Ezetimibe added to ongoing statin therapy reduced LDL cholesterol in primary hypercholesterolemia

Gagné C, Bays HE, Weiss SR, et al. **Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia.** Am J Cardiol. 2002;90:1084-91.

QUESTION

In patients with primary hypercholesterolemia not meeting cholesterol-lowering goals with dietary alteration and statin monotherapy, does the addition of ezetimibe to statin therapy reduce low-density lipoprotein cholesterol (LDL-C) levels more than placebo added to statin?

DESIGN

Randomized {allocation concealed*}†, blinded (patients, clinicians, {data collectors, and data analysts}†),* placebo-controlled trial with 8-week follow-up.

SETTING

80 centers in the United States, Australia, Belgium, Canada, Denmark, Germany, Portugal, Spain, and Switzerland.

PATIENTS

769 patients (mean age 60 y, 58% men) who had primary hypercholesterolemia, were taking a stable dose of a statin for ≥ 6 weeks, and had received instruction on a cholesterol-lowering diet. Patients' mean LDL-C level had to be at or above the recommended target level for their risk category defined by the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) II guidelines. Exclusion criteria included cardiovascular events in the previous 3 months, uncontrolled endocrine or metabolic disease, and impaired renal or hepatic function. Follow-up was 95%.

INTERVENTION

Patients were stratified by severity of hypercholesterolemia at screening (< 18% and ≥ 18% above target LDL-C level), and allocated to ezetimibe, 10 mg/d (n = 379), or placebo (n = 390) while continuing ongoing, open-label statin therapy for 8 weeks.

MAIN OUTCOME MEASURES

Mean percentage change from baseline in LDL-C level. The proportion of patients who achieved NCEP ATP II target levels for LDL-C and adverse events were also assessed.

MAIN RESULTS

Analysis was by intention to treat. The addition of ezetimibe to statin therapy led to a greater reduction in LDL-C level than did placebo (Table). The effectiveness of ezetimibe was not affected by type of statin used. Among patients above their NCEP ATP II target LDL-C level at baseline, more patients who received ezetimibe achieved their LDL-C goal (71.5% vs 18.9%; odds ratio 23.7, P < 0.001). Ezetimibe and placebo groups did not differ for adverse events (21% vs 17%); gastrointestinal events were the most common.

CONCLUSION

In patients with primary hypercholesterolemia, the addition of ezetimibe to statin therapy was more effective than placebo added to statin in reducing low-density lipoprotein cholesterol levels.

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*See Glossary.

†Information provided by author.

Ezetimibe vs placebo added to statin therapy for hypercholesterolemia at 8 weeks‡

Outcome	Ezetimibe		Placebo		*P* value
	Baseline	Mean percent change	Baseline	Mean percent change	
LDL cholesterol level (mmol/L)	3.6	–25%	3.6	–3.7%	< 0.001

‡LDL = low-density lipoprotein.

COMMENTARY

Ezetimibe is a new lipid-lowering agent that works by blocking intestinal cholesterol absorption. It undergoes glucuronidization in the liver and is enterohepatically recirculated. In other studies, ezetimibe as monotherapy lowered LDL-C by 17% to 19% in adults with hypercholesterolemia (1).

In the study by Gagné and colleagues, ezetimibe, when combined with various doses of statin agents, conferred an additional 21% reduction in LDL-C relative to placebo. In other studies by the same team, in patients with homozygous familial hypercholesterolemia the addition of ezetimibe to 40 mg/d of either simvastatin or atorvastatin increased effectiveness almost 4 times more than increasing the statin dosage to 80 mg/d (2).

The remarkable safety and efficacy of statins are supported by several comprehensive studies in many settings. In contrast, 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. Nonetheless, at higher or full doses of statins, some patients are bothered by musculoskeletal symptoms while others do not achieve goal levels of LDL-C. For these patients, the current choices of adding niacin, fibrates, or bile acid resins are less than ideal and often associated with substantial side effects.

Several questions remain. Will the addition of ezetimibe to a low or moderate statin dose bring greater LDL-C reductions than high-dose statins in primary hypercholesterolemia? Will the apparent hepatic and musculoskeletal safety at 12 weeks of combined therapy endure over the long-term? Will ezetimibe yield the same reduction in clinical events seen with statins?

This, and other studies thus far, suggest that ezetimibe is a safe, effective, and complementary treatment option for patients with hypercholesterolemia. Until more data arrive, I will use it in my practice when patients do not tolerate statins or cannot achieve treatment goals despite moderate-to-high statin doses and an effective dietary program.

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References

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2. **Gagné C, Gaudet D, Bruckert E.** Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation. 2002;105:2469-75.