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ORIGINAL RESEARCH

Long-Term Efficacy of Pitavastatin Versus Simvastatin

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ABSTRACT

Introduction: Pitavastatin is a novel, potent, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. This study compared the long-term efficacy of pitavastatin and simvastatin in dyslipidemic patients at high risk of coronary heart disease. ***Methods:*** A 44-week blinded extension study was conducted at 24 centers in five European countries for patients who had previously completed a 12-week randomized, double-blind core study in which they received pitavastatin 4 mg or simvastatin 40 mg once daily. Patients originally randomized to pitavastatin 4 mg continued at the same dose throughout the extension study (n=121). In simvastatin-treated patients (n=57), the dose was increased to 80 mg in five patients who had not attained the National Cholesterol Education Program (NCEP) target for low-density lipoprotein cholesterol (LDL-C) during the core study. Primary endpoints were the proportion of patients attaining the NCEP and European Atherosclerosis Society (EAS) LDL-C targets, and the NCEP target for non-high-density lipoprotein cholesterol (non-HDL-C) at weeks 16 and 44. ***Results:*** Of the 178 patients who entered the extension study, 156 patients (109 in the pitavastatin group, 47 in the simvastatin groups) completed the 44-week treatment period. At week 44, NCEP and EAS targets were attained by 81.7% and 84.2%, respectively, of pitavastatin-treated patients, and 75.4% and 73.7%, respectively, of simvastatin-treated patients. NCEP targets for non-HDL-C were achieved by 79.2% of pitavastatin-treated patients and 70.2% of simvastatin-treated patients. Both treatments were generally well tolerated, but pitavastatin 4 mg was associated with a numerically lower incidence of discontinuations due to treatment-emergent adverse events (5.8% vs. 10.5% of patients) and a lower rate of myalgia (4.1% vs. 12.3%) compared with simvastatin 40-80 mg. ***Conclusion:*** Pitavastatin 4 mg provides long-term efficacy similar to that of simvastatin 40-80 mg. Further studies should ascertain whether trends suggesting that pitavastatin may exhibit a more favorable long-term tolerability profile are statistically significant.

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INTRODUCTION

Elevated serum cholesterol concentrations, particularly low-density lipoprotein cholesterol (LDL-C), is a recognized risk factor for coronary heart disease (CHD), and numerous interventional studies have shown that lowering LDL-C delays the progression of atherosclerotic lesions and reduces cardiovascular mortality and morbidity associated with CHD.[1] As a result, current guidelines for the prevention of CHD recommend the use of lipid-modifying therapy in patients with dyslipidemia.[2,3] 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have become the most widely used lipid-modifying agents, due to their proven efficacy in lowering total cholesterol and LDL-C concentrations and beneficial effects on other lipid fractions, such as high-density lipoprotein cholesterol (HDL-C) and triglycerides.[1,4] However, several observational studies have shown that a significant proportion of patients do not attain recommended LDL-C concentration targets despite treatment with statins.[5-8] Such findings highlight the need for more effective lipid-lowering strategies, which could include the use of more aggressive initial therapy, more potent agents, dose adjustment during treatment, or combination therapy using agents with different mechanisms of action.

Pitavastatin is a novel, highly potent statin that has been shown to provide significant reductions in total cholesterol, LDL-C, and triglyceride concentrations in patients with hyperlipidemia[9] or heterozygous familial hypercholesterolemia.[10,11] Pitavastatin has also been shown to produce sustained increases in HDL-C concentrations over 52 weeks.[12] Unlike other statins, pitavastatin does not undergo extensive metabolism by cytochrome P450 isoenzymes, and hence the potential for interactions with drugs that are metabolized by cytochrome P450 is low.[12,13]

A 12-week, randomized, double-blind trial in patients at high risk of CHD showed that pitavastatin 4 mg was statistically non-inferior to simvastatin 40 mg for the reduction of LDL-C concentrations, and provided larger increases in HDL-C (6.8% vs. 4.5%; *P*=0.083) and reductions in triglycerides (–19.8% vs. –14.8%; *P*=0.044) than simvastatin treatment.[14] We report the results of a 44-week extension study designed to compare the long-term safety and efficacy of pitavastatin 4 mg and simvastatin 40-80 mg. The primary endpoint was the proportion of patients attaining the LDL-C targets recommended by the National Cholesterol Education Program (NCEP)[2] and the European Atherosclerosis Society (EAS).[3] Secondary objectives were to assess the efficacy of the two statins on other lipid fractions and high sensitivity C-reactive protein (hs-CRP) levels.

MATERIALS AND METHODS

Patients

The inclusion and exclusion criteria of the study have been described in detail previously.[14] In brief, patients aged 18-75 years were eligible if they had uncontrolled primary hypercholesterolemia or combined dyslipidemia (LDL-C concentrations of ≥3.4 mmol/L [130 mg/dL] and ≤5.7 mmol/L [220 mg/dL]; triglycerides ≤4.6 mmol/L [400 mg/dL]) and at least two other risk factors for CHD. The principal exclusion criteria were homozygous familial hypercholesterolemia, unstable medical conditions or conditions associated with

secondary dyslipidemia, conditions that might affect drug pharmacokinetics, and significant medical illness. Women of childbearing potential were required to have a negative pregnancy test at the start of the dietary run-in period and before starting treatment, and to use adequate contraception throughout the study.

The study was performed in compliance with the Declaration of Helsinki, the draft Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders by the Committee for Proprietary Medicinal Products, and the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use - Harmonized Tripartite Guidelines for Good Clinical Practice. The protocol was approved by local institutional review boards or independent ethics committees at each center. All participants provided written informed consent before inclusion in the study.

Study Design

The study was a 44-week, double-blind, double-dummy, parallel-group, active-controlled extension study in patients who had completed the core study. It was conducted at 24 centers (predominantly in lipid clinics, cardiology clinics, and university hospitals) in Denmark, the Netherlands, Spain, Sweden, and the United Kingdom.

During the core study, patients were randomized 2:1 to receive pitavastatin 4 mg or simvastatin 40 mg. Randomization was performed using an interactive voice recognition system at each center. Patients entering the extension study were maintained on the same drug they had received during the core study. Pitavastatin-treated patients continued on the same dose (4 mg) throughout the extension study. In the simvastatin group, patients who had reached the NCEP LDL-C target by week 8 of the core study were maintained at a dose of 40 mg during the extension study, whereas in patients who had not reached this target the dose was increased to 80 mg at the start of the extension study. The sponsors, clinical trial team, and patients remained blinded to target achievement during the core study. Treatment was given once-daily in the evening, and all other lipid-modifying therapies were prohibited for the duration of the study. Compliance was checked by counting unused tablets or capsules at each study visit. Throughout the extension study, all patients continued to follow the same fat- and cholesterol-restrictive diet that they had followed during the core study.

During the extension study, treatment was administered following the double-blind protocol used in the core study. However, after 16 weeks the sponsor and statisticians were unblinded to permit reporting of the core study data, while the investigators and patients remained blinded for the duration of the extension study. Treatment was given according to a double-dummy design. Pitavastatin 4 mg tablets and matching placebos were supplied by SkyePharma Production (Saint Quentin-Fallavier, France). Over-encapsulated simvastatin tablets and matching placebos were supplied by Almac (Craigavon, UK).

Blood samples for lipid analyses were obtained after a 12-hour fast at the start of the extension study (ie, after 12 weeks in the core study) and at weeks 4, 8, 16, 24, 32, and 44.

Outcome Measures

The primary lipid-related endpoints in the extension study were the proportion of patients attaining the LDL-C targets, as recommended by the NCEP and EAS, at weeks 16 and 44, and the proportion attaining the NCEP target for

non-HDL-C concentration at the same time points. LDL-C concentrations were calculated using the Friedewald formula,[15] except in patients with triglyceride concentrations above 4.6 mmol/L, where LDL-C was measured by ultracentrifugation due to the known effect of high triglyceride concentrations on the accuracy of the Friedewald formula.[16] A further analysis was based on non-HDL-C and triglyceride concentrations, as described in step 9 of the NCEP criteria.[2] The NCEP criteria provides a stepwise approach to determining and treating lipid-associated risk factors for CHD. In patients who achieved their LDL-C targets at each visit and had triglyceride concentrations above 2.3 mmol/L (200 mg/dL), non-HDL-C targets were assigned that were 0.78 mmol/L (30 mg/dL) higher than their LDL-C target. These patients were required to attain both their LDL-C and non-HDL-C targets to achieve their step 9 target. In patients who did not achieve LDL-C targets, the LDL-C target was regarded as the step 9 target. Secondary lipid assessments and other secondary efficacy endpoints included the percentage changes from baseline in concentrations of LDL-C, total cholesterol, HDL-C, non-HDL-C, triglycerides, apolipoprotein B (Apo-B) and apolipoprotein A1 (Apo-A1), and absolute changes from baseline in oxidized LDL levels, non-HDL-C:HDL-C ratio, total cholesterol:HDL-C ratio, Apo-B:Apo-A1 ratio, and hs-CRP levels. All lipid analyses were performed at a central laboratory.

Safety and Tolerability

Treatment-emergent adverse events (TEAE), defined as any event with onset on or after the first dose of study drug, and serious TEAE were recorded throughout the study. All such events were coded by system organ class preferred term using the Medical Dictionary for Regulatory Activities. Clinical laboratory safety assessments included routine blood chemistry, hematology, urinalysis, liver enzymes (alanine aminotransferase [ALAT] and aspartate aminotransferase [ASAT]) and creatine kinase (CK). Other safety evaluations included physical examination, 12-lead electrocardiogram (ECG) and vital signs.

Statistical Analyses

No formal sample size calculation was performed for this extension study because the number of patients entering the study was dependent on the number completing the core study and agreeing to enter the extension study. It was anticipated that this would be approximately 270 patients.

Efficacy analyses were performed on the efficacy population, which consisted of all patients who received at least one dose of study medication and had at least one lipid assessment during the study. Analyses of safety data were performed on the safety population, which included all patients who received at least one dose of study medication.

For the primary efficacy variables, the proportions of patients attaining NCEP and EAS LDL-C targets and NCEP non-HDL-C targets at weeks 16 and 44 were summarized by visit. For patients who withdrew before these times, the last available LDL-C concentration was used to assess whether targets had been attained. No formal statistical analysis was performed. Secondary efficacy variables were summarized in the same way.

RESULTS

Patient Flow and Baseline Characteristics

The first patient was enrolled into the extension study on June 21 2006 and the final

patient visit was on August 14 2007. In total, 178 patients entered the extension study (Figure 1), of whom 121 had been randomized to receive pitavastatin during the core study and 57 had been randomized to simvastatin. The dose of simvastatin was increased to 80 mg at the start of the extension study in five patients because they had not achieved the NCEP target for LDL-C concentrations by week 8 of the core study. All patients received at least one dose of study medication, and were therefore included in the safety population. One patient in the pitavastatin group had no lipid assessment during the study and was therefore excluded from the efficacy population; hence, the efficacy population consisted of 177 patients (Figure 1). Twenty-two patients withdrew during the study, mainly because of adverse events (Figure 1). Demographic characteristics of the patients entering the extension study are summarized in Table 1. The characteristics of the patients in this study were similar to those of the total patient population enrolled in the core study.[14] There were no clinically relevant differences in demographic characteristics between the pitavastatin and simvastatin groups.

Efficacy

Attainment of EAS and NCEP Lipid Targets

The proportions of patients achieving NCEP or EAS targets for LDL-C concentrations at the end of the extension study are summarized in Table 2. At the start of the extension study, the

Figure 1. Patient disposition. *One patient excluded from the efficacy population completed the core study.

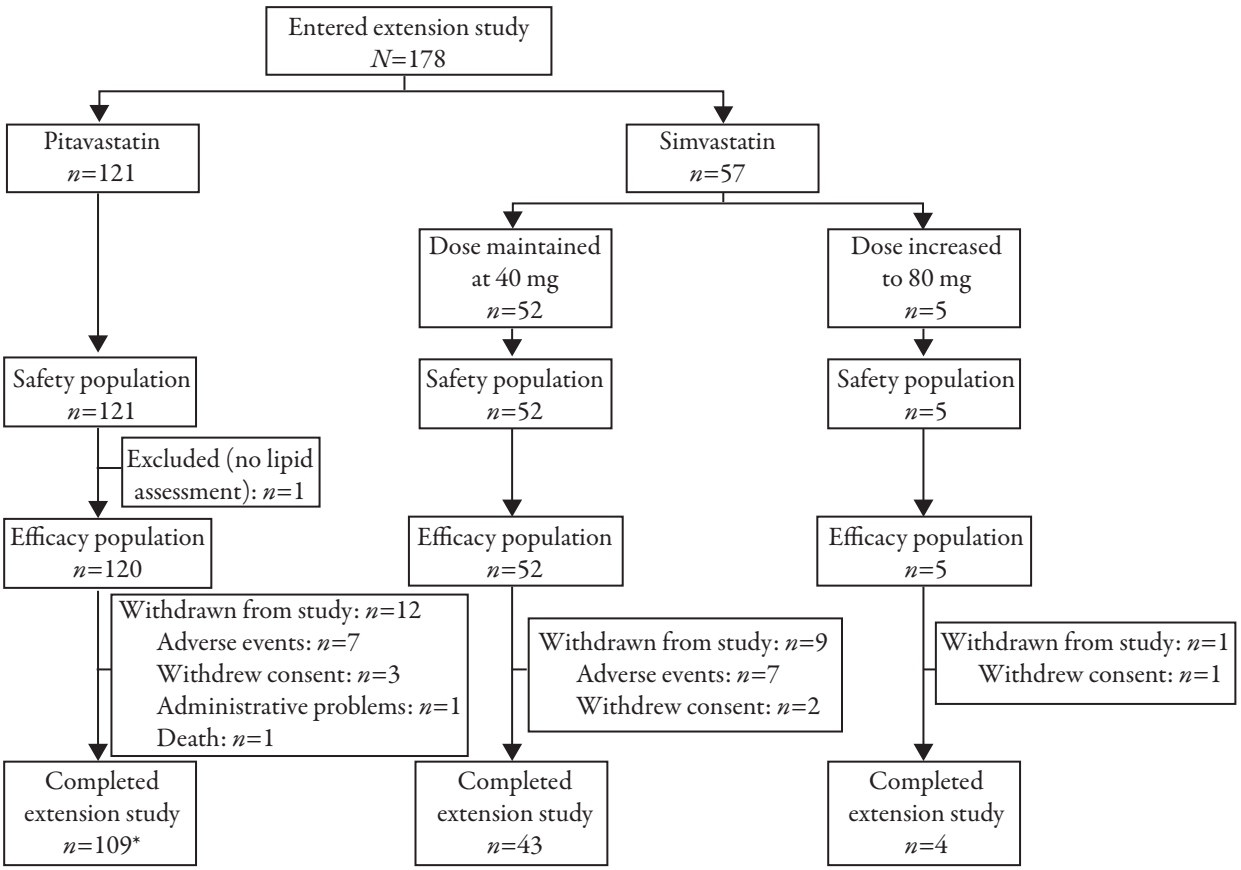

Table 1. Baseline demographic and clinical characteristics.

Characteristic	Pitavastatin 4 mg (*n*=121)	Simvastatin 40-80 mg (*n*=57)
White, *n* (%)	121 (100)	57 (100)
Gender		
Male, *n* (%)	82 (67.8)	39 (68.4)
Female, *n* (%)	39 (32.2)	18 (31.6)
Age (years), mean ± SD	60.4±5.8	60.8±6.5
Age group, *n* (%)		
<65 years	98 (81.0)	44 (77.2)
≥65 years	23 (19.0)	13 (22.8)
Primary diagnosis, *n* (%)		
Primary hypercholesterolemia	108 (89.3)	52 (91.2)
Combined dyslipidemia	10 (8.3)	4 (7.0)
Heterozygous FH	3 (2.5)	1 (1.8)
Time since diagnosis (years), mean ± SD	2.8±4.7	3.2±4.8
Height (m), mean ± SD	1.7±0.1	1.7±0.1
Weight (kg), mean ± SD	81.3±13.1	82.4±12.7
Body mass index (kg/m^2), mean ± SD	27.5±3.4	28.1±3.2
NCEP risk category, *n* (%)		
High	28 (23.1)	19 (33.3)
Moderate	90 (74.4)	37 (64.9)
Low	3 (2.5)	1 (1.8)
Diabetes, *n* (%)	6 (5.0)	3 (5.3)
Hypertension, *n* (%)	68 (56.2)	36 (63.2)

FH=familial hypercholesterolemia; NCEP=National Cholesterol Education Program; SD=standard deviation.

Table 2. Proportion of patients achieving National Cholesterol Education Program (NCEP) or European Atherosclerosis Society (EAS) targets for low-density lipoprotein cholesterol (LDL-C) during treatment with pitavastatin or simvastatin.

Parameter	Number of patients attaining target/ number of patients assessed*	
	Pitavastatin, 4 mg/day (*n*=120)	Simvastatin, 40-80 mg/day (*n*=57)
NCEP criteria, *n/n* (%)		
Week 0	108/118 (91.5)	50/55 (90.9)
Week 16	103/120 (85.8)	45/57 (78.9)
Week 44	98/120 (81.7)	43/57 (75.4)
EAS criteria, *n/n* (%)		
Week 0	112/118 (94.9)	51/55 (92.7)
Week 16	105/120 (87.5)	51/57 (89.5)
Week 44	101/120 (84.2)	42/57 (73.7)

*In patients who withdrew before week 16 or 44, attainment of targets was assessed using the last available lipid determination.

proportion of patients meeting the NCEP or EAS targets was 91.5% and 94.9%, respectively, with pitavastatin and 90.9% and 92.7%, respectively, with simvastatin. At the end of the study, the corresponding proportions were 81.7% for NCEP targets and 84.2% for EAS targets with pitavastatin, and 75.4% and 73.7%, respectively, with simvastatin.

At the start of the extension study, step 9 secondary NCEP targets (non-HDL-C or LDL-C) were attained by 89.8% of patients in the pitavastatin group, and by 87.3% of those in the simvastatin group (Table 3). Corresponding proportions at the end of the study were 79.2% and 70.2%, respectively.

As an additional efficacy endpoint, the proportion of patients achieving NCEP targets was analyzed according to whether or not patients achieved these targets during the core study. Of those who achieved their LDL-C targets during the core study, 94 of 108 patients (87.0%) in the pitavastatin group, and 42 of 52 patients (80.8%) in the simvastatin group attained their LDL-C targets at the end of the extension study. Eleven patients in the pitavastatin group and five in the simvastatin group did not attain their LDL-C targets during the core study. Of these, three (27.3%) pitavastatin-treated patients and one (20.0%) simvastatin-treated patient attained LDL-C targets at the end of the extension study. The

Table 3. Proportion of patients achieving National Cholesterol Education Program (NCEP) step 9* targets during treatment with pitavastatin or simvastatin.

Week†	Number of patients attaining target/ number of patients assessed	
	Pitavastatin 4 mg (*n*=120)	**Simvastatin 40-80 mg (*n*=57)**
Week 0, *n/n* (%)	106/118 (89.8)	48/55 (87.3)
Week 16, *n/n* (%)	99/120 (82.5)	41/57 (71.9)
Week 44, *n/n* (%)	95/120 (79.2)	40/57 (70.2)

*Patients who achieved their low-density lipoprotein cholesterol (LDL-C) targets at each visit and had serum triglyceride concentrations above 2.26 mmol/L (200 mg/dL) were required to attain both their LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) targets to achieve their NCEP step 9 target. In the remaining patients, the LDL-C target was regarded as the NCEP step 9 target.
†In patients who withdrew before week 16 or 44, attainment of targets was assessed using the last available lipid determination.

proportion of patients meeting NCEP step 9 targets was 84.3% with pitavastatin and 75.0% with simvastatin among those who attained their targets during the core study, and 27.3% and 20.0%, respectively, among those who did not.

Secondary Efficacy Variables

Mean changes in secondary lipid variables and hs-CRP levels from baseline (start of the core study) to week 44 are summarized in Table 4. In general, both treatments produced similar changes in these secondary measures. Although at week 16, HDL-C increased by 12.4% with pitavastatin and by 7.3% with simvastatin, the final increase was similar. Triglyceride concentrations decreased by approximately 12%, compared with baseline, whereas the corresponding reductions at the end of the core study were approximately 20% with pitavastatin and 15% with simvastatin.[14] Apo-B:Apo-A1 and non-HDL-C:HDL-C ratios showed large decreases from baseline with both treatments, and only slight increases compared with the end of the core treatment period. Values for the total cholesterol:HDL-C ratio were the same as those for the non-HDL-C:HDL-C ratio. Apo-A1 levels increased during the extension study in the simvastatin group, but remained constant in the pitavastatin group.

Safety and Tolerability

TEAE

TEAE were reported by 92 patients (76.0%) in the pitavastatin group and by 45 patients (78.9%) in the simvastatin group (Table 5). The most common adverse events occurring during the extension study were nasopharyngitis, headache, back pain, and myalgia; most TEAE were mild or moderate in severity. The proportion of patients with TEAE considered to be related to study treatment was 17.5% with simvastatin and 10.7% with pitavastatin; the proportions of patients discontinuing treatment due to a TEAE were 10.5% and 5.8%, respectively. The most common TEAE leading to withdrawal were gastrointestinal disorders, which occurred in three patients in the simvastatin group and in one patient in the pitavastatin group. Myalgia was reported in a higher proportion of patients in the simvastatin group (12.3%) than the pitavastatin group (4.1%); one patient in the simvastatin group discontinued treatment during the extension study because of myositis.

Five serious TEAE (cataract, bronchitis, non-cardiac chest pain, postcholecystectomy syndrome, and fatal myocardial ischemia) occurred in four (3.3%) patients in the pitavastatin group, and seven serious TEAE (myocardial infarction, global amnesia, urinary bladder polyps, angina pectoris, gastroenteritis,

Table 4. Changes in secondary lipid variables and high sensitivity C-reactive protein (hs-CRP) from baseline (start of the core study) to the start of the extension study (week 0) and from baseline to week 44 of the extension study in patients treated with pitavastatin or simvastatin.

Parameter	Change from baseline (mean±SD)	
	Pitavastatin 4 mg (*n*=120)	**Simvastatin 40-80 mg (*n*=57)**
Total cholesterol		
Baseline mean (mmol/L)	6.33±0.66	6.47±0.75
Baseline to extension week 0 (%)	−33.0±6.6	−35.4±8.5
Baseline to extension week 44 (%)	−27.4±11.8	−27.4±12.0
LDL-C		
Baseline mean (mmol/L)	4.27±0.53	4.38±0.60
Baseline to extension week 0 (%)	−46.30±9.0	−49.54±10.8
Baseline to extension week 44 (%)	−41.81±15.1	−41.37±16.4
HDL-C		
Baseline mean (mg/dL)	1.21±0.27	1.18±0.20
Baseline to extension week 0 (%)	9.3±13.1	7.0±10.8
Baseline to extension week 44 (%)	14.1±17.3	14.6±16.4
Non-HDL-C		
Baseline mean (mmol/L)	5.12±0.66	5.29±0.73
Baseline to extension week 0 (%)	−43.1±7.8	−44.8±9.9
Baseline to extension week 44 (%)	−37.2±14.2	−36.8±15.6
Non-HDL-C:HDL-C ratio (%)		
Baseline mean	4.5±1.2	4.6±1.1
Baseline to extension week 0 (%)	−2.1±0.9	−2.2±0.8
Baseline to extension week 44 (%)	−1.9±1.8	−2.0±1.1
Total cholesterol: HDL-C ratio (%)		
Baseline mean	5.5±1.2	5.6±1.1
Baseline to extension week 0 (%)	−2.1±0.9	−2.2±0.8
Baseline to extension week 44 (%)	−1.9±1.8	−2.0±1.1
Triglycerides		
Baseline mean (mmol/L)	1.86±0.81	1.99±0.84
Baseline to extension week 0 (%)	−24.4±18.9	−22.6±20.3
Baseline to extension week 44 (%)	−11.5±42.7	−12.3±22.7
Apo-B		
Baseline mean (mg/dL)	151.7±21.8	156.0±22.4
Baseline to extension week 0 (%)	−35.3±9.7	−37.5±10.7
Baseline to extension week 44 (%)	−35.1±13.3	−34.7±12.0
Apo-A1		
Baseline mean (mg/dL)	159.6±26.4	158.4±20.4
Baseline to extension week 0 (%)	7.7±13.3	7.5±12.0
Baseline to extension week 44 (%)	7.2±15.7	10.7±13.5

Table 4 ***(continued)*****.** Changes in secondary lipid variables and high sensitivity C-reactive protein (hs-CRP) from baseline (start of the core study) to the start of the extension study (week 0) and from baseline to week 44 of the extension study in patients treated with pitavastatin or simvastatin.

Parameter	Change from baseline (mean±SD)	
	Pitavastatin 4 mg (*n*=120)	**Simvastatin 40-80 mg (*n*=57)**
Apo-B:Apo-A1 ratio		
Baseline mean	0.98±0.2	1.00±0.2
Baseline to extension week 0 (%)	−0.4±0.2	−0.4±0.2
Baseline to extension week 44 (%)	−0.4±0.3	−0.4±0.2
Oxidized LDL		
Baseline mean (U/L)	79.8±16.5	82.4±18.5
Baseline to extension week 0 (U/L)	−26.6±14.3	−29.4±17.5
Baseline to extension week 44 (U/L)	−30.0±16.4	−28.9±19.1
hs-CRP		
Baseline mean (mg/L)	3.5±5.9	4.1±10.5
Baseline to extension week 0 (mg/L)	−0.7±6.8	0.4±5.4
Baseline to extension week 44 (mg/L)	−0.4±6.8	−1.8±10.8

Apo-A1=apolipoprotein A1; Apo-B=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol.

bladder cancer, and transient ischemic attack) occurred in seven patients (12.3%) in the simvastatin group. None of these adverse events was considered to be treatment related.

Table 5. Summary of treatment-emergent adverse events (TEAE) during treatment with pitavastatin or simvastatin.

TEAE	Number (%) of patients with a TEAE	
	Pitavastatin 4 mg (*n*=121)	**Simvastatin 40-80 mg (*n*=57)**
Any TEAE	92 (76.0)	45 (78.9)
Serious TEAE	4 (3.3)	7 (12.3)
Treatment-related TEAE	13 (10.7)	10 (17.5)
Discontinuations due to TEAE	7 (5.8)	6 (10.5)
TEAE occurring in ≥2% of patients in either group		
Headache	2 (1.7)	5 (8.8)
Nasopharyngitis	24 (19.8)	15 (26.3)
Constipation	4 (3.3)	2 (3.5)
Myalgia	5 (4.1)	7 (12.3)
Back pain	10 (8.3)	3 (5.3)
Influenza	7 (5.8)	3 (5.3)

Laboratory Abnormalities

Long-term treatment with pitavastatin 4 mg was associated with a very low incidence of notable elevations of either liver enzymes (ASAT or ALAT) or CK. One patient in the pitavastatin group showed a single instance of elevations of ASAT and ALAT to above five times the upper limit of normal (ULN). There were isolated cases of CK elevations above three or five times the ULN in the pitavastatin-treated group, but no cases where such elevations were reported on two consecutive visits. No clinically relevant findings were observed on urinalysis, physical examination, vital signs, or ECG.

DISCUSSION

This 44-week extension study has shown that long-term treatment with pitavastatin 4 mg provides similar efficacy to simvastatin 40-80 mg and may have a more favorable tolerability profile in patients with primary hypercholesterolemia or combined (mixed) dyslipidemia at high

risk of CHD. In the initial 12-week core study,[14] pitavastatin 4 mg was shown to be statistically non-inferior to simvastatin 40 mg in lowering LDL-C concentrations, and more than 80% of patients reached the LDL-C targets recommended in the NCEP and EAS guidelines. By the end of the extension study, LDL-C target attainment rates in pitavastatin-treated patients remained above 80%, compared with 74%-75% in simvastatin-treated patients. Similar results were seen when the proportions of patients achieving the more stringent NCEP step 9 targets were analyzed. Taken together, the results of the core and extension studies therefore show that pitavastatin provides effective control of LDL-C concentrations in dyslipidemic patients. The finding in the core study[14] that pitavastatin is non-inferior to simvastatin in this respect is important because LDL-C concentration is a recognized risk factor for atherosclerotic cardiovascular disease,[17] and major outcome trials have shown that simvastatin significantly reduces cardiovascular mortality and morbidity in at-risk patients.[18,19] Further studies to assess morbidity and mortality are currently underway in Japan to determine the long-term efficacy and safety of pitavastatin.

In addition to lowering LDL-C concentrations, pitavastatin treatment exerted beneficial effects on the broader lipid profile by increasing HDL-C and Apo-A1 levels and reducing levels of triglycerides, Apo-B, and oxidized LDL. The marked increase from baseline in HDL-C concentrations provided by pitavastatin after 12 weeks of treatment in the core study continued during the extension study, such that a larger increase was observed after 44 weeks (14.1% vs. 9.3% at extension study baseline). These results are consistent with previous studies, which have shown that pitavastatin provides progressive, large increases in HDL-C concentrations during long-term treatment.[12] The clinical relevance of changes in HDL-C concentrations during statin treatment is highlighted by a sub-analysis from the Scandinavian Simvastatin Survival Study (4S), in which simvastatin produced significantly greater reductions in cardiovascular mortality and morbidity in patients with the lowest HDL-C and highest triglyceride levels compared with patients with the highest HDL-C and the lowest triglyceride levels.[20]

Both treatments were well tolerated, but this extension study raises the prospect that pitavastatin may exhibit a more favorable long-term tolerability profile than simvastatin. For example, pitavastatin was associated with a lower rate of TEAE considered to be related to study treatment (10.7% vs. 17.5% of patients on simvastatin), a lower rate of discontinuations due to TEAE (5.8% vs. 10.5% with simvastatin), and a lower incidence of myalgia (4.1% vs. 12.3% with simvastatin). These differences do not reflect the use of a higher dose of simvastatin (80 mg), which has been reported to be associated with an increased risk of myopathy;[21,22] among the five patients who were titrated to simvastatin 80 mg at the start of the extension study, none discontinued treatment due to a TEAE and only one patient reported myalgia. The low risk of muscular adverse events, such as myalgia and liver enzyme elevations, observed during long-term pitavastatin treatment in the present study is consistent with previous trials that have shown a favorable safety and tolerability profile of pitavastatin in a broad range of patients.[9-12]

The limitations of this study should be noted. The protocol was developed primarily to compare pitavastatin 4 mg with simvastatin 40 mg (the most commonly prescribed statin regimen), and the effects of simvastatin 80 mg daily were evaluated in only a limited number of patients. The patient population for the extension study was entirely White, and so caution should be exercised in extrapolating the

results to other races or ethnic groups (eg, Black subjects) who were not represented. Finally, although pitavastatin was shown to provide similar lipid-modifying efficacy to simvastatin, the results of ongoing large-scale studies with sufficient statistical power to evaluate effects on "hard" clinical endpoints are required to confirm the benefits of pitavastatin on clinical outcomes.

CONCLUSION

In conclusion, this study has shown that long-term treatment with pitavastatin 4 mg provides LDL-C concentration-lowering efficacy similar to simvastatin 40-80 mg. More than 80% of pitavastatin-treated patients reached the NCEP and EAS targets for LDL-C concentrations, and a similar proportion reached the NCEP targets for non-HDL-C concentrations. Further studies are required to ascertain whether the numerical trends suggesting that pitavastatin may exhibit a more favorable long-term tolerability profile than simvastatin, indicated particularly by the lower incidence of study discontinuations due to TEAE and a lower rate of myalgia, are statistically significant. These findings suggest that pitavastatin is an effective option for the management of dyslipidemia in patients at high cardiovascular risk.

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