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Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia

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Aims This randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of ezetimibe 10 mg/day in patients with primary hypercholesterolemia.

Methods and results Following dietary stabilization, a 2–12-week washout period, and a 4-week, single-blind, placebo lead-in period, 827 patients with baseline low-density lipoprotein cholesterol (LDL-C) ≥3.36 mmol/l (130 mg/dl) to ≤6.47 mmol/l (250 mg/dl) and triglycerides ≤3.95 mmol/l (350 mg/dl) were randomized 3:1 to receive ezetimibe 10 mg or placebo orally once daily in the morning for 12 weeks. The primary efficacy endpoint was percentage reduction in direct plasma LDL-C. Ezetimibe reduced direct LDL-C by a mean of 17.7% from baseline to endpoint, compared with an increase of 0.8% with placebo (P<0.01). Response to ezetimibe was generally consistent across all subgroups analyzed. Ezetimibe also significantly improved levels of plasma total cholesterol, apolipoprotein B, high-density lipoprotein$_2$-cholesterol and lipoprotein(a), and elicited a trend toward lower triglyceride levels. Ezetimibe did not alter the serum concentrations of lipid-soluble vitamins or significantly affect baseline or stimulated cortisol production. Ezetimibe was well tolerated, with a safety profile similar to that of placebo.

Conclusions Ezetimibe, which significantly reduces LDL-C and favorably affects other lipid variables, may provide a well tolerated and effective new option for lipid management in the future.

Introduction

Ezetimibe is a novel cholesterol absorption inhibitor that prevents the absorption of cholesterol by

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inhibiting the passage of cholesterol of dietary and biliary origin across the intestinal wall.[1,2] Ezetimibe is rapidly absorbed, extensively conjugated to glucuronide in the intestine, and excreted mainly in the stool.[2–4] Ezetimibe has a long half-life (24 h), and is administered once daily at any time, without regard to meals.[5] No clinically important gender or food effects, cytochrome P450 enzyme interactions, or drug–drug interactions have been identified.[4,6–10] Ezetimibe has been well tolerated in studies involving over 4000 patients, with a safety profile similar to that of placebo. A pooled analysis of results from two studies in patients with primary hypercholesterolemia showed that ezetimibe 10 mg significantly decreased low-density lipoprotein cholesterol (LDL-C) by 18.5% ($P<0.01$ versus placebo) and significantly increased high-density lipoprotein cholesterol (HDL-C) by 3.5% ($P<0.05$ versus placebo) after 12 weeks of once daily, oral treatment.[5] The objective of this study was to evaluate the efficacy and safety of ezetimibe 10 mg/day in a large population of patients with primary hypercholesterolemia.

Materials and methods

Patients

All patients provided written informed consent before enrollment. Adult women and men ≥18 years of age with a diagnosis of primary hypercholesterolemia (calculated LDL-C 3.36 mmol/l [130 mg/dl] to 6.47 mmol/l [250 mg/dl], and plasma triglycerides ≤3.95 mmol/l [350 mg/dl] after adequate lipid-lowering drug washout) were eligible for participation. A medical history was recorded, including presence of a family history of cardiac disease and presence of cardiovascular risk factors. During the screening/drug-washout phase, patients received dietary counseling, and all prior lipid-altering drugs were discontinued. A registered dietitian instructed all patients to follow a low-fat, low-cholesterol diet (National Cholesterol Education Program [NCEP] Step I[11] or stricter diet) to be started during this period and maintained throughout the 12-week study.

If the patient had ever taken probucol, the last dose had to have been at least 1 year before enrollment. Adequate washout requirements for other lipid-altering agents included 12 weeks for fibric acid derivatives and 6 weeks for nicotinic acid, bile acid sequestrants, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), garlic, fish oil, plant stanols, or other agents or supplements administered specifically to modulate lipid levels.

Key exclusion criteria included: pregnancy or lactation; congestive heart failure (New York Heart Association Class III or IV);[12] uncontrolled cardiac arrhythmia, myocardial infarction, coronary bypass surgery, or angioplasty within 6 months of study entry; history of unstable or severe peripheral artery disease within 3 months of study entry; unstable angina pectoris; disorders of the hematologic, digestive, or central nervous systems that would limit evaluation or participation; uncontrolled or newly diagnosed diabetes mellitus; uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; known impairment of renal function; active or chronic hepatic or hepatobiliary disease; positive test for human immunodeficiency virus; and coagulopathy.

Study design

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 54 centers in the United States. The study protocol was approved by the Institutional Review Board of each participating study center and conducted according to Good Clinical Practice guidelines. The study consisted of 3 phases: a 2–12-week initial screening/drug-washout phase (no treatment); a 4-week single-blind, placebo run-in phase; and a 12-week double-blind treatment phase (Fig. 1). If the patient was taking other lipid-lowering medication in the initial phase, washout was begun and the next visit (Visit 2) was scheduled so that the required 6–12 weeks of drug washout would be complete by the time of the first qualifying lipid sample in the prerandomization/placebo run-in phase.

Study drug

Patients who satisfied the eligibility requirements were randomly assigned to treatment with either ezetimibe 10 mg or placebo in a 3:1 ratio according to a computerized randomization schedule with treatment codes in blocks of 4. A single tablet was administered orally once daily in the morning for 12 weeks, without reference to meals. Bulk ezetimibe was manufactured by Schering-Plough Research Institute (Kenilworth, NJ). Ezetimibe 10 mg and placebo were provided in identically appearing, white, capsule-shaped, unscored tablets.

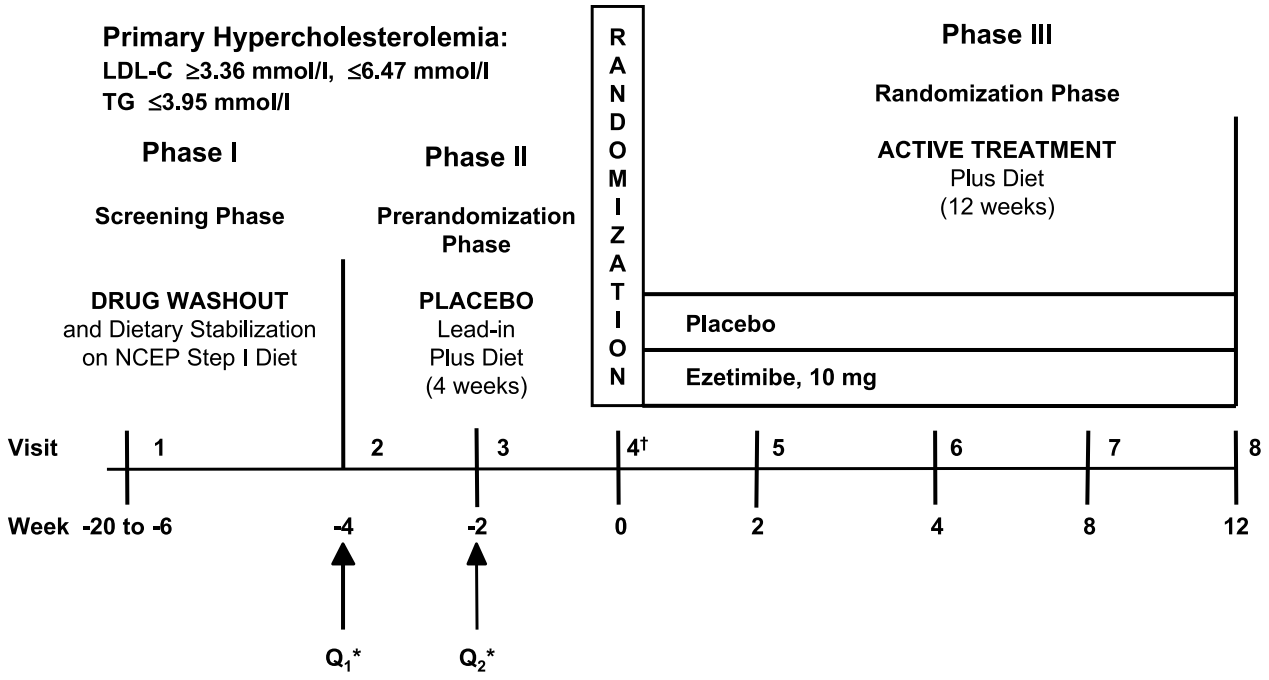

Fig. 1 Study design. All study medication was administered once daily in the morning without regard for meals. *Q_1=the first qualifying LDL-C using the Friedewald calculation, and *Q_2=the second qualifying low-density LDL-C using the Friedewald calculation; blood samples for Q_1 and Q_2 were drawn ≥1 week apart. †Randomization to double-blind treatment occurred at Visit 4. NCEP, National Cholesterol Education Program; TG, triglycerides.

Concomitant therapy

Therapies specifically prohibited during the study included oral corticosteroids, cyclosporine, and orlistat, as well as any other investigational drug (within 30 days before study entry). Treatment with psyllium or other fiber-based laxatives was not allowed unless the patient was treated with a stable regimen for ≥4 weeks before the first qualifying visit (Q_1). Cardiovascular drugs such as α-adrenergic blockers, β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, nitrates, and thiazide diuretics were allowed during the study provided that the patient had received a stable dose for 8 weeks before Q_1, and would be anticipated to maintain the same drug regimen throughout the study. Aspirin ≤325 mg/day was permitted. Hormone replacement therapy for postmenopausal women was allowed if the regimen was kept constant throughout the study.

Measurement of lipids

The primary efficacy variable was percentage change from baseline to endpoint (Week 12) in the plasma concentration of direct LDL-C, which was determined following standard ultracentrifugation/precipitation procedures (β-quantification). Secondary variables included changes and percentage changes from baseline in LDL-C calculated via the Friedewald equation,[13] total cholesterol, triglycerides, and HDL-C over time and at endpoint, and HDL-C subfractions HDL_2-C and HDL_3-C, apolipoprotein (apo) A-I, apo B, and lipoprotein(a) (Lp(a)) at endpoint. After baseline measurements and randomization, samples for lipid measurements were collected at Weeks 2, 4, 8, and 12, although the HDL-C subfractions, apolipoproteins, and Lp(a) were measured only from the sample collected at Week 12. Medical Research Laboratories (Highland Heights, KY) performed all clinical laboratory analyses for this study, including analyses of lipids and safety parameters. Total plasma cholesterol and triglycerides were quantified enzymatically with the Hitachi 747 analyzer (Roche Diagnostics Corporation, Indianapolis, IN). Total HDL-C was determined enzymatically after LDL-C and very LDL-C had been selectively removed by heparin and manganese chloride precipitation. The HDL_3-C subfraction was quantified enzymatically after separation by ultracentrifugation of unfrozen plasma. The HDL_2-C subfraction was calculated by subtracting HDL_3-C from total HDL-C. Apo A-I and apo B levels were determined by fixed-rate nephelometry. Lp(a) was quantified by competitive enzyme-linked immunosorbent assay.

Assessment of diet

Patients recorded dietary intake for representative 3-day periods throughout the study. Diet diaries were distributed to the patients at the screening visit and at Visits 2, 4, 6, and 7 and returned each following visit. A registered dietitian reviewed the completed 3-day diary with the patient, and appropriate counseling was provided. The 3-day diet diaries were sent to Professional Nutrition Systems, Inc. (Overland Park, KS) for central analysis. The results of the central diet analysis for each patient were reported as a RISCC score[14] (Ratio of Ingested Saturated Fat and Cholesterol to Calories) and as dietary components (total calories, milligrams of cholesterol, and grams of saturated fat) for the 3 days. RISCC scores indicate the potential for a diet to influence plasma lipid levels. Ranges of scores generally correlate to diets as follows: ≤13=NCEP Step II, 14–20=NCEP Step I, and 24–29=typical American diet.[14]

Assessment of lipid-soluble vitamins

Blood samples for determination of serum concentrations of carotenoids and vitamins A, D (25-hydroxy vitamin D and 1,25-dihydroxy vitamin D), and E (α-and γ-tocopherol) were collected from patients at a subset of centers both at baseline (after washout period, at randomization, Visit 4) and again at the 12-week study endpoint (Visit 8). Prothrombin time (a surrogate marker of vitamin K concentration) was determined for the entire study population at the same timepoints. The endpoint was the percentage change in serum concentration levels of lipid-soluble vitamins and prothrombin time from baseline (at randomization, Visit 4) to treatment endpoint, after 12 weeks of treatment (Visit 8).

Assessment of response to cosyntropin stimulation

A second subset analysis was performed to determine the 30- and 60-min cortisol response to intravenous cosyntropin (synthetic ACTH) stimulation of ezetimibe-treated patients compared with that of patients receiving placebo. At randomization (Visit 4) and at treatment endpoint (Visit 8), patients at a subset of centers received an intravenous injection of 0.25 mg cosyntropin in the morning after a 12-h fast. Plasma cortisol levels were determined before injection and at 30 and 60 min after injection. The endpoint was the change in plasma cortisol levels from pre-injection level at 30 and 60 min after cosyntropin injection at treatment initiation and at treatment endpoint.

Safety and tolerability

Safety was evaluated through reports of patients, observations of investigators, and results of specific tests and measurements. At each visit, the investigator or designated staff recorded adverse events reported by patients since the last visit or directly observed by the investigator or staff. Other measures of safety included the results of laboratory tests, physical examinations (including vital signs and body weight), electrocardiograms (ECGs), and tests for fecal occult blood.

Statistical analysis

The total target sample size was approximately 800 patients: 600 treated with ezetimibe 10 mg and 200 treated with placebo. This sample size enabled detection of a difference of at least 3 percentage points between treatment groups in the mean percent change from baseline in LDL-C with 90% power, assuming a standard deviation of approximately 10 and a two-tailed significance level of 0.05. The primary efficacy analysis included all patients who received randomized treatment assignment and had at least one postbaseline lipid determination. A two-way analysis of variance (ANOVA) model that extracted sources of variation due to treatment and center was used to evaluate the effect of ezetimibe on the percentage change in each of the lipid parameters from baseline to endpoint. The baseline value for the lipid variables was defined as the average of the determinations at Visit 2 through Visit 4, except for those variables determined only at Visit 4 (Week 0), for which the single determination was to be the baseline value. Pairwise comparisons between treatment groups were made using the ANOVA model specified above. Significance was defined as $P<0.05$. Statistical analysis was conducted using SAS® software Version 6.12 (SAS Institute, Inc., Cary, NC).

Results

Patient disposition

A total of 2085 subjects was enrolled in the study and screened for eligibility. Of these, 1258 (60%) discontinued before receiving randomized treatment assignment and 827 (40%) continued in the randomization/active treatment phase. Of the 827 randomized patients, 622 were assigned to ezetimibe and 205 to placebo. Two patients who

were to receive ezetimibe had no record of treatment. Overall, 766 of the 827 patients (93%) completed the study. Forty-eight patients in the ezetimibe group (8%) and 13 (6%) in the placebo group discontinued treatment for the following reasons: adverse events (22 in the ezetimibe group [4%] and five in the placebo group [2%]); patient request (17 in the ezetimibe group [3%] and six in the placebo group [3%]); loss to follow-up (five in the ezetimibe group [<1%] and 0 in the placebo group); noncompliance with protocol (two in the ezetimibe group [<1%] and two in the placebo group [<1%]); and administrative reason (two in the ezetimibe group [<1%] and 0 in the placebo group). The distribution of the reasons for discontinuation was similar between the two treatment groups.

Demographics and baseline characteristics

Demographic characteristics and habits were similar between treatment groups (Table 1). The baseline lipoprotein and apolipoprotein measurements for placebo and ezetimibe groups are shown in Table 2. All values were nearly identical. For instance, the mean baseline plasma concentration of direct LDL-C was 4.25 and 4.27 mmol/l (164 and 165 mg/dl) for patients in placebo and ezetimibe groups, respectively. In general, the two treatment groups were well balanced regarding diet, weight, sex, age, race, physical activity, and smoking history. Approximately one-third of the patients had a known family history of coronary artery disease, and approximately one-third had some degree of hypertension. Other cardiovascular risk factors were present among fewer patients (≤12% of patients in either treatment group).

RISCC scores during treatment were generally within a range indicative of the NCEP Step I diet (14–20), and relatively few scores represented failure to follow the diet (≥24), indicating adequate consistency of dietary compliance during the study.

Changes in lipid parameters

Ezetimibe reduced the plasma concentration of direct LDL-C from baseline to endpoint by a mean of 17.7%, compared with an increase of 0.8% with placebo ($P<0.01$) (Fig. 2; Table 2). Approximately 60% of ezetimibe-treated patients compared with approximately 8% of placebo recipients had a ≥15% reduction in direct LDL-C from baseline to endpoint. The full effect of ezetimibe on LDL-C was observed by Week 2 and was maintained throughout the 12-week treatment period (Fig. 3). The effects of ezetimibe on LDL-C were generally consistent across all subgroups analyzed, regardless of risk-factor status, gender, age, race, baseline lipid profile, hypertension, diabetes mellitus, body mass index, menopausal status, known coronary heart disease, and number of cardiovascular risk factors (Fig. 4). Compared with placebo, ezetimibe also significantly decreased calculated LDL-C, apo B, total cholesterol, and Lp(a) and significantly increased HDL-C and HDL_2-C ($P\leq0.01$) (Table 2).

Effect of ezetimibe on lipid-soluble vitamins

Concentrations of all vitamins at baseline and treatment endpoint were similar between the ezetimibe and placebo groups. There was no significant change in values of any vitamin between either timepoint in either group (Table 3). There was no apparent difference in concentrations.

For all patients, levels of vitamin A were greater than or equal to normal levels at baseline and remained so after 12 weeks of therapy. All placebo recipients had normal α- and β-carotene levels at baseline and at 12 weeks. α- and β-carotene levels were normal at baseline and at 12 weeks for 82 (97%) and 78 (92%) ezetimibe patients, respectively; two and four patients who received ezetimibe, respectively, had levels below baseline with 2 and 1, respectively, which were normal at 12 weeks. One and three patients who received ezetimibe had normal levels of α- and β-carotene, respectively, at baseline and below-normal levels at 12 weeks.

For all patients, levels of α-tocopherol and 1,25-dihydroxy vitamin D were greater than or equal to normal levels at baseline and remained so after 12 weeks of therapy.

Seventy-two ezetimibe patients (85%) had normal γ-tocopherol levels at baseline and at 12 weeks, 10 had below-normal levels at baseline with five becoming normal at 12 weeks, and three had normal levels at baseline that were below-normal at 12 weeks. Twenty-three placebo recipients (82%) had normal γ-tocopherol levels at baseline and at 12 weeks, three had below-normal levels at baseline that were normal at 12 weeks, and two had normal levels at baseline and below-normal levels at 12 weeks.

One ezetimibe and one placebo patient had 25-hydroxy vitamin D levels below-normal at baseline. Both had normal levels at 12 weeks.

Table 1 Baseline demographic characteristics and habits for all randomized patients[a]

Characteristics and habits	Placebo (*n*=205)	Ezetimibe 10 mg (*n*=622)
Age (years)		
Mean	57.6	58.3
Range	24–79	20–86
Age (no. patients, %)		
<65 years	139 (68)	414 (67)
≥65 years	66 (32)	208 (33)
Sex (no. patients, %)		
Female	110 (54)	320 (51)
Male	95 (46)	302 (49)
Race (no. patients, %)		
White	181 (88)	565 (91)
Black	12 (6)	34 (5)
American Indian	1 (<1)	0
Asian	1 (<1)	7 (1)
Hispanic	10 (5)	15 (2)
Pacific Islander	0	1 (<1)
Body weight (kg)		
Mean	84.0	83.3
Range	48.2–145.4	44.5–170.4
Body mass index (kg/m^2)[b]		
Mean	29.6	29.1
Range	19.4–45.7	17.8–49.6
Diet (RISCC) scores[c]		
Mean	17	17
Range	5–38	3–34
Physically active (no. patients, %)		
No	107 (52)	308 (50)
Yes	98 (48)	314 (50)
Smoker (no. patients, %)		
No	183 (89)	528 (85)
Yes	22 (11)	94 (15)
Prior lipid-altering drug washout (no. patients, %)		
No	155 (76)	442 (71)
Yes	50 (24)	180 (29)
Statin	38 (19)	135 (22)
Fibrate	2 (<1)	1 (<1)
Bile acid sequestrant	0	3 (<1)
Nicotinic acid	3 (1)	10 (2)
Other	8 (4)	45 (7)
Risk factors/history/known CHD		
Hypertension		
Yes	65 (32)	222 (36)
No	140 (68)	400 (64)
Diabetes mellitus		
Yes	9 (4)	38 (6)
No	196 (96)	584 (94)
Myocardial infarction		
Yes	2 (1)	24 (4)
No	203 (99)	596 (96)
Unknown	0	1 (<1)
Missing	0	1 (<1)
Postmenopausal[d]		
Yes	87 (79)	255 (80)
No	23 (21)	65 (20)
Family history of coronary artery disease		
Yes	70 (34)	207 (33)
No	127 (62)	404 (65)
Unknown	8 (4)	11 (2)
Known coronary heart disease		
Known CHD	7 (3)	49 (8)
No CHD	198 (97)	573 (92)
Risk factor		
−1	6 (3)	17 (3)
0	38 (19)	127 (20)

Table 1 (continued)

Characteristics and habits	Placebo (*n*=205)	Ezetimibe 10 mg (*n*=622)
1	88 (43)	226 (36)
2	57 (28)	157 (25)
>2	9 (4)	46 (7)

RISCC=Ratio of ingested saturated fat and cholesterol to calories (a single score that conveys the potential effect of the diet on lipoproteins).

[a]Mean values in this table are arithmetic means.
[b]*n*=204 for placebo, *n*=621 for ezetimibe.
[c]*n*=618 for ezetimibe.
[d]Female subjects only.

Table 2 Baseline values (mean) and least-square mean percentage changes (SEM) in plasma concentrations of various lipid-related variables from baseline to endpoint for all randomized patients

Variable	Placebo (*n*=204)[a]		Ezetimibe 10 mg (*n*=621)[a]		*P* value
	Baseline	% Change	Baseline	% Change	
Direct LDL-C	4.25 mmol/l	0.79 (0.87)	4.27 mmol/l	−17.69 (0.59)	<0.01
Calculated LDL-C	4.23 mmol/l	1.36 (0.79)	4.0 mmol/l	−18.24 (0.51)	<0.01
Apolipoprotein B	1.61 g/l	−1.01 (0.81)	1.62 g/l	−15.38 (0.52)	<0.01
HDL-C	1.32 mmol/l	−1.26 (0.78)	1.35 mmol/l	1.01 (0.50)	<0.01
HDL_2-C	0.52 mmol/l	−1.14 (2.34)	0.53 mmol/l	5.03 (1.61)	0.01
HDL_3-C	0.80 mmol/l	3.94 (1.53)	0.83 mmol/l	2.84 (1.05)	0.49
Apolipoprotein A-I	1.51 g/l	1.20 (0.88)	1.53 g/l	2.26 (0.57)	0.27
TC	6.43 mmol/l	0.57 (0.60)	6.44 mmol/l	−12.40 (0.38)	<0.01
Direct LDL-C:HDL-C	3.38	2.27 (1.00)	3.36	−18.25 (0.68)	<0.01
TC:HDL-C	5.10	2.12 (0.82)	5.04	−12.78 (0.52)	<0.01
Triglycerides	1.93 mmol/l	2.43 (2.24)	1.84 mmol/l	−1.71 (1.43)	0.09
Lipoprotein(a)	336 mg/l	1.76 (2.88)	308 mg/l	−7.50 (1.86)	<0.01

LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TC=total cholesterol.

[a]Not every patient had an end-of-treatment measurement for every variable; during the study, '*n*' varied from 184 to 205 for the placebo group and from 563 to 622 for the ezetimibe group.

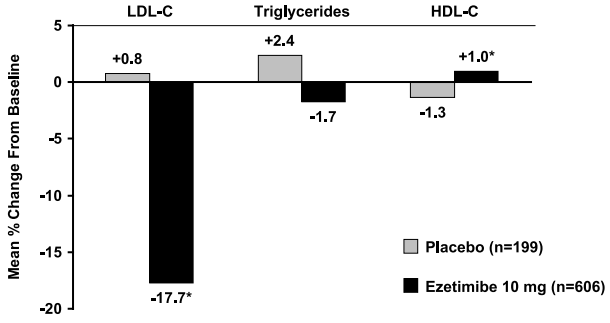

Fig. 2 Mean percentage change in plasma concentrations of direct LDL-C, triglycerides, and HDL-C from baseline to endpoint for all randomized patients. *Significantly different than placebo (*P*<0.01).

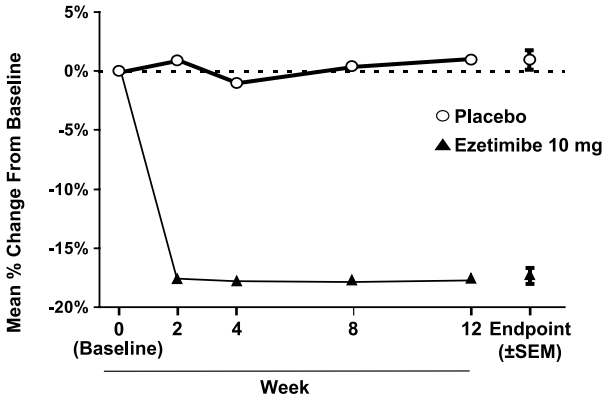

Fig. 3 Mean percentage change from baseline in plasma concentration of direct LDL-C over time and at endpoint in the two treatment groups. SEM, standard error of the mean.

Prothrombin time was similar between treatment groups at baseline (11.7 s for ezetimibe and 11.6 s for placebo) and at treatment endpoint (11.6 s for both groups), and there was no change in prothrombin values between baseline and treatment endpoint.

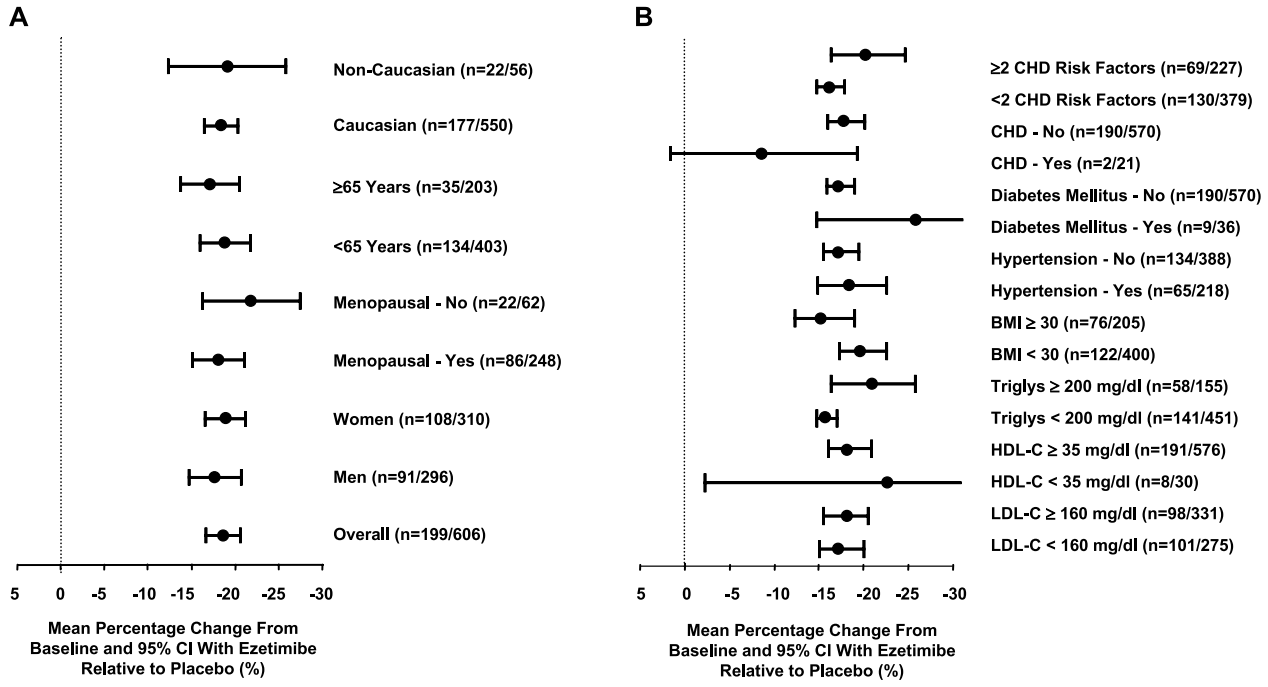

Fig. 4 Subgroup analysis: point estimate and 95% confidence interval of the difference between response (raw mean percentage change from baseline) to ezetimibe 10 mg and placebo in direct LDL-C in various subgroups of the population defined by (A) demographics and (B) baseline characteristics.

Effect of ezetimibe on response to cosyntropin stimulation

The response to cosyntropin stimulation for the ezetimibe-treated group was nearly identical to the placebo group at endpoint, indicating no evidence of impaired cortisol release with ezetimibe administration (Table 4). Likewise, there was no difference in response to cosyntropin at baseline and treatment endpoint in either group.

Adverse events

Treatment-emergent adverse events were reported for 62% of all patients (513/827): 61% of patients treated with ezetimibe (379/622) and 65% of placebo recipients (134/205). No individual adverse event was particularly prevalent in either treatment group. The two adverse events that were most commonly reported in both groups were headache (4% of ezetimibe patients compared with 11% of placebo recipients) and upper respiratory tract infection (8% of ezetimibe patients compared with 7% of placebo recipients) (Table 5). The investigators considered most (approximately 95%) of the treatment-emergent adverse events to be mild or moderate in intensity. Overall, the adverse event profiles were similar between the two treatment groups.

One patient died during the study. A patient in the ezetimibe group drowned accidentally; the investigator did not consider the drowning to be related to study treatment.

Twenty-seven patients (3%) discontinued randomized treatment because of adverse events: 22 (4%) in the ezetimibe group and 5 (2%) in the placebo group. Five of the ezetimibe-treated patients discontinued treatment because of increased hepatic enzyme activities (increased alanine aminotransferase [ALT], aspartate aminotransferase [AST], or γ-glutamyltransferase [GGT]), compared with none of the placebo recipients. All five patients had elevated hepatic enzymes at baseline, and the levels of these enzymes increased during treatment. All five patients were asymptomatic when these elevations occurred. In addition, there was no concomitant increase in bilirubin, jaundice, or symptoms of liver injury.

Laboratory test results

Results of laboratory tests were generally similar between the treatment groups in terms of mean and median changes over time and numbers of patients having predefined high or low values or shifts from baseline. Mean and median changes from baseline for ALT activity and, to a lesser extent, AST activity tended to be approximately

Table 3 Concentrations of fat-soluble vitamins at baseline and treatment endpoint

Vitamin	Placebo				Ezetimibe			
	n	Mean	SD	25th–75th percentile	*n*	Mean	SD	25th–75th percentile
Vitamin A (μmol/l)								
Baseline	29	2.33	0.43	2.06–2.58	91	2.27	0.43	2.02–2.48
Endpoint	28	2.11	0.38	1.90–2.23	85	2.13	0.46	1.82–2.44
% Change		−8.15	14.50	−18.30–2.04		−5.54	15.45	−15.15–3.18
α-Carotene (μmol/l)								
Baseline	29	0.15	0.09	0.09–0.19	91	0.13	0.11	0.05–0.14
Endpoint	28	0.12	0.09	0.07–0.16	85	0.10	0.07	0.05–0.12
% Change		−6.89	47.15	−36.80–13.64		−6.62	88.55	−40.35–22.92
β-Carotene (μmol/l)								
Baseline	29	0.57	0.31	0.32–0.78	91	0.47	0.44	0.20–0.68
Endpoint	28	0.53	0.30	0.27–0.75	85	0.39	0.33	0.19–0.49
% Change		10.58	100.10	−30.91–14.33		2.28	66.76	−37.56–22.08
α-Tocopherol (μmol/l)								
Baseline	29	46.61	16.84	33.21–54.10	91	49.21	19.68	33.67–58.05
Endpoint	28	42.44	14.07	30.53–53.06	85	42.07	16.03	29.95–52.94
% Change		−8.37	14.20	−18.48 to −0.53		−13.79	18.08	−24.51 to −4.64
γ-Tocopherol (μmol/l)								
Baseline	29	5.09	3.26	1.63–6.73	91	4.63	3.20	2.09–6.73
Endpoint	28	4.95	3.29	2.09–7.43	85	4.10	2.67	2.09–6.04
% Change		7.78	44.56	−21.21–28.29		8.29	53.21	−25.93–20.00
1,25-Dihydroxy vitamin D (pmol/l)								
Baseline	25	112.13	35.28	88.80–127.20	87	116.94	38.59	88.80–139.20
Endpoint	20	96.72	27.12	70.80–114.00	68	111.53	36.55	84.00–132.00
% Change		−8.50	34.13	−30.88–4.46		−0.56	36.50	−28.02–24.86
25-Hydroxy vitamin D (nmol/l)								
Baseline	29	56.46	24.36	42.43–69.89	91	62.49	27.09	44.93–79.87
Endpoint	27	62.49	28.52	44.93–77.38	85	74.15	33.18	52.42–92.35
% Change		15.51	43.04	−14.29–33.33		29.18	57.85	−7.14–50.00

Table 4 Mean plasma cortisol levels before and after injection of cosyntropin 0.25 mg at treatment initiation and treatment endpoint[a]

	Placebo			Ezetimibe		
	n	Mean	SD	*n*	Mean	SD
Treatment initiation						
Pre-cosyntropin	28	559 (20.3)	162 (5.9)	90	623 (22.6)	263 (9.5)
30 min	24	1313 (47.6)	231 (8.4)	84	1323 (47.9)	289 (10.5)
60 min	24	1517 (55.0)	255 (9.2)	84	1530 (55.5)	325 (11.8)
Treatment endpoint						
Pre-cosyntropin	27	506 (18.3)	192 (7.0)	88	578 (20.9)	239 (8.7)
30 min	23	1264 (45.8)	234 (8.5)	78	1255 (45.5)	241 (8.7)
60 min	23	1468 (53.2)	292 (10.6)	78	1460 (52.9)	253 (9.1)

[a]All values expressed as SI units (nmol/l), with μg/dl reported in parentheses.

1–2 mU/ml greater with ezetimibe than with placebo during treatment; there was no such finding for GGT activity, alkaline phosphatase activity, or total bilirubin.

Identifiable category shifts from baseline in ALT or AST activity consisted mainly of changes from within the reference ranges to values less than twice the upper reference limits. Almost half of the patients with postbaseline values reported as at least twice the upper limit of normal (ULN) also had baseline values that were above the upper limits of the reference ranges: 11 of 16 patients for ALT (10

Table 5 Safety profile of ezetimibe 10 mg versus placebo

	Placebo (*n*=205)	Ezetimibe 10 mg (*n*=622)
Most common treatment-emergent AEs[a]	134 (65%)	379 (61%)
Headache	22 (11%)	25 (4%)
Upper respiratory infection	15 (7%)	51 (8%)
Back pain	8 (4%)	24 (4%)
Musculoskeletal pain	9 (4%)	19 (3%)
Constipation	9 (4%)	10 (2%)
Laboratory tests assessing liver and muscle function		
Liver function tests (≥3×ULN)		
Alanine aminotransferase[b]	0	4 (<1%)
Aspartate aminotransferase[b]	0	1 (<1%)
γ-Glutamyltransferase	6 (3%)	10 (2%)
Creatine phosphokinase		
≥10×ULN	0	0

[a] Incidence ≥4%.
[b] Consecutive (defined as: (1) two or more consecutive values ≥3×ULN in the subject's record; (2) last value in subject's record ≥3×ULN [presumed consecutive]; or (3) a value ≥3×ULN either during treatment or ≤2 days after the end of treatment followed by a value <3×ULN when sample for second value was collected >2 days after the subject's last day of dosing [presumed consecutive]).

in the ezetimibe treatment group and one in the placebo treatment group) and two of eight patients for AST, both in the ezetimibe treatment group. Among the 16 patients with ALT activity at least twice the ULN, most of the high values were isolated and transient or reversible following treatment discontinuation. Few values were ≥3 times the upper reference limit on two consecutive (or presumed consecutive) measurements, with a similar proportion of occurrences in the ezetimibe and placebo group (Table 5).

An equivalent proportion of ezetimibe-treated and placebo recipients had values for creatine phosphokinase (CPK) activity at least three times the upper reference limit at some time during double-blind treatment (16/615 [2.6%] with ezetimibe versus 3/203 [1.5%] with placebo) (*P*=NS). In both treatment groups, these values were transient despite continued treatment or reversible following treatment discontinuation and were not correlated with musculoskeletal adverse events. Six of the 16 patients in the ezetimibe group and one of the three patients in the placebo group had coincident conditions, such as exercise, surgery, or trauma. Ten of the 19 patients (all of whom were in the ezetimibe group) had baseline values that were already greater than the upper reference limit. None of the subjects in either group had postbaseline CPK activities that reached 10 times the upper reference limit at any point during the study.

Results of additional measures of safety, including vital signs and ECGs, were not different between ezetimibe and placebo groups.

Discussion

Ezetimibe caused a mean percentage change from baseline to endpoint in direct LDL-C of approximately −18%, relative to an increase of <1% with placebo. This result is similar to those of previous, smaller trials,[5,15] wherein mean percentage changes from baseline to endpoint of approximately −16 to −19% were observed over 8–12 weeks with the 10-mg dose. Present results are also similar to a companion study of equivalent size and design,[16] wherein the mean percentage change from baseline to endpoint was −17%. LDL-C reduction was apparent at 2 weeks and was maintained to endpoint. Thus, the results of controlled trials with ezetimibe monotherapy have been uniformly positive and consistent. Approximately 62% of the ezetimibe-treated patients had a mean percentage reduction from baseline to endpoint in direct LDL-C of at least 15%, compared with 8% of the placebo recipients. This result for ezetimibe is consistent with that in the companion trial[16] (approximately 60%) and with the results of the three earlier Phase II trials (61–78%).[5,15]

In this trial and the others cited above, the concentration of apo B decreased significantly relative to placebo. Because apo B is the major protein constituent of low-density lipoproteins, and relatively little of this molecule is found in other lipoprotein fractions in patients without hypertriglyceridemia, ezetimibe would appear to lower LDL-C at least partially by decreasing the number of circulating LDL-C particles.

Ezetimibe had a favorable effect on the concentration of HDL-C in the present trial. A mean percentage change from baseline to endpoint of 1.0% was seen with ezetimibe versus a mean percentage change from baseline to endpoint of −1.3% with placebo ($P<0.01$). Separation between the treatment groups was seen early during the double-blind treatment phase and was maintained throughout treatment. A similar pattern was observed in the companion study[16] and in an earlier Phase II study.[5] The observed increases in HDL-C are consistent with the observation of numerically greater increases in the concentration of apo A-I with ezetimibe relative to placebo in all the cited studies.[17]

Relative to placebo, ezetimibe decreased the plasma concentration of triglycerides from baseline to endpoint, although the difference was not statistically significant. The trend toward lower values was seen early during the double-blind treatment phase and was maintained throughout treatment. A statistically significant reduction was observed in the companion study.[16] The decrease in concentration of triglycerides with ezetimibe versus placebo contrasts with the increase in plasma triglyceride levels associated with the administration of bile acid binding agents.[18,19]

Finally, the mean and median concentration of Lp(a) appeared to be favorably affected by ezetimibe relative to placebo during treatment, a result duplicated in the companion study.[16] In Phase II studies, results numerically favoring ezetimibe 10 mg over placebo were observed in two of the three studies,[17] but differences were relatively small. Because Lp(a) may be an independent risk factor for the development of coronary artery disease, these results could be associated with potential benefit to patients.

Adverse events were reported in similar proportions of patients and with similar degrees of intensity in the placebo and ezetimibe groups. The three most frequently reported events were similar in both treatment groups—headache, upper respiratory tract infection, and back pain—and each was reported with similar occurrence in the two groups (approximately 4–11%, depending on the event). The number and pattern of occurrences of events suggested no differential risk with active treatment relative to placebo. The causes of discontinuation did not point to a specific target-organ toxicity related to administration of ezetimibe compared with placebo.

Results of the additional measures of safety—laboratory tests, vital signs, ECGs, etc.—revealed no evidence of an adverse effect of active treatment compared with placebo. Overall, the increases in mean ALT and AST activities from baseline are not considered clinically significant and may represent a secondary effect of changes in lipid metabolism observed with lipid-altering agents, as has been suggested previously.[18–21] Mean and median changes in CPK activity from baseline over time were similar between the two groups for the duration of this study. Thus, it is likely that the changes in CPK activity represent isolated observations in individual patients with a predisposition toward increased CPK activity or a nondrug related reason for increase in CPK activity, as opposed to an ezetimibe-related treatment effect.

Administration of ezetimibe 10 mg did not alter the serum concentrations of the lipid-soluble vitamins A, α- and β-carotene, and D (25-hydroxy and 1,25-dihydroxy), or α- and γ-tocopherol. Nor did ezetimibe affect the ability to respond to cosyntropin by release of cortisol after 12 weeks of treatment. Thus, it is unlikely that ezetimibe, despite inhibiting intestinal absorption of cholesterol, a complex lipid precursor of steroid hormones, adversely affects absorption of lipid-soluble vitamins or the production of steroid hormones. These results are in concert with earlier nonclinical data that indicate that ezetimibe does not affect the absorption of triglycerides, fatty acids, the sterols progesterone and ethinyl estradiol, or lipid-soluble vitamins A and D.[22] Prothrombin time was unaffected by 12 weeks' treatment with ezetimibe 10 mg daily.

Conclusions

In this randomized, double-blind trial with more than 800 patients, ezetimibe 10 mg taken orally once daily in the morning for 12 weeks by patients with mild-to-moderate primary hypercholesterolemia was an effective LDL-C-lowering agent with favorable effects on other lipid variables, and exhibited a safety and tolerability profile similar to that of placebo. Therefore, ezetimibe, a novel cholesterol absorption inhibitor, may provide a well tolerated and effective new option for lipid management in the future.

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Appendix A

The Ezetimibe study group

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