Ezetimibe plus simvastatin lowered lipid levels more than simvastatin monotherapy in primary hypercholesterolemia

Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB. **Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial.** Mayo Clin Proc. 2004;79:620-9.

QUESTION

In patients with primary hypercholesterolemia, is ezetimibe plus simvastatin more effective and safe than simvastatin alone?

METHODS

Design: Randomized placebo-controlled trial.
Allocation: Concealed.*
Blinding: Blinded {patients, clinicians, data collectors, outcome assessors, data analysts, monitoring committee, and manuscript writers}†.*
Follow-up period: 12 weeks.
Setting: 31 sites in the United States and 40 sites in 22 other countries.
Patients: 887 patients ≥ 18 years of age (mean age 56 y, age range 22 to 81 y, 53% women) with primary hypercholesterolemia (low-density lipoprotein cholesterol [LDL-C] 145 to 250 mg/dL [3.76 to 6.48 mmol/L] and triglycerides ≤ 350 mg/dL [≤ 3.97 mmol/L]), liver transaminase levels ≤ 2 times the upper limit of normal with no active liver disease, and creatine kinase levels ≤ 1.5 times the upper limit of normal. Exclusion criteria included various concomitant conditions and procedures and use of nonstatin lipid-lowering drugs, immunosuppressant drugs, and inhibitors of cytochrome P-450 3A4.
Intervention: Ezetimibe, 10 mg (n = 92); simvastatin, 10, 20, 40, or 80 mg (total n = 349 [pooled simvastatin monotherapy group]); ezetimibe, 10 mg, plus simvastatin, 10, 20, 40, or 80 mg (total n = 353 [pooled ezetimibe plus simvastatin group]); or placebo (n = 93) given orally once daily in the evening for 12 weeks. All patients were instructed to follow a National Cholesterol Education Program (NCEP) Step 1 diet throughout the study.
Outcomes: Mean percentage change from baseline in lipid levels and adverse events.
Patient follow-up: 92% (100% in intention-to-treat analysis).

MAIN RESULTS

The pooled ezetimibe plus simvastatin group had greater reductions in LDL-C, total cholesterol, non–high-density lipoprotein cholesterol, and apolipoprotein B levels than the pooled simvastatin monotherapy group (Table); these 2 groups increased high-density lipoprotein cholesterol levels to a similar extent (Table) and had similar overall safety and tolerability outcomes.

CONCLUSION

In patients with primary hypercholesterolemia, ezetimibe plus simvastatin was more effective than simvastatin monotherapy for improving lipid levels and had a similar overall safety and tolerability profile.

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For correspondence: Dr. A.C. Goldberg, Lipid Research Clinic, Washington University, St. Louis, MO, USA. E-mail agoldber@im.wustl.edu. ■

*See Glossary.

†Information provided by author.

Ezetimibe plus simvastatin (pooled across all simvastatin doses) vs simvastatin alone (pooled across all simvastatin doses) at mean 12 weeks‡

Outcomes	Difference (95% CI)	*P* value
Mean percentage change from baseline in low-density lipoprotein cholesterol level	−14.8 (−16.9 to −12.7)	< 0.001
Mean percentage change from baseline in total cholesterol level	−11.3 (−13.0 to −9.7)	< 0.001
Mean percentage change from baseline in non–high-density lipoprotein cholesterol level	−14.4 (−16.5 to −12.4)	< 0.001
Mean percentage change from baseline in apolipoprotein B level	−12.9 (−15.1 to −10.7)	< 0.001
Mean percentage change from baseline in high-density lipoprotein cholesterol level	0.6 (−1.2 to 2.4)	0.53

‡CI defined in Glossary and CIs provided by author.

COMMENTARY

Ezetimibe is a novel lipid-lowering agent that works by blocking intestinal cholesterol absorption. It is now compounded with several doses of simvastatin as a single pill preparation. Ezetimibe as monotherapy lowers LDL-C by 17% to 19% in adults who have hypercholesterolemia (1).

The design of the study by Goldberg and colleagues parallels that of a previous study of ezetimibe and atorvastatin, which had nearly identical results (2). It showed that ezetimibe (10 mg), when combined with a variety of doses of simvastatin (10 to 80 mg), reduced LDL-C from 46% to 61% compared with a 31% to 46% reduction with the same doses of simvastatin alone. Other studies have also reported impressive results with the addition of ezetimibe to ongoing statin therapy (3). Moreover, it is most reassuring to see that the combination of simvastatin with ezetimibe has a similar incidence of adverse effects as simvastatin alone. Nevertheless, the reported studies of ezetimibe are only 8 to 12 weeks in duration and lack the broad base of evidence of efficacy in preventing clinical events.

Some questions remain. Is the apparent hepatic and musculoskeletal safety at 12 weeks of combined therapy durable over the long term? Will ezetimibe yield the same reduction in clinical events as that seen with statins? Is ezetimibe similarly effective with statins in patients with diabetes?

For patients bothered by musculoskeletal symptoms at high doses of statins or who cannot achieve goal LDL-C levels despite high statin doses, the addition of ezetimibe appears to be a safe and effective option. This study adds to the evidence of the safety of combined statin and ezetimibe and their efficacy in lowering cholesterol. With current NCEP recommendations of even lower levels of LDL-C in patients with coronary artery disease or diabetes, ezetimibe combined with a statin is a valuable addition to treatment options.

David L. Bronson, MD
Cleveland Clinic Foundation
Cleveland, Ohio, USA

References

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