of ezetimibe. Combining drugs with effects on different pathways of cholesterol metabolism may result in some benefits that are complementary and additive to those of the statins.

What Is the Mechanism of Action of Ezetimibe?
Ezetimibe is a potent and selective inhibitor of cholesterol absorption that has been shown to reduce the overall delivery of cholesterol to the liver, thereby promoting the synthesis of LDL receptors, with a subsequent reduction of serum LDL-C. In addition to inhibiting cholesterol absorption, ezetimibe also inhibits net phytosterol absorption. Its mechanism of action is different from that of other intestinal-acting lipid-altering agents such as phytosterols/phytostanols, resins, and polymers.

The level of plasma cholesterol is influenced not only by de novo biosynthesis but also by the absorption of dietary cholesterol and the removal of cholesterol from the blood. Interrupting the absorption of cholesterol has therefore become an important target for lowering serum cholesterol levels. In this way, the effects of plant sterols and stanols reduce serum cholesterol by their competitive mode of action at the limited space available in mixed micelles (the packages in which the intestinal lumen delivers lipids for absorption into mucosal cells).

Recent evidence supports the presence of a specific transporter that facilitates the movement of cholesterol from bile acid micelles into the brush border membrane of enterocytes. This mechanism of cholesterol transport has been exploited as a therapeutic target in the development of new drugs such as ezetimibe.

Pharmacology of Ezetimibe: What Should the Clinician Know?
Ezetimibe undergoes rapid and extensive glucuronidation in the intestinal wall and the liver. The elimination half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours, which allows for once-daily dosing. Pharmacokinetics of ezetimibe do not depend on sex, age, and renal or hepatic function. Nevertheless, given its unknown long-term safety, ezetimibe should not be recommended in patients with moderate or severe liver dysfunction.

The lipid lowering effect of ezetimibe correlates well with dose and plasma concentration. A pooled analysis of 399 patients receiving either placebo or ezetimibe 0.25, 1, 5, or 10 mg once daily showed a median percentage reduction of LDL-C of 0%, 12.7%, 14.7%, 15.8%, and 19.4%, respectively. Ten milligrams of ezetimibe a day reduced the fractional cholesterol absorption by 54% compared with placebo. This effect was accompanied by a decrease in LDL-C of 20.4%, a compensatory increase of 89% in cholesterol synthesis (versus placebo), and a decrease in the absorption of plant sterols that are highly structurally related to cholesterol.

Because of its mechanism of action, ezetimibe is a drug for concomitant use with statins. Pharmacokinetic studies of statins, fibrates, and ezetimibe have not revealed any significant interactions. Moreover, ezetimibe had no effect on the activity of drug metabolism enzymes, such as cytochrome P450 or N-acetyltransferase. Thus, the pharmacokinetic interaction potency of ezetimibe seems to be low, as illustrated by the lack of clinically significant interactions with warfarin, glipizide, digoxin, oral contraceptives, antacids, or cimetidine. Nevertheless, cholestyramine was shown to reduce the systemic plasma concentrations of ezetimibe by about 55%.

Main Characteristics of Ezetimibe

- Selective mode of action: Selective inhibition of intestinal absorption of cholesterol
- Convenient dosing: 10 mg once daily
- Consistency: Consistent plasma LDL-C reduction of more than 20% and favorable effects on HDL-C and triglycerides
- Safety: Clinical and laboratory safety in monotherapy or in combination with statins (no increase of the potential liver or muscular toxicity of statins)
- Good tolerability: No drug interactions, few side effects

When to Use Ezetimibe in Patients With Mild to Moderate Primary Hypercholesterolemia

Monotherapy Studies
In an assessment of 432 patients with primary hypercholesterolemia in 2
Ezetimibe 10 mg significantly decreased LDL-C by 18% (P<0.01), increased HDL-C by 3.5% (P<0.05), and produced a nonsignificant reduction in TG blood levels of about 5% compared with placebo. Two large phase III placebo-controlled studies conducted on 1719 patients with primary hypercholesterolemia confirmed that 10 mg of ezetimibe a day lowered LDL-C by approximately 18%. Ezetimibe was well-tolerated and, overall, there was no evidence of any clinically meaningful differences between the adverse effect profile of ezetimibe and placebo. Ezetimibe is therefore a safe lipid-lowering agent that may be of particular interest in patients who do not tolerate first-line treatment with statins.

Combination Studies
Combination therapy with statins and other currently available lipid-altering agents may offer an advantage over statin monotherapy. However, combination therapy with these agents can be limited by an increased risk for side effects, intolerance, non-compliance, and drug interactions. The mechanism of action of ezetimibe is complementary to that of statins, which inhibit cholesterol synthesis in the liver. Using both agents could therefore produce additive effects on LDL-C reduction. Moreover, the addition of 10 mg of ezetimibe to a low dose of a statin can avoid the risk of potentially serious adverse effects associated with the use of a high dose of a statin. The efficacy and safety of adding ezetimibe to ongoing statin monotherapy was evaluated in 769 patients with primary hypercholesterolemia, all of whom required further LDL-C lowering than that obtained on statin monotherapy. In statin plus ezetimibe patients, there was an additional mean 21.4% reduction in LDL-C compared with statin plus placebo patients (25.1% versus 3.7%, P<0.001). In this add-on study, among patients not at National Cholesterol Education Program LDL-C goals at baseline, 71.5% receiving statin plus ezetimibe reached their goal at final assessment compared with only 18.9% receiving statin plus placebo (P<0.001).

In 4 phase III studies that included 2382 patients with primary hypercholesterolemia (LDL-C 140 to 250 mg/dL), coadministration of ezetimibe 10 mg once daily with statin provided an incremental reduction in LDL-C of about 13% compared with statin monotherapy (pooled doses) regardless of statin type (simvastatin, atorvastatin, pravastatin, and lovastatin). The average incremental LDL-C reduction achieved by combination of ezetimibe plus statin was on average 21% (18% to 24% depending on the statin), which is the same benefit as seen in the add-on study. TG reductions ranged from 20% to 28% and HDL-C increased 8% to 11%, depending on the simvastatin dose. The clinical and laboratory safety profile of ezetimibe coadministered with a statin was similar to that of statin monotherapy and to that of placebo. Elevations in either ALT or AST ≥3× ULN were nearly similar in treated and placebo groups (statin plus ezetimibe, n=4, 1%; ezetimibe plus placebo, n=1, <1%). No case of rhabdomyolysis was reported in either treatment group.

Ezetimibe in Heterozygous Familial Hypercholesterolemia and Other High-Risk Patients
A 14-week randomized, response-based study was conducted to evaluate the LDL-C lowering efficacy of 10 mg of ezetimibe added to 10 mg of atorvastatin mg followed by response-based titration compared with atorvastatin titration alone. The atorvastatin dose in each treatment group was doubled after 4 and/or 9 weeks in patients whose LDL-C was >100 mg/dL, to a maximum of 80 mg in the monotherapy group and 40 mg in the coadministration group. This study particularly examined high-risk patients with CHD or refractory hypercholesterolemia with a mean LDL-C of about 187 mg/dL while receiving 10 mg of atorvastatin a day.

After 14 weeks of treatment, 22% of patients in the ezetimibe group reached their LDL-C goal (versus 7% in atorvastatin group, P<0.01). At week 4, adding 10 mg of ezetimibe to 10 mg of atorvastatin produced higher LDL-C levels in heterozygous familial hypercholesterolemia (HeFH) than doubling the atorvastatin dose to 20 mg (−23.6% versus −7.4%, P<0.01). Ezetimibe can facilitate LDL-C goal attainment even in difficult to treat high-risk patients with CHD and refractory hypercholesterolemia. Ezetimibe should therefore be combined with a statin in all patients who do not reach LDL-C goals with diet and statin therapy.

A Significant Advance in Treatment of the Homozygous Form of Familial Hypercholesterolemia and Sitosterolemia
Homozygous Familial Hypercholesterolemia
Homozygous familial hypercholesterolemia (HoFH) is a rare disorder occurring in about 1 per 1 000 000 persons. LDL-C levels are severely elevated, resulting in an extremely high risk for premature CHD. Despite aggressive therapy combining diet, high doses of statins, and other lipid-lowering agents in combination, LDL-C remains high in most patients. LDL apheresis is a key treatment, but it is expensive, time-consuming, and not available to many patients.

In a double-blind, parallel-group study, the efficacy, safety, and tolerability of ezetimibe were evaluated as an adjunct to diet and statin, with or without LDL apheresis, to treat one of the largest cohorts of patients with HoFH. From baseline to final assessment (12 weeks), treatment with 10 mg of ezetimibe plus a statin (either 40 or 80 mg) produced a greater reduction in LDL-C (20.7% versus 6.7%, P=0.007).

In HoFH, pharmacological therapies, including high-dose statin monotherapy, have met with limited success in the management of high values of LDL-C.
The primary lipid-lowering mechanism of ezetimibe, inhibition of cholesterol absorption at the intestinal brush border, appears to be largely unaffected by the pathophysiology of HoFH.16

**Sitosterolemia**
Sitosterolemia is a very rare inherited disorder that results in increased absorption and decreased excretion of plant sterols (sitosterol, campesterol). The genetic defect was recently identified.17 Thus, levels of plant sterols in plasma and tissue are markedly elevated and can lead to premature atherosclerosis. A double-blind, placebo-controlled study was conducted in 37 patients with homozygous sitosterolemia.18 After 8 weeks of treatment with 10 mg of ezetimibe, plasma concentrations of sitosterol decreased by a mean of 21% from baseline in the ezetimibe-treated group (P<0.001) and increased by 4% in placebo patients (intergroup difference, P<0.001). Similar results were seen for plasma concentrations of campesterol, which were reduced by 27.5% from baseline to 8 weeks, for a between-treatment difference of 27.5%. Ezetimibe was safe and well tolerated in this patient group.

**References**
16. Gagne C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with

---

**IDEAL TARGET POPULATIONS FOR TREATMENT WITH EZETIMIBE**

Patients with elevated LDL-C and one of the following conditions:
- Poor tolerance to statins (monotherapy)
- Persistent elevation of LDL-C despite adequate dosage of statins (combination)
- Homozygous form of familial hypercholesterolemia: (combination)
- Patients with elevated sitosterol: first-line treatment and monotherapy

**What Is the Next Step?**
Data on the effect of a combination of plant sterols and stanols with ezetimibe must be further evaluated. Other lipid-modifying agents, including new classes, may also hold promise. Fibrates increase hepatic output of cholesterol, and we demonstrated that the combination of fibrate and plant sterols has a synergistic effect.19 A small, randomized, placebo-controlled trial20 has shown that the coadministration of 10 mg of ezetimibe and 200 mg of fenofibrate produced a significant (P<0.03) reduction in LDL-C levels (36.3%) compared with placebo (10.1%), fenofibrate alone (22.3%), or ezetimibe alone (13.5%). Future studies will need to examine peroxisome proliferator-activator receptor-γ agonists such as rosiglitazone and pioglitazone, because these compounds improve insulin sensitivity, reduce TG, and raise HLDC, but rosiglitazone is associated with increased LDL-C.

Ezetimibe and niacin with or without a statin may be an option for aggressive treatment of some severe lipid disorders. Additional data are needed to assess efficacy of the coadministration of ezetimibe and bile acid resins because of the drug-drug interaction.12

The next step is to conduct clinical outcome studies. The additional effect of ezetimibe on top of statin treatment on both atherosclerosis and clinical events is needed not only to embrace “the lower, the better” hypothesis but also to provide long-term evaluation of the benefit-risk ratio of ezetimibe.

**Conclusion**
Ezetimibe is a new once-daily inhibitor of intestinal cholesterol absorption.

It provides an additional LDL-C decrease of up to 20%. Such additive effect is needed in the treatment of difficult-to-treat lipid disorders, including the rare familial homozygous hypercholesterolemia or sitosterolemia. More generally, it will enable more patients to reach the LDL-C target with a good short-term safety profile. Large outcome trials will help select patients more likely to benefit from ezetimibe therapy.


Perspectives in Cholesterol-Lowering Therapy: The Role of Ezetimibe, a New Selective Inhibitor of Intestinal Cholesterol Absorption

Eric Bruckert, Philippe Giral and Philippe Tellier

_Circulation._ 2003;107:3124-3128
doi: 10.1161/01.CIR.0000072345.98581.24

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/25/3124

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/