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Lipid-Altering Efficacy and Safety of Simvastatin 80 mg/Day: Long-Term Experience in a Large Group of Patients with Hypercholesterolemia

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Summary

Background: Elevated levels of low-density lipoprotein (LDL) cholesterol promote the development of atherosclerosis and coronary heart disease.

Hypothesis: Simvastatin 80 mg/day will be more effective than simvastatin 40 mg/day at reducing LDL cholesterol and will be well tolerated.

Methods: Two similar, randomized, multicenter, controlled, double-blind, parallel-group, 48-week studies were performed to evaluate the long-term lipid-altering efficacy and safety of simvastatin 80 mg/day in patients with hypercholesterolemia. One study conducted in the US enrolled patients meeting the National Cholesterol Education Program (NCEP) LDL cholesterol criteria for pharmacologic treatment. In the other multinational study, patients with LDL cholesterol levels ≥4.2 mmol/l were enrolled. At 20 centers in the US and 19 countries world-wide, 1,105 hypercholesterolemic patients, while on a lipid-lowering diet, were randomly assigned at a ratio of 2:3 to receive simvastatin 40 mg (n = 436) or 80 mg (n = 669) once daily for 24 weeks. Those patients completing an initial 24-week base study were enrolled in a 24-week blinded extension. Patients who had started on the 80 mg dose in the base study continued on the same dose in the extension, while those who had started on the 40 mg dose were rerandomized at a 1:1 ratio to simvastatin 40 or 80 mg in the extension.

Results: There was a significant advantage in the LDL cholesterol-lowering effect of the 80 mg dose compared with that of the 40 mg dose, which was maintained over the 48 weeks of treatment. The mean percentage reductions (95% confidence intervals) from baseline in LDL cholesterol for the 40 and 80 mg groups were 41% (42, 39) and 47% (48, 46), respectively, for the 24-week base study, and 41% (43, 39) and 46% (47, 45), respectively, after 48 weeks of treatment ($p < 0.001$ between groups). Larger reductions in total cholesterol and triglycerides were also observed with the 80 mg dose compared with the 40 mg dose at Weeks 24 and 48. Both doses were well tolerated, with close to 95% of patients enrolled completing the entire 48 weeks of treatment. Myopathy (muscle symptoms plus creatine kinase increase > 10 fold upper limit of normal) and clinically significant hepatic transaminase increases (> 3 times the upper limit of normal) occurred infrequently with both doses. There was no significant difference between the groups in the number of patients with such increases, although there were more cases for both with the 80 mg dose.

Conclusions: Compared with the 40 mg dose, simvastatin 80 mg produced greater reductions in LDL cholesterol, total cholesterol, and triglycerides. Both doses were well tolerated.

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Introduction

The efficacy and safety of the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor simvastatin at doses up to 40 mg have been extensively documented in large, long-term clinical studies.[1,2] In the Scandinavian Simvastatin Survival Study (4S),[1] simvastatin produced a 42% reduction in fatal coronary events compared with placebo, leading to a 30% reduction in the risk of all-cause mortality. Although the majority of patients in 4S reached the study goal of a total cholesterol level < 5.2 mmol/l, a small number was unable to reach this goal, indicating a need for greater cholesterol lowering. It has previously been shown that the dose–response curve for the low-density lipoprotein (LDL) cholesterol-lowering effect of HMG-CoA reductase inhibitors is log-linear, with an additional 6% reduction in LDL cholesterol occurring with each doubling of the dose.[3] In light of these findings, and in view of the excellent safety profile of simvastatin 20 to 40 mg/day,[1,2] the efficacy and safety of simvastatin at a dose of 80 mg/day was evaluated in two large, 48-week clinical studies of similar design. The initial 24-week base study results for the US[4] and multinational[5] studies have been reported separately. The present report describes the combined results from the two studies for the entire 48-week treatment period.

Patients and Methods

Patients

Ethical review board approval was obtained at each study center for the initial 24-week base study and the 24-week extension. All patients provided written informed consent. Details of the base study design, including inclusion and exclusion criteria, have been described previously.[4,5] Men, postmenopausal women, or women highly unlikely to conceive, age 21 to 70, were eligible for inclusion. The lipid eligibility requirement for entry in the US study was the National Cholesterol Education Program Adult Treatment Program II (NCEP ATP II) criteria for pharmacologic treatment, and in the multinational study, an LDL cholesterol level of > 4.2 mmol/l. Both studies excluded patients with triglyceride levels > 4.0 mmol/l. Patients were begun on an American Heart Association Step I diet[6] during a 4-week placebo run-in period and were instructed to continue the diet throughout the 48 weeks of treatment. Patients who were receiving bile acid sequestrants, HMG-CoA reductase inhibitors, or nicotinic acid as lipid-lowering agents prior to the start of the study were instructed to discontinue these therapies 6 weeks before study start. Patients who were receiving fibrates as lipid-lowering agents discontinued these therapies 8 weeks before study start. Patients receiving immunosuppressant drugs, systemic azole antifungal agents, or anticoagulants, were not eligible for study participation. Patients who completed the initial 24-week base study period and had an LDL cholesterol level ≥ 1.3 mg/dl were eligible for enrollment in a 24-week blinded extension period.

Study Design

Both studies were controlled, double-blind, randomized, and parallel-group in design. The US study was conducted at 20 centers and the multinational study in 29 centers in 19 countries located in Central, North, and South America, and in Europe and Asia. The studies began in February 1996 and concluded in May 1997. Visits were scheduled at weeks −4, −1, 0 (Day 1), 6, 12, 18, 24, 32, 40, and 48.

Patients meeting eligibility requirements were randomly assigned according to a computer-generated allocation schedule to receive simvastatin 40 or 80 mg once daily in the evening at a 2:3 ratio for the initial 24-week base study. In the 24-week extension, patients who had started on the 80 mg dose and who were eligible for entry in the extension continued on that dose. Patients who had initially received 40 mg and who were eligible for entry in the extension were rerandomized at a 1:1 ratio to simvastatin 40 or 80 mg/day. Double-blinding was achieved by administration of simvastatin 40 and 80 mg tablets (ZOCOR, Merck & Co., Inc., Whitehouse Station, N.J.) and matching-image placebo tablets.

Efficacy Criteria

The primary efficacy endpoints were the average of the change from baseline in LDL cholesterol at Weeks 18 and 24 combined in the 24-week base study, and the change from baseline in LDL cholesterol at Week 48 in the extension. Secondary endpoints included change from baseline in total cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides at Weeks 18/24 and 48. In addition, in the US, all patients were assessed as to whether they had met their LDL cholesterol goal, as defined by the NCEP ATP II guidelines.

Safety Criteria

Safety and tolerability were evaluated by adverse event reporting, clinical and laboratory evaluation, and vital sign recording. At each visit, patients were questioned in a nonleading manner about the occurrence of adverse events. A physical examination and electrocardiogram (ECG) were performed at randomization and at Weeks 24 and 48. An ophthalmologic examination was performed at initial randomization for baseline information only. Vital signs were recorded at each clinic visit.

A fasting serum chemistry analysis was performed at each visit. Thyroxine, thyroid-stimulating hormone, and glycosylated hemoglobin (for patients with type 2 diabetes mellitus), were measured at Week −4. A complete blood count and urinalysis were performed at Weeks −4, −1, 0, 12, and 24, and 48. Cortisol and, for male patients, testosterone and follicle-stimulating hormone (FSH) and luteinizing hormone (LH),

were measured at randomization and at Weeks 24 and 48. Patients with alanine aminotransferase or aspartate aminotransferase levels ≥ 3 times the upper limit of normal (ULN) were retested within 1 week. Persistent transaminase elevations ≥ 3 times ULN resulted in patient discontinuation from the study. Similarly, patients with unexplained elevations in creatine kinase ≥ 10 times ULN were discontinued from the study.

Laboratory Methods

All assays were performed at a central laboratory, Medical Research Laboratories International, at two locations: Highland Heights, Kentucky, and Brussels, Belgium. The laboratory at Highland Heights assayed blood samples collected at the Australian and North, South, and Central American study centers, and the laboratory at Brussels assayed blood samples from the European and South African centers. Throughout the study, the laboratory participated in and remained certified by the National Heart Lung and Blood Institute—Centers for Disease Control Part III program.[7] Blood samples for lipoproteins were collected in ethylenediaminetetraacetate (1 mg/ml) and centrifuged within 30 min. The plasma was separated and shipped overnight at 4°C to the central laboratory. Total cholesterol and triglycerides were analyzed by enzymatic methods as previously described.[8] High-density lipoprotein cholesterol was isolated using heparin-2M manganese chloride,[9] and LDL cholesterol was determined using the Friedewald equation. Plasma samples obtained from a subset of patients were ultracentrifuged, and LDL cholesterol was obtained by subtracting HDL cholesterol from the $d > 1.006$ g/ml fraction cholesterol.[10] The very low-density lipoprotein (VLDL) cholesterol level was obtained by subtracting the $d > 1.006$ g/ml cholesterol from total cholesterol. In this same subset, apolipoprotein A-I (apo A-I) and B (apo B) analyses were performed using immunonephelometry (BNA-100-Behring Diagnostics, Westwood, Mass.), calibrated using World Health Organization traceable standards.[11] Serum concentrations of follicle-stimulating hormone and luteinizing hormone were analyzed using a competitive binding assay with I_{125}-radiolabeled hormone using an antihormone antibody,[12, 13] and serum cortisol was measured using a fluorescence polarization immunoassay.[14] Total serum testosterone was measured in a solid-phase radioimmunoassay using a competitive binding assay.[15]

Statistical Methods

An analysis of variance was used to test for between-group differences in lipid parameters. Baseline was defined as the average of the values at Weeks −1 and 0 (Day 1). Efficacy analyses were based on the intention-to-treat principle, that is, all patients with a baseline and at least one post-baseline measurement were included. Efficacy data and values for alanine aminotransferase, aspartate aminotransferase, and creatine kinase, were carried forward for patients with missing data after Week 6. The primary efficacy endpoints were the average lipid value of the Week 18 and Week 24 values combined, and the Week 48 value. Efficacy endpoints were analyzed using an analysis of variance model with factors for treatment, study center, and LDL-cholesterol stratum. Interaction terms were tested and removed from the model when found to be not statistically significant ($p > 0.050$). Fisher's exact test was used to evaluate between-group differences in frequency of adverse events. In addition, a subgroup analysis was performed using nonparametric summary statistics comparing percent change in triglycerides according to baseline triglyceride level (triglyceride level ≤ 2.3 mmol/l vs. triglyceride level > 2.3 mmol/l).

With a patient population of 500 for the initial 24-week base study period, each study had 90% power to detect a difference between treatments in percent change from baseline in LDL cholesterol of 4.2%, assuming a between-patient standard deviation of 14%. All statistical tests were two-tailed, with $\alpha = 0.050$. P-values were rounded to three decimal places, and $p \leq 0.050$ was considered statistically significant.

Results

Patients

In all, 1,105 patients were randomized to simvastatin 40 or 80 mg/day. Both treatment groups had similar demographic characteristics at baseline (Table I). The disposition of patients randomized into the study is shown in Table II. Of the 1,105 patients initially randomized, 1,031 (93%) completed the initial 24-week base study period, with a similar number of pa-

TABLE I Summary of demographic characteristics

	Simvastatin 40 mg (n = 436)	Simvastatin 80 mg (n = 669)
Gender (%)		
Women	193 (44.3)	272 (40.7)
Men	243 (55.7)	397 (59.3)
Age (years)		
Mean	52.7	52.9
Standard deviation	11.5	10.8
Median	55.0	54.0
Range	21 to 70	20 to 71
Race (%)		
Asian	9 (2.1)	8 (1.2)
Black	9 (2.1)	20 (3.0)
Hispanic	30 (6.9)	50 (7.5)
Multiracial	7 (1.6)	12 (1.8)
Other	1 (0.2)	3 (0.4)
White	380 (87.2)	576 (86.1)
Secondary diagnoses (%)		
Hypertension	105 (24.1)	144 (21.5)
Coronary vascular surgery	47 (10.8)	74 (11.1)
Myocardial infarction	47 (10.8)	62 (9.2)
Coronary artery disease	31 (7.1)	43 (6.4)
Angina pectoris	29 (6.7)	35 (5.2)

TABLE II Disposition of patients in base study and extension

	Simvastatin 40 mg	Simvastatin 80 mg
24-Week base study		
Number of patients randomized to 24-week base study	436	669
Number of patients completing 24-week base study (%)	413 (94.7)	618 (92.3)
Number of patients withdrawing from 24-week base study (%)	23 (5.3)	51 (7.7)
24-Week extension		
Number of patients randomized to 24-week extension	188	765
Number of patients completing 24-week extension (%)	178 (94.6)	715 (93.4)
Number of patients withdrawing from 24-week extension (%)	10 (5.4)	50 (6.6)

tients in each group discontinuing treatment prematurely during this period ($p > 0.200$ for between-group difference). Of the 1,031 patients completing the initial 24-week base study, 953 continued into the 24-week extension. Patients completing the extension numbered 893, with similar proportions of patients in each group discontinuing treatment prematurely during this period ($p > 0.200$).

Lipids and Lipoproteins

The baseline lipid and lipoprotein levels were comparable between the two treatment groups (Table III). There was a greater mean percent decrease from baseline in LDL cholesterol in the 80 mg group than in the 40 mg group, and this difference was maintained over the 48-week treatment period (Table III; Fig. 1). At Week 24, the LDL cholesterol level in the 80 mg group was reduced to 3.1 mmol/l from a baseline level of 5.8 mmol/l, while the level in the 40 mg group decreased to 3.5 mmol/l from a baseline of 5.9 mmol/l. The mean (95% confidence interval [CI]) percent change from baseline in LDL cholesterol for the 40 and 80 mg groups, expressed as the average of the percent change for Weeks 18 and 24 combined, was −40.5% (−41.7, −39.2) and −47.2% (−48.2, −46.3; between group $p < 0.001$), respectively. At Week 48, the respective mean LDL cholesterol reductions were −40.7% (−42.8, −38.7) and −45.7% (−46.7, −44.6; $p < 0.001$). In the US study, overall and in each risk category, more patients attained their NCEP LDL cholesterol-lowering goal at Week 24 in the 80 mg group than in the 40 mg group. This difference was especially prominent in patients with coronary heart disease (CHD), where more than twice the number of these patients achieved their NCEP goal in the 80 mg group than those in the 40 mg group (Table IV). The results at Week 48 were generally consistent with those at Week 24 (data not shown).

In addition to having a superior LDL cholesterol-lowering effect, the 80 mg dose was also more effective than the 40 mg dose at reducing total cholesterol and triglycerides (Table III). In the 80 mg group, triglyceride levels were reduced from the median baseline level of 1.8 to 1.3 mmol/l, while the levels in the 40 mg group were reduced from 1.8 to 1.4 mmol/l. At Week 24, the median percent change in triglycerides (95% CI) for the 40 and 80 mg groups was −17.8% (−20.5, −15.1) and −24.4% (−26.4, −22.5; $p < 0.001$), respectively, and at Week 48, it was −18.6% (−23.8, −13.3) and −21.5%

TABLE III Effects of simvastatin 40 and 80 mg on serum lipid and lipoprotein levels

		Weeks 18 and 24[c]				Week 48			
Parameter	Simvastatin dose (mg)	N	Baseline Mean[a] ± SD	Week 18/24 Mean[a] ± SD	p Value between group[b]	N	Baseline Mean[a] ± SD	Week 48 Mean[a] ± SD	p Value between group[b]
Total-C	40	433	8.1 ± 1.6	5.6 ± 1.2	<0.001	186	8.2 ± 1.8	5.7 ± 1.3	<0.001
(mmol/l)	80	663	7.9 ± 1.5	5.1 ± 1.1		753	8.0 ± 1.5	5.2 ± 1.2	
LDL-C	40	432	5.9 ± 1.6	3.5 ± 1.1	<0.001	183	6.0 ± 1.7	3.6 ± 1.2	<0.001
(mmol/l)	80	663	5.8 ± 1.5	3.1 ± 1.1		749	5.8 ± 1.5	3.2 ± 1.1	
HDL-C	40	433	1.3 ± 0.3	1.4 ± 0.3	0.463	186	1.3 ± 0.3	1.4 ± 0.4	0.883
(mmol/l)	80	664	1.3 ± 0.3	1.3 ± 0.3		753	1.2 ± 0.3	1.4 ± 0.3	
Triglycerides	40	433	1.8 ± 0.9	1.4 ± 0.8	<0.001	186	1.8 ± 1.0	1.5 ± 0.9	<0.018
(mmol/l)	80	664	1.8 ± 1.0	1.3 ± 0.6		753	1.8 ± 1.0	1.4 ± 0.7	
VLDL-C	40	66	1.0 ± 0.7	0.6 ± 0.3	0.676	29	1.0 ± 0.5	0.7 ± 0.5	<0.055
(mmol/l)	80	103	0.9 ± 0.6	0.6 ± 0.4		116	1.0 ± 0.6	0.5 ± 0.3	

[a] Median values shown for triglycerides and VLDL-C.

[b] p Value based on % change comparison.

[c] Average of values at Weeks 18 and 24 combined.

Abbreviations: SD = standard deviation, C = cholesterol, LDL = low-density lipoprotein, HDL = high-density lipoprotein, VLDL = very low density lipoprotein.

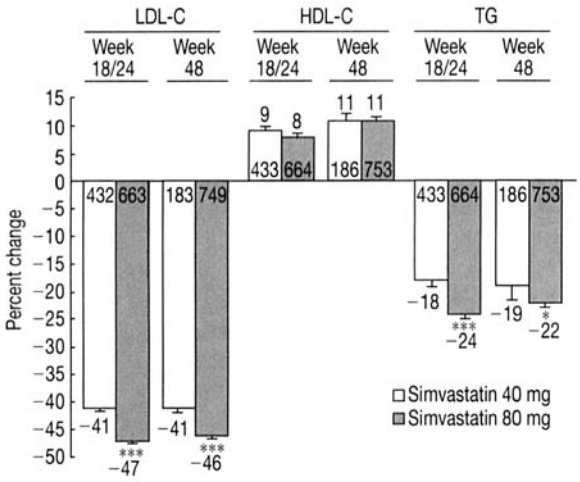

FIG. 1 Percent change (± standard error) from baseline in serum lipid and lipoprotein levels at Weeks 18/24 and 48 in patients receiving simvastatin 40 or 80 mg/day. The percent change is shown as the median for triglyceride and the mean for all other parameters. Values at Weeks 18/24 represent average of 18- and 24-week data. Group numbers are shown within the bars, and the percent change from baseline is indicated above or below each bar. Asterisks indicate significance levels for between-group comparisons: ***$p < 0.001$, *$p < 0.050$. LDL-C = LDL cholesterol, HDL-C = HDL cholesterol, TG = triglycerides.

(−23.5, −19.4; $p < 0.001$), respectively. Although both the 40 and 80 mg groups showed significant increases from baseline in HDL cholesterol at Weeks 24 and 48, there was no significant difference between the treatment groups (Table III). At Week 24, the mean percent change in HDL cholesterol (95% CI) for the 40 and 80 mg groups was 8.5% (7.2, 9.8) and 8.1% (7.1, 9.0; $p = 0.463$), respectively, and at Week 48 it was 10.6% (8.2, 12.9) and 10.9% (9.8, 11.9; $p = 0.883$), respectively. There was also a greater decrease in apo B with the 80 mg dose, the mean percent decrease from baseline in apo B for the 40 and 80 mg groups at Week 24 being −31.4% (−34.0, −28.7) and −37.9% (−40.2, −35.6; $p < 0.001$), respectively. There was an increase in apo A-I for both groups, although the increase was larger with simvastatin 40 mg. The mean percent change from baseline in apo A-I for the 40 and 80 mg groups at Week 24 was 8.6% (5.3, 11.8) and 3.5% (1.2, 5.7; $p < 0.010$), respectively.

The effect of simvastatin 40 and 80 mg on LDL cholesterol was also evaluated in several subgroups. There was no evidence of an effect of gender, age, or baseline LDL cholesterol on the change in LDL cholesterol produced by either dose (data not shown). The effects of baseline triglyceride levels (≤2.3 or >2.3 mmol/l on the lipoprotein changes produced by simvastatin 40 and 80 mg were also assessed (Fig. 2). In both treatment groups, the LDL cholesterol changes were consistent in the lower and higher triglyceride strata; however, the triglyceride-lowering effect and the increase in HDL cholesterol appeared greater in the subgroup with baseline triglycerides >2.3 mmol/l.

Safety

Simvastatin 40 and 80 mg were well tolerated over the 48-week treatment period. There was no difference between the two groups in the incidence of drug-related clinical or laboratory adverse events leading to treatment discontinuation at Weeks 24 or 48. During the initial 24-week base study, drug-related clinical adverse events that resulted in treatment discontinuation occurred in 6 (1.4%) patients in the 40 mg group and 10 (1.5%) in the 80 mg group ($p > 0.200$). During the 24-week extension period, no patients in the 40 mg group and 14 (1.8%) patients in the 80 mg group ($p = 0.085$) were discontinued due to drug-related clinical adverse events. There was no consistent pattern in the drug-related adverse events that resulted in discontinuation for either treatment group. The most common drug-related clinical adverse events leading to discontinuation were myalgia (five patients), asthenia/fatigue (four patients), and rash (three patients) in the 80 mg group,

TABLE IV Patients reaching low-density lipoprotein cholesterol goal (responders) by National Cholesterol Education Program risk categories at Week 24[a]

		Simvastatin 40 mg		Simvastatin 80 mg	
NCEP risk category	Goal	No. of patients completing 24 weeks	No. (%[b]) of responders	No. of patients completing 24 weeks	No. (%[b]) of responders
CHD & LDL-C ≥3.4 mmol/l	LDL-C ≤2.6 mmol/l	33	10 (30)	58	40 (69)
≥2 risk factors & LDL-C ≥4.2 mmol/l	LDL-C < 3.4 mmol/l	94	64 (68)	138	108 (78)
<2 risk factors & LDL-C ≥4.9 mmol/l	LDL-C < 4.2 mmol/l	78	65 (83)	114	106 (93)
All categories		205	139 (68)	310	254 (82)

[a]United States study participants only.
[b]Percent of completers at 24 weeks.
Abbreviations: NCEP = National Cholesterol Education Program, CHD = coronary heart disease, LDL-C = low-density lipoprotein cholesterol.

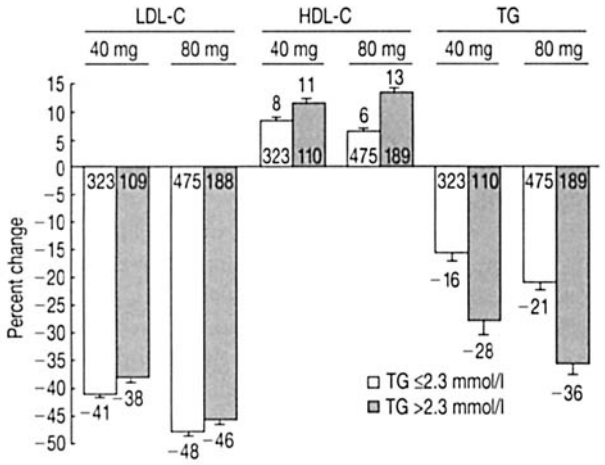

FIG. 2 Percent change (± standard error) from baseline in serum lipid and lipoprotein levels at Week 24 presented by baseline triglyceride level (triglyceride levels ≤ 2.3 or > 2.3 mmol/l) in patients receiving simvastatin 40 or 80 mg/day. The percent change is shown as the median for triglyceride and the mean for all other parameters. Values represent average of 18- and 24-week data. Group numbers are shown within the bars, and the percent change is indicated above or below the bars. Abbreviations as in Figure 1.

and asthenia/fatigue (two patients) in the 40 mg group. Drug-related laboratory adverse events that resulted in treatment discontinuation during the initial 24-week base study occurred in 3 (0.7%) patients in the 40 mg group and 13 (1.9%) in the 80 mg group ($p = 0.124$). During the 24-week extension period, no patient in the 40 mg group and four (0.5%) patients in the 80 mg group ($p > 0.200$) were discontinued due to drug-related laboratory adverse events.

All HMG-CoA reductase inhibitors have been infrequently found to cause adverse events related to muscle and liver. During the initial 24 weeks of treatment, six patients developed myopathy defined as the presence of muscle symptoms and elevations in creatine kinase of > 10 times ULN; one in the 40 mg group and five in the 80 mg group ($p > 0.200$). All of these cases resolved completely following discontinuation of treatment. In the 24-week extension, there were no additional cases of myopathy reported. With regard to hepatic adverse events, after 24 weeks of treatment, 3 (0.7%) patients in the 40 mg group and 12 (1.8%) in the 80 mg group developed persistent hepatic transaminase increases > 3 times ULN. One of these patients, a 62-year-old woman in the 80 mg group, was hospitalized with acute hepatitis. Among the unusual aspects of the case was the fact that the patient was prescribed nitrofurantoin, a drug known to cause hepatitis, for a urinary tract infection, 2 weeks prior to the episode, although the patient claims not to have taken any. In addition, the patient was seen at the center 6 days prior to her presentation for her Week 6 visit and had normal transaminase levels. The investigator judged that her transaminase elevation was possibly related to simvastatin. Following drug discontinuation, the liver function abnormalities resolved. In the 24-week extension, none of the patients who had remained on their initial starting doses of 40 or 80 mg developed clinically significant increases in hepatic transaminases. Of the 193 patients who had been rerandomized from their base study starting dose of 40 to 80 mg in the extension, 3 (1.5%) developed increases of > 3 times ULN in hepatic transaminases during the extension.

Due to a theoretical concern about the effect of higher doses of HMG-CoA reductase inhibitors on the production of steroid hormones, baseline and on-treatment levels of cortisol were assessed in all patients, and testosterone, FSH, and LH levels were assessed in male patients. There were no clinically significant differences between treatment groups in changes from baseline in serum cortisol, testosterone, FSH, or LH. The median change from baseline in serum cortisol for the 40 and 80 mg groups was −3% (95% CI: −6.8, 1.0) and −7% (−10.1, −3.7), respectively, at Week 24 (between group $p > 0.200$), and 6% (−0.8, 12.7) and −1% (−4.5, 1.6), respectively, at Week 48 (between group $p < 0.050$). In both treatment groups, male patients had a slight decrease from baseline in serum testosterone at Weeks 24 and 48. The median decrease from baseline in serum testosterone among male patients for the 40 and 80 mg treatment groups was −10% (−13.6, −6.3) and −12% (−14.3, −8.9), respectively, at Week 24 (between group $p > 0.200$), and −7.5% (−13.3, −1.7) and −10.3% (−12.9, −7.7), respectively, at Week 48 (between group $p > 0.200$). No changes from baseline in LH or FSH levels were seen in male patients of either treatment group at Weeks 24 or 48.

Discussion

The present findings from two similar, large, randomized, controlled, long-term studies in hypercholesterolemic patients demonstrated the 80 mg dose of simvastatin to be more effective than the 40 mg dose in reducing LDL cholesterol. Doubling the dosage of simvastatin from 40 to 80 mg produced a 6% greater decrease from baseline in LDL cholesterol, and this difference was generally maintained over 48 weeks of treatment. This observed difference in LDL cholesterol reduction was in good agreement with the anticipated 6% treatment difference based on previous studies with simvastatin and other HMG-CoA reductase inhibitors.[16,17] Use of the 80 mg dose should also allow more patients to attain their NCEP target LDL cholesterol goal, especially those patients with CHD, among whom more than twice the number in the 80 mg group attained their NCEP LDL cholesterol target level after 24 weeks of treatment compared with the 40 mg group. Decreases in total cholesterol, apo B, and triglycerides, but not increases in HDL cholesterol, were also greater with the 80 mg dose than with the 40 mg dose. Also of note was the apparent greater reduction in triglycerides and increase in HDL cholesterol in patients with higher baseline triglyceride levels, which is in agreement with the findings of previous studies with HMG-CoA reductase inhibitors.[18,19] Although this may partially be explained by regression to the mean, the results suggest that simvastatin may be an important therapeutic option in patients with combined hyperlipidemia.[18,19,21–23]

The 80 mg dose of simvastatin was recently approved in the US and several major countries for the treatment of hypercholesterolemia. Prior to this approval, simvastatin 10 to 40 mg/day had been demonstrated to be well tolerated, as exemplified by the more than 2,000 patients treated with dose levels of 20 to 40 mg for over 5 years in 4S.[1] The presently reported combined results from two large phase III studies involving more than 650 patients treated with simvastatin 80 mg/day for 48 weeks show both doses of simvastatin to be well tolerated, and the clinical adverse event profile was comparable between the two treatment groups. Similarly, the overall laboratory adverse event profile was favorable and comparable between the two groups.

Muscle adverse events with simvastatin occurred rarely in this study. There was no difference between the groups in the incidence of myopathy, although there were numerically more cases in the 80 mg group. None of these patients developed the more severe form of muscle inflammation and rhabdomyolysis, and all of the cases resolved spontaneously with drug discontinuation. Moreover, all of the myopathy cases were reported in the initial 24-week base study period; none was reported in the 24-week extension period. There was one report of hepatitis during the trial, although, based on the circumstances, it is unclear whether the event was related to simvastatin. There was no significant between-group difference in the incidence of sustained elevations in hepatic transaminases ≥ 3 times ULN, however, slightly more cases were reported in the 80 mg group than in the 40 mg group. Dose-dependent increases in hepatic transaminases have been previously reported with lovastatin and atorvastatin.[24, 25]

In male patients who had completed 48 weeks of therapy, small reductions in testosterone were observed in both groups with no difference between groups. No compensatory rise in LH or FSH was seen, and in view of the fact that there were no reports of adverse events related to sexual function, the present findings suggest that the decrease in testosterone was not clinically significant. Data from previous studies with cholesterol-lowering therapy showed similar reductions in testosterone, but no effect on human chorionic gonadotropin-stimulated testosterone release.[26, 27] In the presently reported studies, small reductions in morning cortisol levels occurred in both the 40 and 80 mg simvastatin dose groups. The 80 mg dose has been demonstrated to have no effect on cortrosyn-stimulated cortisol production, suggesting that the cortisol reductions were not clinically significant (data on file).

Conclusions

In patients with primary hypercholesterolemia, as in the two presently reported studies, simvastatin 80 mg/day provides substantial long-term reductions in LDL cholesterol and triglycerides, greater than those achieved with simvastatin 40 mg/day. In patients with high baseline triglycerides, simvastatin 80 mg provides even greater triglyceride reductions and HDL cholesterol increases than those found in patients with normal triglycerides. Thus, monotherapy with simvastatin up to doses of 80 mg daily provides an option for comprehensively managing the lipid profiles of the majority of dyslipidemic patients. Over a 1-year treatment period, both doses were well tolerated.

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References

1. Pedersen TR, Berg K, Cook TJ, Faergeman O, Haghfelt T, Kjekshus J, Miettinen T, Musliner TA, Olsson AG, Pyorala K, Thorgeirsson G, Tobert JA, Wedel H, Wilhelmsen L: Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1996; 156:2085–2092

2. MAAS Investigators: Effect of simvastatin on coronary atheroma: The Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994;344: 633–638
3. Davidson MH, Stein EA, Dujovne CA, Hunninghake DB, Weiss SR, Knopp RH, Illingworth DR, Mitchel YB, Melino MR, Zupkis RV, Dobrinska MR, Amin RD, Tobert JA: The efficacy and six-week tolerability of simvastatin 80 and 160 mg/day. *Am J Cardiol* 1997;79:38–42
4. Stein EA, Davidson MH, Dobs AS, Schrott H, Dujovne CA, Bays H, Weiss SR, Melino MR, Stepanavage ME, Mitchel YB: Efficacy and safety of simvastatin 80 mg/day in hypercholesterolemic patients. *Am J Cardiol* 1998;82:311–316
5. Ose L, Kastelein JJP, Scott R, Stein EA, Campodonico S, Escobar JD, Tate AC, Corsetti L, Shahane A, Mitchel YB, Mercuri M: Efficacy and six-month safety of simvastatin 80 mg/day: Results from the Worldwide Simvastatin Expanded Dose Program (WSEDP). *Nutr Metab Cardiovasc Dis* 1998;8:143–151
6. Krauss RM, Deckelbaum RJ, Ernst N, Fisher E, Howard BV, Knopp RH, Kotchen T, Lichtenstein AH, McGill HC, Pearson TA, Prewitt TE, Stone NJ, Horn LV, Weinberg R: Dietary guidelines for healthy American adults. A statement for health professionals from the Nutrition Committee, American Heart Association. *Circulation* 1996;94:1795–1800
7. Myers GL, Cooper GR, Winn CL, Smith SJ: The Centers for Disease Control-National Heart, Lung, and Blood Institute Lipid Standardization Program: An approach to accurate and precise lipid measurements. *Clin Lab Med* 1989;9(1):105–135
8. Steiner P, Freidel J, Bremner W, Stein E: Standardization of micromethods for plasma cholesterol, triglyceride and HDL-cholesterol with the lipid clinics' methodology (abstr). *J Clin Chem Clin Biochem* 1981;19:850
9. Warnick G, Albers J: A comprehensive evaluation of the heparin manganese precipitation procedure for estimating high-density lipoprotein cholesterol. *J Lipid Res* 1978;19:65–76
10. Program LRC: Manual of Laboratory Operations: Lipid and Lipoprotein Analysis. Washington, DC: US Dept. of Health Education and Welfare. *NIH publication* no. 361-132 1982;678:66–70
11. Stein E, Kreisberg R, Miller V, Mantell G, Washington L, Shapiro DR: Effects of simvastatin and cholestyramine in familial and nonfamilial hypercholesterolemia. Multicenter Group I. *Arch Intern Med* 1990;150:341–345
12. Santer S, Santen R, Kulin H, Demers L: A model for validation of radioimmunoassay kit reagents: Measurement of follitropin and lutropin in blood and urine. *Clin Chem* 1981;27:1892–1895
13. Kubasik N, Hallaver G, Brodows R: Evaluation of direct solid phase radioimmunoassay for progesterone, useful for monitoring luteal function. *Clin Chem* 1984;30:284–286
14. Tdx System Operator's Manual, Abbot Diagnostics, Abbot Park, Ill. 1993
15. Newton WT, McGuigan JE, Jaffe BM: Radioimmunoassay of peptides lacking tyrosine. *J Lab Clin Med* 1970;75:886–892
16. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD: Cholesterol reduction yields clinical benefit: A new look at old data. *Circulation* 1995;91:2274–2282
17. Pedersen TR, Olsson AG, Faergeman O, Kjekshus J, Wedel H, Berg K, Wilhelmsen L, Haghfelt T, Thorgeirsson G, Pyorala K, Miettinen T, Christophersen B, Tobert JA, Musliner TA, Cook TJ: Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1998;97:1453–1460
18. Stein EA, Lane M, Laskarzewski P: Comparison of statins in hypertriglyceridemia. *Am J Cardiol* 1998;81:66B–69B
19. Bakker-Arkema RG, Davidson MH, Goldstein RJ, Davignon J, Isaacsohn JL, Weiss SR, Keilson LM, Brown WV, Miller VT, Shurzinske LJ, Black DM: Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *J Am Med Assoc* 1996;275:128–133
20. Pedersen TR, Tobert JA: Benefits and risks of HMG-CoA reductase inhibitors in the prevention of coronary heart disease: A reappraisal. *Drug Safety* 1996;14:11–24
21. Shear CL, Franklin FA, Stinnett S, Hurley DP, Bradford RH, Chremos AN, Nash DT, Langendorfer A: Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. Effect of patient characteristics on lovastatin-induced changes in plasma concentrations of lipids and lipoproteins. *Circulation* 1992;85:1293–1303
22. Stein EA, Davidson MH, Dujovne CA, Hunninghake DB, Goldberg RB, Illingworth DR, Knopp RH, Miller VT, Frost P, Isaacsohn JL, Mitchel YB, Melino MR, Shapiro D, Tobert JA: Efficacy and tolerability of low-dose simvastatin and niacin, alone and in combination, in patients with combined hyperlipidemia: A prospective trial. *J Cardiovasc Pharmacol Ther* 1996;1:107–116
23. Bruckert E, De Gennes JL, Malbecq W, Baigts F: Comparison of the efficacy of simvastatin and standard fibrate therapy in the treatment of primary hypercholesterolemia and combined hyperlipidemia. *Clin Cardiol* 1995;18:621–629
24. Bradford RH, Shear CL, Chremos AN, Dujovne C, Downton M, Franklin FA, Gould AL, Hesney M, Higgins J, Hurley DP, Langendorfer A, Nash DT, Pool JL, Schnaper H: Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia. *Arch Intern Med* 1991;151: 43–49
25. Parke-Davis Pharmaceuticals: Domestic Product circular: Lipitor tablets (atorvastatin calcium) (1997)
26. Data on file at Merck.
27. Pedersen T, Faergeman O: Simvastatin seems unlikely to cause impotence (letter). *Br Med J* 1999;318:192