Ease: Ezetimibe Add-on to Statin for Effectiveness Trail

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Results from the largest community-based clinical trial to date, involving more than 3000 patients, has shown that adding the cholesterol absorption inhibitor ezetimibe to ongoing stable statin therapy in patients with hypercholesterolemia produces a significant additional reduction in low-density lipoprotein (LDL)- cholesterol compared with adding a placebo.[1] In addition, more patients who added ezetimibe achieved their National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) If LDL-cholesterol targets. The Ezetimibe Add-on to Statin for Effectiveness (EASE) trial included a total of 3030 patients on a stable dose of a statin but not yet at their NCEP ATP III LDL-cholesterel goal,[2] Patients were recruited into the study from 299 practices around the United States, including practices especially selected to encourage the involvement of African American and Hispanic patients (about 9% and 5%, respectively, of the final patient population). All patients were aged >/= 18 years, had LDL-cholesterol level above NCEP ATP III target by risk category after being on a stable dose of any statin for >/= 5 weeks, and had triglyceride level < 350 mg/dL. According to NCEP ATP III risk criteria, approximately 77% of the patients had coronary heart disease (CHD) or CHD risk, and about 17% of patients had >/= 2 CHD risk factors. About 40% of patients were taking atorvastatin 10-90 mg, 30% were taking similar doses of simvastatin, 20% were on pravastatin, and other patients were on fluvastatin or lovastatin, At the time the study was started. rosuvastatin was not commercially available. Patients on lipid-lowering therapy other than a statin were excluded from the study. Randomization on a 2 to 1, double-blind basis resulted in 2020 patients continuing with their original statin treatment (same brand and dose) with the addition of ezetimibe 10 mg, and 1010 patients with their original statin treatment plus a placebo. Treatment lasted for 6 weeks. The endpoints of EASE were percentage reduction in LDL-cholesterol level and percentage of patients not at goal level at baseline who reached their NCEP ATP III LDL-cholesterol goal.

Results

In the overall population, LDL-cholesterol was further reduced in the statin plus ezetimibe group from a mean of 129 mg/dL at baseline to 95 mg/dL, a reduction of approximately 23% compared with placebo (Table 1). A similarly significant percentage reduction was seen for the CHD risk factor categories.

Table 1. EASE: Mean LDL-Cholesterol Levels (mg/dL)

	Statin + Ezetimibe			Statin + Placebo		
Patient Group	Baseline	Week 6	% Change	Baseline	Week 6	% Change
Total	129	95	-25.8*	129	125	-2.7%
CHD or CHD equivalent	123	90	-25.1*	124	120	-1.1%
>/= 2 CHD risk factors	147	111	-23.8*	148	140	-4.1%
< 2 CHD risk factors	162	118	-25.7*	167	152	-5.8%

*P <= .0O1 vs statin + placebo CHD, coronary heart disease

These effects were consistent across a number of prespecified treatment groups, including those classified according to age, gender, race (including , Caucasian (n=2471), African-American (n=279) and Hispanic patients (n=162) [other, n= 118], diabetes (38%) or metabolic syndrome (60%), and statin brand and dose. Overall, more patients on statin plus ezetimibe reached their NCEP ATP III LDL-cholesterol goal than those on statin plus placebo (Table 2). A particularly high rate, over 90%, was seen in the patients with >/= 2 CHD risk factors.

Table 2. EASE: Percent Changes of Patients Achieving NCEP ATP III LDL-Cholesterol Goal

Patient Group	Statin + Ezetimibe	Statin + Placebo
Total	71.0 % *	20.6 %
CHD or CHD Equivalent	69.5 % *	17.3 %
> / = 2 CHD risk factors	75.1 % *	32.2 %
< 2 CHD risk factors	90.7 % *	52.4 %

*P < .001 vs statin + placebo.CHD, coronary heart disease

Significant improvements were also seen in other efficacy parameters, including triglyceride, high-density lipoprotein (HDL)-cholesterol, non-HDL-cholesterol, and apolipoprotein B levels.

Safety and Tolerability

There were no differences in liver- or muscle-related side effects between the 2 treatment groups (Table 3).

Table 3. EASE: Liver and Muscle Safety

Parameter	Statin + Ezetimibe	Statin + Placebo
ALT >/= 3 x ULN	0.2% *	0.4%
AST >/= 3 x ULN	0.1 % *	0.2 %
CK >/=10 x ULN Without muscle symptoms	0.1 % *	0.0 %

"P = NS.ALT, alanine transaminase; AST aspartate transaminase; CK, creatine kinase: ULN, upper limit of normal

Implications

The 23% additional reduction in LDL-cholesterol seen with ezetimibe added to ongoing statin monotherapy compares favorably with the 6% to 8% reduction usually seen when the dose of the original statin is doubled. Dr. Pearson commented. The results of the EASE study suggest that the addition of ezetimibe to statin therapy should be considered in patients who have not achieved their NCEP ATP III goal on statin therapy alone.

Ezetimibe/Simvastatin Dual Therapy

Ezetimibe has been available in the United States as a 10-mg once-daily formulation since November 2002 and has also been launched in a number of countries worldwide, including some European countries, A regulatory submission for a combination dual-therapy formulation of ezetimibe and simvastatin, as adjunctive to diet in the treatment of hypercholesterolemia, is currently under review by the US Food and Drug Administration,

References

1. Pearson T, Denke M, McBride P, Battisti W, Brady W, Palmisano J, Ezetimibe added to statin therapy reduces LDL-C and improves goal attainment in patients with hypercholesterolemia, Program and abstracts from the American College of Cardiology 53rd Annual Scientific Session; March 7-10, 2004; New Orleans, Louisiana. Late Breaking Clinical Trials III.

2. National Cholesterol Education Program, Third Report of the National Cholesterol Education Program (NCEP) on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III. Bethesda, Maryland: National Heart, Lung, and Blood Institute, National Institutes of Health; 2001.