Original Article

Double-Dose Pravastatin Versus Add-On Ezetimibe with Low-Dose Pravastatin - Effects on LDL Cholesterol, Cholesterol Absorption, and Cholesterol Synthesis in Japanese Patients with Hypercholesterolemia (PEAS study)

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Aim: This study compared the effect of doubling the dose of pravastatin with that of adding ezetimibe to low-dose pravastatin on the LDL cholesterol (LDL-C) level and on cholesterol absorption and synthesis markers. The tolerability of the 2 regimens was also compared.

Methods: This was a multicenter, open-label, parallel-group trial. Subjects were aged from 20 to 74 years and had an LDL-C ≥ 120 mg/dL despite pravastatin therapy at 5-10 mg/day. They were randomly allocated to receive either add-on ezetimibe (10 mg/day) or double-dose pravastatin, and follow-up was performed for 12 weeks. The primary endpoints were the changes of LDL-C and apolipoprotein (apo) B levels after 12 weeks of treatment. Cholesterol absorption and synthesis markers were also determined.

Results: LDL-C and apo B decreased by 16% and 14% in the ezetimibe add-on group versus 5.9% and 4.4%, respectively, in the pravastatin double-dose group. The between-group differences of these decreases were highly significant. Cholesterol absorption markers (sitosterol, campesterol, and cholesterol) were reduced by 48%, 36%, and 10%, respectively, in the ezetimibe add-on group, and were increased by 17%, 14%, and 6%, respectively, in the pravastatin double-dose group. Lathosterol (a cholesterol synthesis marker) increased by 76% in the ezetimibe add-on group and by 24% in the pravastatin double-dose group. The difference was statistically significant. No serious adverse effect was observed in either group.

Conclusions: Adding ezetimibe to low-dose pravastatin achieves greater decreases in LDL-C, apo B, and cholesterol absorption markers than doubling the dose of pravastatin.

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Key words; Cholesterol, Absorption, Synthesis, Pravastatin, Ezetimibe

Introduction

An elevated blood level of cholesterol is a major

risk factor for cerebrovascular and cardiovascular diseases. Cholesterol is supplied by two sources, i.e., synthesis in the liver and absorption from the small intestine. Currently, statin, a HMG-CoA reductase inhibitor, therapy targeting the inhibition of hepatic cholesterol synthesis is the mainstay for reducing low-density lipoprotein cholesterol (LDL-C), with a decrease of overall mortality being confirmed by meta-analysis¹⁾. Subgroup analysis of the Scandinavian Simvastatin

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Survival Study (4S), a secondary prevention trial using simvastatin, revealed that statin therapy was effective for preventing coronary events in patients with low dietary cholesterol absorption, whereas the efficacy of statins was not sufficient in patients with increased cholesterol absorption²⁾. The Drugs and Evidence-based Medicine in the Elderly (DEBATE) study prospectively examined the relation between cholesterol absorption and cerebrovascular and cardiovascular events, and demonstrated that total mortality and the risk of cerebrovascular/cardiovascular events were higher in patients with increased cholesterol absorption than in those without an increase, even though LDL-C levels were similar³⁾. In other words, for LDL-C-lowering therapy to achieve more efficient suppression of cerebrovascular/cardiovascular events, inhibition of cholesterol absorption from the small intestine is required, in addition to inhibition of hepatic cholesterol synthesis.

Ezetimibe is a selective inhibitor of the cholesterol transporter Niemann Pick C1 Like 1 (NPC1L1) expressed in the brush border membrane of the small intestine. This has expanded our treatment options, making it possible to improve the management of hypercholesterolemia.

Doubling the dose of a statin only achieves a small additional LDL-C-lowering effect (about 6%), probably due to a compensatory increase of cholesterol absorption⁴⁾. Because there is an inverse correlation between the LDL-C-lowering effect of the cholesterol absorption inhibitor ezetimibe and statins⁵⁾, it is possible that patients who do not achieve a sufficient reduction in LDL-C concentrations in response to statin monotherapy may benefit from additional treatment with ezetimibe to inhibit cholesterol absorption; however, the effectiveness of low-dose pravastatin combined with ezetimibe has not been established. We investigated the effects of adding ezetimibe on serum lipids and cholesterol absorption and synthesis in patients with high LDL-C levels who had not shown a sufficient response to low-dose pravastatin (5-10 mg/day), a standard treatment in Japan, by comparing the effects of doubling the pravastatin dose.

Patients and Methods

Patients

The subjects were outpatients aged 20 to 74 years who had LDL-C ≥ 120 mg/dL after treatment with pravastatin (5 mg or 10 mg per day) for 4 weeks or longer. LDL-C < 120 mg/dL is the target of cholesterol-lowering therapy for high-risk patients without coronary artery disease according to the Japan Athero-

sclerosis Society⁶⁾. The exclusion criteria were use of a drug or drugs for hyperlipidemia other than the study drugs, insulin, or thiazolidinediones; a history of hypersensitivity to the study drugs, severe liver or kidney diseases; acute coronary syndrome (myocardial infarction and unstable angina) or stroke in the past 3 months, familial hypercholesterolemia or secondary hyperlipidemia; pregnancy including possible pregnancy or breast-feeding; and use of fats/oils enriched with plant sterols. Patients could also be ineligible if the study physician considered that participation was inappropriate.

Study Design

Eligible patients were enrolled at the registration center and were randomly allocated to either the ezetimibe add-on group or pravastatin double-dose group. The ezetimibe group received ezetimibe 10 mg/day as add-on therapy, and the pravastatin group started a doubled dose of pravastatin. The study period was 12 weeks. The patients visited their study physician every 4 weeks. Drugs other than those specified above were allowed, but study physicians were asked to maintain the dose during the study period. The study was approved by the Ethics Committee of the International University of Health and Welfare. Written informed consent was obtained from all the participants.

Recorded at the beginning of the study were height (cm), smoking and alcohol use, comorbid conditions, and concomitant medications. Serum lipids and lipoproteins, markers of cholesterol absorption and synthesis, and other biochemical items, as well as weight (kg) and waist circumference (cm), were measured at the beginning of the study and after 12 weeks of treatment. Changes of medications and adverse events were recorded during the course of the study. Adherence was assessed on the basis of self-reported compliance in the past 4 weeks assessed at week 4, 8 and 12 each. Frequency of use of the prescribed drug was elicited by a closed-ended question per week (daily; 5-6, 3-4 or 1-2 days per week; and null per week), and the average of the three frequencies was obtained as global compliance.

The primary outcome variables were the percent changes of LDL-C, apolipoprotein (apo B) and markers of cholesterol absorption and synthesis. The secondary outcome variables were serum lipids other than LDL-C, glucose metabolism parameters, C-reactive protein (CRP), and adiponectin.

Tolerability was assessed at each study visit and included adverse events, physical examination findings, and clinical laboratory test results. Abnormal

laboratory test results were defined as >3 times of the upper limit of normal for alanine aminotransferase (ALT) or aspartate aminotransferase (AST), 10 times the upper limit of normal for creatine kinase (CK), or 1.5 times the upper limit of normal for creatinine.

Laboratory Assays

All laboratory measurements were conducted at an external laboratory (SRL, Tokyo). Serum total cholesterol (TC) and triglycerides (TG) were measured by enzymatic methods, and high-density lipoprotein cholesterol (HDL-C) and LDL-C were measured by direct methods using commercial reagents (Sekisui Medical Co. Ltd., Tokyo). Apo AI, apo B, and apo E were measured by an immunoturbidimetric method. Fasting blood glucose was measured by the hexokinase method, HbA1c by the latex agglutination immunoassay, and fasting insulin by chemiluminescent enzyme immunoassay. Homeostasis model assessment of insulin resistance index (HOMA-IR) was calculated by dividing the product of fasting plasma glucose (mg/dL) and fasting serum insulin (IU/L) by 405.

Cholesterol absorption was assessed by sitosterol, campesterol, and cholestanol; sitosterol, campesterol are plant sterols that are not synthesized *de novo*, and cholestanol is a bile acid metabolite. Lathosterol, an intermediate metabolite in the cholesterol-biosynthesis pathway, was used as a marker of cholesterol synthesis. These cholesterol absorption and synthesis markers were determined by gas chromatography according to the method of Miettinen *et al.*⁴⁾. Sterol measurements below the detection limit, 1.0 $\mu\text{g/mL}$, were assigned a value of 0.5 $\mu\text{g/mL}$.

High-sensitivity CRP (hs-CRP) was measured by immunonephelometry, and high molecular weight adiponectin was measured by ELISA (Sekisui Medical Co. Ltd., Tokyo). CRP >10 mg/mL was discarded because acute inflammation was suspected⁷⁾.

The detection limit of CRP concentrations was 0.05 mg/L, and undetectable values were recoded as 0.025 mg/L. AST, ALT and CK were measured by the Japanese Society of Clinical Chemistry standard methods, and serum creatine was determined by enzymatic methods.

Statistical Analysis

Mean and SD are presented for continuous variables. Between-group and within-group comparisons were statistically tested by the Wilcoxon rank-sum test (Mann-Whitney *U* test) and Wilcoxon signed-rank test. Analysis of covariance was used when adjustment was needed for differences at the baseline. Fisher's exact test was used for comparison of categorical vari-

ables at the baseline. $P < 0.05$ was considered significant.

As for markers of cholesterol absorption and synthesis, limited information was available to assess the expected magnitude of the between-group difference and variance of the percent change; therefore, we arbitrarily decided that the sample size should be 100 patients for each group (200 subjects).

Results

Study Population

A total of 198 patients were enrolled in the study, and 101 and 97 patients were randomly assigned to the ezetimibe add-on group and pravastatin double-dose group, respectively. Except for one patient in the latter group who withdrew before the start of treatment, 197 patients started the treatment as assigned. Of these, 191 patients ($n=96$ in the ezetimibe add-on group and $n=95$ in the pravastatin double-dose group) completed a 12-week study (**Fig. 1**). The efficacy analysis population was composed of these 191 patients. Three patients in the pravastatin group were found to have used pioglitazone through the study period. The population for tolerability evaluation consisted of all the patients who started the treatment, including those who ceased the treatment due to adverse events ($n=3$), did not visit after 4 weeks ($n=1$), had no blood sampling at 12 weeks ($n=1$), were treated with the opposite modality ($n=1$); the patient in the last category also had no blood sampling at 12 weeks.

There was no difference between the two groups in terms of subject characteristics, except for a higher prescription of anti-diabetic drug in the pravastatin double-dose group (**Table 1**). The ezetimibe add-on group had higher concentrations of TC, non-HDL-C, LDL-C, apo B, and fasting serum insulin than the pravastatin double-dose group (**Table 2**).

Efficacy

Table 3 summarizes the percent changes of lipids and apolipoproteins, glucose metabolism parameters, CRP, and adiponectin after 12-week treatment. TC, non-HDL-C, LDL-C, and apo B concentrations were decreased significantly in both groups, but the decreases were more marked in the ezetimibe add-on group showing significant between-group differences. Add-on ezetimibe resulted in a 16% decrease in LDL-C while no more than 6% decrease in LDL-C was observed in the double-dose pravastatin treatment. TG increased significantly in the pravastatin double-dose group only, and apo E decreased signifi-

Fig. 1. Disposition of the subjects.

cantly in the ezetimibe add-on group only. The between-group difference was significant for the percent change of TG and apo E.

Fasting glucose and HbA1c did not change after either treatment, but fasting insulin and HOMA-IR increased in both groups, the increases being significant in the pravastatin double-dose group. There was no effect of the treatment on CRP and adiponectin concentrations. Waist circumference showed a statistically significant decrease in the ezetimibe add-on group, and the decrease was significantly different from that of the pravastatin double-dose group. Decreases in body weight showed no difference between the two groups (**Table 3**).

Because the baseline levels of TC, non-HDL-C, LDL-C, and apo B were higher in the ezetimibe group, we performed analysis of covariance to adjust for the baseline concentrations. The between-group differences in the percent changes of TC, non-HDL-C, LDL-C, and apo B were almost the same as those unadjusted for the baseline concentrations. Adjusted means of the percent decrease in LDL-C were 14.4% (95% confidence interval [CI] 12.0 to 18.2) in the ezetimibe add-on group and 7.2% (95% CI 4.0 to 10.4) in the pravastatin double-dose group. The corresponding

values for apo B were 13.1 (95% CI 10.4 to 15.9) and 5.2% (95% CI 2.5 to 8.0).

The markers of cholesterol absorption decreased substantially in the ezetimibe add-on group (**Table 4**). The percent decreases of ratios of absorption markers to cholesterol were also remarkable, i.e., 48% for campesterol, 36% for sitosterol, and 10% for cholestanol. On the other hand, these absorption markers increased in the pravastatin double-dose group; the percent increases of the ratios to cholesterol were 17% for campesterol, 14% for sitosterol, and 6% for cholestanol. In contrast, lathosterol (a marker of cholesterol synthesis) increased in both groups, but more markedly in the ezetimibe add-on group. The increase of lathosterol adjusted for total cholesterol concentrations was 76% in the ezetimibe add-on group and 24% in the pravastatin double-dose group.

Tolerability

The overall compliance was estimated for 73 patients in the ezetimibe add-on group and 74 in the pravastatin double-dose group. On average, the prescribed drug was taken 6.8 days per week in the former and 6.9 days per week in the latter.

Adverse effects numbered 18 among 17 patients

Table 1. Characteristics of the study subjects at baseline

Characteristic	Pravastatin + ezetimibe (<i>n</i> = 96)	Double-dose pravastatin (<i>n</i> = 95)	<i>p</i> value *
Female, <i>n</i> (%)	63 (65.6)	69 (72.6)	0.35
Age (year), mean (SD)	66.3 (9.7)	69.0 (9.6)	0.05
Smoking, <i>n</i> (%)	15 (15.6)	8 (8.4)	0.18
Regular alcohol use, <i>n</i> (%)	27 (28.1)	17 (17.9)	0.12
Body weight (kg), mean (SD)	58.7 (10.5)	57.9 (10.8)	0.54
BMI (kg/m ²), mean (SD)	24.2 (3.5)	24.1 (3.6)	0.67
Waist (cm), mean (SD)	87.5 (8.0)	88.0 (8.3)	0.87
Comorbidity			
Liver diseases, <i>n</i> (%)	3 (3.1)	2 (2.1)	1.00
Hypertension, <i>n</i> (%)	64 (66.7)	69 (72.6)	0.43
Antihypertensive drug, <i>n</i> (%)	55 (57.3)	61 (64.2)	0.37
Diabetes/IGT, <i>n</i> (%)	35 (36.5)	40 (42.1)	0.46
Antidiabetic drug, <i>n</i> (%)	9 (9.4)	19 (20.0)	0.04
CAD, <i>n</i> (%)	8 (8.3)	16 (16.8)	0.08
Prior history			
Myocardial infarction, <i>n</i> (%)	1 (1.0)	4 (4.2)	0.21
Cerebral infarction, <i>n</i> (%)	14 (14.6)	8 (8.4)	0.26
Parental CAD, <i>n</i> (%)	35 (36.5)	28 (29.5)	0.36
Pravastatin 10 mg, <i>n</i> (%)	30 (31.3)	29 (30.5)	1.00

CAD = coronary artery diseases; IGT = impaired glucose tolerance

*Based on Fisher's exact test for proportions and Wilcoxon rank-sum test for continuous variables.

in the ezetimibe add-on group and 10 among 7 patients in the pravastatin double-dose group. Of these, 3 cases (diarrhea, rash, and insomnia) in the ezetimibe add-on group and 2 cases (leg cramps and mild liver dysfunction) in the pravastatin double-dose group were considered by study physicians to be probably and possibly related to the study drug, respectively. Rather serious cases of adverse effects, to which the trial drug was unrelated, were ankle sprain with an episode of abnormal elevation of CK from excessive exercise in the ezetimibe add-on group and fracture of the femoral neck in the pravastatin double-dose group. None had an episode of abnormal elevation of AST, ALT, or creatinine as specified a priori.

Discussion

Compared with doubling the dose of pravastatin, add-on ezetimibe resulted in greater decreases in LDL-C and apo B concentrations in patients under treatment with a low-dose pravastatin. The add-on ezetimibe also produced substantial decreases in cholesterol-absorption markers and an increase in a cholesterol-synthesis marker.

Several studies have examined the effect of add-on ezetimibe therapy in patients under statin treat-

ment. Among patients on basal statin treatment, add-on ezetimibe resulted in a 21% to 27% additional reduction in LDL-C compared to add-on placebo⁸⁻¹⁰. In the EASE study, which included 3,030 patients under statin treatment who had failed to attain the LDL-C target set by the National Cholesterol Education Program Adult Treatment Panel III, a 23% reduction of LDL-C was obtained in the add-on ezetimibe group compared with the add-on placebo group¹¹. Furthermore, in a pooled analysis of 4 studies (2,382 patients) that compared the effects of statin monotherapy and combination therapy of statin and ezetimibe, the percent decrease of LDL-C was 33% in the former and 47% in the latter¹².

In a study that investigated the combination use of pravastatin (10, 20, or 40 mg/day) and ezetimibe (10 mg/day) for 12 weeks, pravastatin plus ezetimibe resulted in an average 39% decrease of LDL-C while pravastatin alone decreased LDL-C by 25% on average¹³. The decreases in LDL-C were dependent on the pravastatin dose, but further decreases in LDL-C by the addition of ezetimibe were almost consistent across pravastatin doses (12-14%). The combination of pravastatin (10 mg/day) and ezetimibe (10 mg/day) decreased LDL-C by 34% while the decreases by 20 mg/day and 40 mg/day of pravastatin alone were 24%

Table 2. Serum lipids and lipoproteins and glucose metabolism parameters at baseline

Variable (unit)	Pravastatin + ezetimibe		Double-dose pravastatin		<i>p</i> value
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	
Total cholesterol (mg/dL)	96	228.4 (26.9)	95	218.7 (29.5)	0.008
Non-HDL-C (mg/dL)	96	171.5 (26.6)	95	161.6 (27.5)	0.003
LDL-C (mg/dL)	96	142.5 (21.5)	95	133.0 (23.1)	0.002
HDL-C (mg/dL)	96	56.9 (12.4)	95	57.1 (13.6)	0.96
TG (mg/dL)	91	133.7 (62.1)	89	123.8 (71.0)	0.09
Apo A (mg/dL)	96	147.4 (23.2)	95	145.1 (26.2)	0.36
Apo B (mg/dL)	96	115.8 (17.8)	95	109.0 (18.2)	0.005
Apo E (mg/dL)	96	4.65 (1.09)	95	4.61 (1.35)	0.63
Fasting glucose (mg/dL)	91	97.3 (12.4)	89	101.1 (19.6)	0.50
Fasting insulin (μ U/mL)	91	6.38 (3.82)	89	5.35 (2.71)	0.07
HOMA-IR [†]	91	1.56 (1.00)	89	1.37 (0.83)	0.21
HbA1c (%)	96	5.61 (0.51)	95	5.77 (0.79)	0.42
hs-CRP (mg/L)	95	1.04 (1.54)	92	0.93 (1.23)	0.78
Adiponectin (μ g/mL) [†]	94	6.94 (4.78)	95	8.00 (4.44)	0.04

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; Apo=apolipoprotein; HOMA-IR=homeostasis model assessment of insulin resistance index; hs-CRP=high-sensitivity C-reactive protein.

[†]High-molecular weight adiponectin.

and 29%, respectively¹³). Another study also showed that a combination of pravastatin (10 mg/day) and ezetimibe (10 mg/day) produced a greater decrease in LDL-C than a single treatment with pravastatin of 40 mg/day (26% versus 20%)¹⁴. In the present study, 10 mg/day of ezetimibe added to low-dose pravastatin (5-10 mg/day) decreased LDL-C by 16% while doubling the dose of pravastatin resulted in only a 6% decrease in LDL-C. The observed magnitude of the incremental decrease in LDL-C resulted by ezetimibe (10 mg/day) is very similar to that reported for combination therapy^{13, 14}.

The ezetimibe add-on decreased cholesterol-absorption markers and increased a cholesterol-synthesis marker. The present findings corroborate the previous observation in terms of the magnitude of the changes in the markers. It was reported that 2-week treatment with ezetimibe 10 mg/day resulted in a 41% decrease in the campesterol/cholesterol ratio (an indicator of cholesterol absorption) and a 72% increase in the lathosterol/cholesterol ratio (an indicator of cholesterol synthesis)¹⁵. A unique finding in the present study was that similar changes were observed after administration of ezetimibe in addition to pravastatin. In the ezetimibe add-on group, the campesterol/cholesterol ratio and sitosterol/cholesterol ratio decreased by 48% and 36%, respectively, and the lathosterol/cholesterol ratio increased by 76%. It is hypothesized that inhibition of cholesterol absorption by ezetimibe

leads to a compensatory increase of cholesterol synthesis¹⁴, but the increase of cholesterol synthesis by ezetimibe does not deteriorate LDL-C concentrations. A previous report suggested that ezetimibe increased the serum level of lathosterol while coadministration of ezetimibe and statin increased the fractional catabolic rate of apo B containing lipoproteins¹⁶. In the present study, rather surprisingly, a double dose of pravastatin increased a cholesterol synthesis marker, although the increase was modest. In the double-dose pravastatin group, 13 patients showed a more than 2-fold increase in the lathosterol/cholesterol ratio. Even after exclusion of these patients, there was no indication of a decrease in the cholesterol synthesis marker associated with double-dose pravastatin; mean percent change of the lathosterol/cholesterol ratio was -0.4% (SD 34.1%, $p=0.95$).

As confirmed in the present study, doubling the dose of a statin conferred only a small, additional effect and LDL-C could be further decreased by 5-6%¹⁷. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study¹⁸, LDL-C increased gradually at later periods of long-term treatment with standard (pravastatin 40 mg/day) or intensive (atorvastatin 80 mg/day) therapy. A compensatory increase in cholesterol absorption secondary to the inhibition of cholesterol synthesis by statin is the most likely explanation for the so-called escape phenomenon^{17, 18}. Addition of ezetimibe to statin monotherapy

Table 3. Percent changes in serum lipids and apolipoproteins and glucose metabolism parameters after 12-week treatment

Variable	Pravastatin + ezetimibe			Double-dose pravastatin			<i>p</i> value [†]
	<i>n</i>	Means (SD)	<i>p</i> value [*]	<i>n</i>	Means (SD)	<i>p</i> value [*]	
Body weight	96	−0.3 (1.6)	0.02	95	−0.4 (2.1)	0.02	0.72
Waist circumference	96	−1.1 (2.3)	<0.0001	95	−0.4 (2.3)	0.10	0.02
Total cholesterol	96	−11.1 (11.7)	<0.0001	95	−3.6 (13.9)	0.0004	<0.0001
Non-HDL-C	96	−16.1 (14.1)	<0.0001	95	−5.0 (17.7)	0.0002	<0.0001
LDL-C	96	−15.6 (15.4)	<0.0001	95	−5.9 (18.3)	0.0004	<0.0001
HDL-C	96	4.4 (12.7)	0.002	95	1.4 (14.1)	0.53	0.08
TG	84	−4.8 (29.3)	0.06	87	17.4 (47.3)	0.01	0.002
Apo A	96	4.1 (10.8)	0.0005	95	4.3 (13.0)	0.002	0.71
Apo B	96	−13.9 (13.2)	<0.0001	95	−4.4 (14.9)	0.0007	<0.0001
Apo E	96	−5.9 (12.4)	<0.0001	95	1.9 (14.8)	0.88	0.0002
Fasting glucose	84	0.5 (7.5)	0.82	87	1.7 (9.3)	0.10	0.32
Fasting insulin	84	17.8 (66.4)	0.10	87	33.8 (70.3)	<0.0001	0.03
HOMA-IR	84	20.0 (71.7)	0.09	87	38.9 (82.7)	<0.0001	0.04
HbA1c	96	0.3 (3.5)	0.26	95	−0.5 (4.1)	0.28	0.13
hs-CRP	94	28.3 (134)	0.82	90	25.1 (133)	0.83	0.996
Adiponectin [‡]	94	3.4 (27.1)	0.88	95	7.0 (44.1)	0.30	0.58

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; Apo=apolipoprotein; HOMA-IR=homeostasis model assessment of insulin resistance index; hs-CRP=high-sensitivity C-reactive protein.

* Within-group comparison for difference from the baseline.

† Between-group comparison.

‡ High-molecular weight adiponectin

selectively inhibits intestinal cholesterol absorption, thereby conferring a greater LDL-lowering effect than a higher dose of statin.

The waist circumference decreased after the addition of ezetimibe, but not after doubling the dose of pravastatin. In obesity-model rats, ezetimibe not only improved blood levels of chylomicrons and fatty acids but also suppressed the expression of sterol regulation element binding protein-1c (SREBP-1c), a transcription factor involved in hepatic fatty acid synthesis¹⁹. Two-month administration of ezetimibe 10 mg/day markedly inhibited postprandial increases of apo B48, a dominant apolipoprotein almost exclusively contained in chylomicrons, and free fatty acids in patients with type IIb hyperlipidemia²⁰. The suppression effect of ezetimibe on the postprandial increase of chylomicrons is probably attributed to inhibition of chylomicron secretion in the small intestine. Chylomicrons are formed through the aggregation of cholesterol ester, TG, and apo B48 in intestinal cells. Ezetimibe was shown to reduce the expression of fatty acid transfer protein-4 (FATP-4) and suppress the absorption of saturated fatty acids²¹. It is possible that ezetimibe causes the depletion of cholesterol from intestinal cells and inhibits the formation of chylomicrons, thereby being protective against the accumulation of

abdominal fat.

High molecular weight adiponectin did not change at all in either group in the present study. Previously, 2-week monotherapy or combination therapy with ezetimibe and/or simvastatin did not affect serum concentrations of leptin and high molecular weight adiponectin²².

Meta-analysis of 23 placebo-controlled studies of lipid-lowering therapy confirmed a strong correlation between the decrease of the hs-CRP level and the decrease of LDL-C²³. Combination therapy with ezetimibe (10 mg/day) and simvastatin resulted in a more than 2-fold decrease of hs-CRP compared to simvastatin monotherapy²⁴. The present study failed to find such an effect of ezetimibe in combination with pravastatin on hs-CRP.

With regard to safety, there were no serious adverse events possibly or probably related to the study drugs. Although there were no significant changes in fasting glucose and HbA1c in either group, fasting serum insulin and HOMA-IR increased significantly after 12 weeks to almost the same extent in both groups. The latter findings were rather unexpected because pravastatin possibly exerts a protective, rather than adverse, effect on insulin resistance²⁵ and glucose metabolism²⁶.

Table 4. Baseline values and percent changes of non-cholesterol sterols after 12-week treatment

Sterol ($\mu\text{g/mL}$)	Baseline value			Percent change		
	Pravastatin + ezetimibe ($n=94$)	Double-dose pravastatin ($n=95$)	<i>p</i> value	Pravastatin + ezetimibe ($n=94$)	Double-dose pravastatin ($n=95$)	<i>p</i> value
Lathosterol	1.6 (0.8)	1.5 (1.0)	0.14	57.0 (92.1) [†]	20.9 (87.2)	<0.0001
Campesterol	4.0 (2.4)	3.6 (1.7)	0.36	-52.9 (24.3) [†]	13.7 (42.6)*	<0.0001
Sitosterol	2.7 (1.4)	2.6 (1.1)	0.44	-42.7 (25.5) [†]	10.8 (42.5)	<0.0001
Cholestanol	3.0 (0.9)	2.8 (0.8)	0.13	-20.3 (17.7) [†]	2.1 (26.0)	<0.0001
(Ratio to TC $\times 10000$)						
Lathosterol/TC	7.0 (3.5)	6.6 (4.4)	0.36	76.0 (97.9) [†]	24.2 (77.1)*	<0.0001
Campesterol/TC	17.2 (9.3)	16.4 (7.1)	0.68	-48.0 (22.9) [†]	17.0 (34.8) [†]	<0.0001
Sitosterol/TC	11.9 (5.4)	11.7 (4.8)	0.95	-36.3 (24.9) [†]	14.1 (35.1) [†]	<0.0001
Cholestanol/TC	13.2 (3.6)	13.0 (3.2)	0.66	-10.0 (18.4) [†]	6.0 (22.8)*	<0.0001

Values are the means (SD).

* $p < 0.05$ as compared with the baseline value.

[†] $p < 0.0001$ as compared with the baseline value.

Conclusion

Among patients under low-dose pravastatin treatment who had high LDL-C levels, add-on ezetimibe decreased LDL-C and apo B levels more markedly than a double dose of pravastatin. Add-on ezetimibe increased cholesterol synthesis, but resulted in substantial decreases in cholesterol absorption markers. Add-on ezetimibe should be the treatment of choice when statin treatment has not attained a sufficient reduction in LDL-C.

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