Long-Term Safety and Efficacy Profile of Simvastatin

Stephen J. Boccuzzi, PhD, Tomas S. Bocanegra, MD, J. Findlay Walker, MD, Deborah R. Shapiro, DrPH, and Maureen E. Keegan, MS

Simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, has been administered to approximately 2,400 patients with primary hypercholesterolemia with a mean follow-up of 1 year in controlled clinical studies and their open extensions. Approximately 10% of this population received simvastatin for a period of ≥2 years. The population on whom this safety analysis is based had a mean age of 50 years; 62% were men and approximately 27% had preexisting coronary artery disease. Simvastatin was titrated to the maximal daily dose of 40 mg each evening in 56% of the study population (last recorded dose). The most frequently reported drug-related clinical adverse experiences were constipation (2.5%), abdominal pain (2.2%), flatulence (2.0%) and headaches (1%). Persistent elevations of serum transaminase levels >3 times the upper limit of normal were observed in only 1% of this cohort with only 0.1% of the total population requiring discontinuation of therapy. There were no clinically apparent episodes of hepatitis. Discontinuation of therapy due to myopathy was extremely rare (0.08%). Only minimal increases in the frequency of lens opacities (1%) were observed from baseline to the last lens examination during follow-up, consistent with the expected increase in lens opacity development due to normal aging. Patients who were ≥65 years old had a clinical and laboratory safety profile comparable to the nonelderly population. An evaluation of long-term efficacy indicates that the magnitude of total and low-density lipoprotein cholesterol reduction and high-density lipoprotein cholesterol increases initially observed were maintained after 3 years of chronic treatment with simvastatin. Long-term clinical experience with simvastatin continues to indicate that it is an efficacious and well-tolerated lipid-lowering agent.

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Address for reprints: Stephen J. Boccuzzi, PhD, Merck & Co. Inc., P.O. Box 2000, WBD-375, Rahway, New Jersey 07065-0914.

Simvastatin is a potent inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. Like lovastatin, the first in this class of drugs to be approved for treatment of hypercholesterolemia,[1] simvastatin also inhibits cholesterol biosynthesis resulting in a compensatory increase in the number of hepatic low-density lipoprotein (LDL) receptors. This LDL receptor increase results in greater uptake of LDL cholesterol particles from the blood and lowering of circulating cholesterol levels.[2–4] Structurally, simvastatin is very similar to lovastatin except for the presence of an additional methyl group on the ester side chain and is more potent on a milligram to milligram basis than lovastatin. Simvastatin is administered as a lactone that is hydrolyzed primarily in the liver to the biologically active β-hydroxyacid form. The lactone form of this drug has been found to be more liver-specific in that it undergoes a greater degree of first-pass extraction by the liver,[5] where it is converted to various active and inactive metabolites. Less than 5% of an administered simvastatin dose is available to the systemic circulation as active inhibitors, with <0.5% of a test dose recovered in the urine as total HMG-CoA reductase inhibitors.[6,7] Simvastatin in therapeutic doses has been efficacious in the treatment of primary hypercholesterolemia, producing marked mean reductions in plasma total and LDL cholesterol. Mean reductions in total cholesterol and LDL cholesterol of 21 to 33% and 24 to 40%, respectively, as well as mean increases in high-density lipoprotein cholesterol of 8 to 13% have been observed with a single evening dose of 10 to 40 mg.[8] In the initial clinical trials,[9–11] simvastatin was well tolerated with most clinical adverse experiences related to the gastrointestinal tract with no greater incidence than control agents. Laboratory adverse events were related to elevations of liver transaminases and creatine kinase. Ophthalmologic evaluations revealed that simvastatin had no detectable adverse effects on the human lens.[8,12] In this report, we present longer-term clinical experience in 2,361 patients treated with simvastatin for up to 3 years.

METHODS

The patients included in this review participated in the phase I, IIa, IIb, and III controlled clinical trials

TABLE I Population Demographics (n = 2,361)

Race/Gender	No. of Pts.	%
Men		
(mean age 46 yrs)	1,457	62
Women		
(mean age 56 yrs)	904	38
Caucasian	2,268	96
Black	47	2
Other	46	2
Dosage distribution		
1–10 mg*	410	17
20–30 mg*	557	24
40 mg+*	1,394	59
Baseline lipids		mg/dl
Mean total cholesterol	2,243	345
Mean LDL-C	2,217	269
Mean HDL-C	2,233	46
Mean triglycerides	2,221	165

*Total dosage each evening.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

TABLE II Most Frequently Reported Clinical Adverse Experiences Considered by the Investigators to be Related to Simvastatin Therapy

Adverse Experience	No. of Pts.	%
Constipation	52	2.2
Abdominal pain	60	2.5
Flatulence	47	2.0
Nausea	26	1.1
Headache	23	1.0

and their open extensions conducted by Merck Sharp & Dohme Research Laboratories.[9–11] The population comprised patients from 27 domestic and international clinical trials and their open extensions including studies to evaluate efficacy in comparison to other hypolipidemic agents or placebo, as well as bioavailability, kinetic and metabolic interaction studies. All patients received routine clinical evaluations and laboratory studies and were monitored for adverse clinical and laboratory events. Plasma lipids, lipoproteins, serum transaminases, creatine kinase and other hematologic and biochemical measures were obtained regularly. Ophthalmologic examinations were conducted periodically during chronic administration of the drug.

Demographics: The total population consisted of 2,361 patients; 1,457 (62%) men and 904 (38%) women with a mean population age of 50 years. The dosage distribution of simvastatin from the last recorded dose and other baseline characteristics are summarized in Table I. The mean duration of therapy was approximately 1 year (357 days) with 25% (595) of patients receiving simvastatin for ≥18 months and 233 (10%) for a period of ≥2 years. The maximal duration of therapy was 3 years. The concomitant use of other lipid-lowering agents was permitted during the open extensions with 577 patients (24%) receiving other lipid-lowering agents. Most of these patients (92%) received concomitant bile acid sequestrants.

TABLE III Prevalence of Serum Transaminase Elevations

	Total Patients Tested	Patients with Elevations* No. (%)	Patients with Persistent Elevations† No. (%)	Patients with Therapy Interrupted or Discontinued No. (%)
SGOT	2,360	34 (1.4)	—	5 (0.2)
SGPT	2,280	61 (2.7)	—	7 (0.3)
Either	2,361	73 (3.0)	25 (1.0)	7 (0.3)

*Elevations >3 times upper limit of the normal range.
†Elevations >3 times upper limit of the normal range on 2 consecutive laboratory assays.
SGOT = aspartate aminotransferase; SGPT = alanine aminotransferase.

Adverse experiences: The most frequently observed drug-related clinical adverse experiences were gastrointestinal in nature including abdominal pain, constipation, flatulence and nausea. These events were usually mild and transient and required discontinuation of therapy in only 0.3% of the population (Table II). Laboratory adverse events were most often related to elevations in serum transaminases. Only 0.7% of this cohort was withdrawn because of a drug-related laboratory adverse event.

In patients taking concomitant therapy with β blockers, calcium antagonists, nonsteroidal antiinflammatory agents, diuretics, angiotensin-converting enzyme inhibitors or anticoagulants, the frequency of clinical adverse events was not significantly different from that observed in patients receiving monotherapy with simvastatin. The higher incidences of other adverse events were usually related to the specific adverse event profiles for the concomitant drug (e.g., fatigue with β blockers, headaches and constipation with calcium antagonists) and the medical conditions for which these agents would have been prescribed (e.g., β blockers for coronary artery disease).

Hepatic evaluation: The use of HMG-CoA reductase inhibitors has been associated with infrequent elevations of serum transaminase levels which are usually mild and transient. Table III summarizes data from patients taking simvastatin who experienced elevations of hepatic enzymes to >3 times the upper limit of the normal range. Twenty-five patients (1%) had persistent elevations >3 times the upper limit of the normal range ≥2 consecutive laboratory assays. Seven of these patients (0.3%) required a temporary interruption (n = 4) or discontinuation (n = 3) of simvastatin therapy. The remaining patients continued with simvastatin therapy because their transaminase levels spontaneously returned to within normal limits. None of these elevations were associated with clinical evidence of hepatotoxicity and all of these transaminase elevations were reversible with an interruption of simvastatin therapy. None of

the transaminase elevations in this population were associated with significant elevations in other laboratory parameters including bilirubin and alkaline phosphatase.

Muscle evaluation: Thirteen patients (0.6%) had single elevations in creatine kinase >10 times the upper limit of the normal range. Diffuse muscle pain or weakness associated with an elevation >10 times the upper limit of the normal range in creatine kinase not due to trauma or strenuous exercise (myopathy) was observed in 2 open-extension patients (0.08%). The first case involved a 32-year-old hypercholesterolemic man initially treated with fenofibrate in a comparative study with simvastatin. He was switched to simvastatin 20 mg/day in an open-extension phase and his dose increased to 40 mg/day 2 months later. Cholestyramine 16 g/day was added 4 months later. At the same time simvastatin was started the patient began an intensive exercise program and experienced persistent muscle pain with creatine kinase levels of 12,510 U/liter (normal range 15 to 120 U/liter). Myoglobinuria was not reported. After simvastatin was discontinued, his symptoms abated and the creatine kinase level decreased to within 2 times the upper limit of the normal range. It was not clear, however, whether this myopathy was drug-induced or secondary to intense exercise. A second open-extension patient, a 28-year-old hypercholesterolemic man receiving combined simvastatin and fibrate therapy, also developed myopathy. On further evaluation he was found to have Hashimoto's thyroiditis (peak creatine kinase 1,427 U/liter). The myopathy resolved with correction of his hypothyroidism and his therapy with simvastatin was reinstituted without further incident. One patient who underwent cardiac transplantation took simvastatin and cyclosporine concomitantly with no reports of myopathy to date.

Ophthalmologic evaluation: Ophthalmologic examinations were performed on all study participants at baseline (before treatment) and usually every 6 months to 1 year during treatment. To determine the effect of normal aging on lens opacity prevalence, the frequency of lens opacities at baseline is plotted against age in Figure 1. Based on this cross-sectional analysis, the expected increase in the prevalence of lens opacities due to normal aging in this cohort would be approximately 1.2%/year.[13]

TABLE IV Prevalence of Lens Opacities

	Lens Opacities	
	Baseline No. (%)	Final Examination* No. (%)
Total population (n = 2,014)	765 (38)	806 (40)
Treatment of ≥ 18 months (n = 721)	279 (39)	291 (40)

*Includes only patients with data at both examination periods.

An analysis of slit-lamp examinations in simvastatin-treated patients (n = 2,014) and patients who received simvastatin for ≥18 months (n = 721) revealed only minimal increases (1 to 2%) in the frequency of lens opacities to the last ophthalmologic examination (Table IV). These increases were consistent with both the expected prevalence related to the age of the population (mean age 50 years) and the calculated incidence due to normal aging (1.2%).

Fatal and nonfatal cardiovascular events: A previous history of coronary artery disease was present in 27% of this hypercholesterolemic population. Despite this prevalence of preexisting coronary artery disease the incidence of nonfatal cardiovascular adverse experiences was low: 26 patients (1.1%) with new-onset angina pectoris and 29 patients (1.2%) with a newly documented nonfatal myocardial infarction. The coronary heart disease mortality rate was 5 of 1,000 per year (12 of 2,361 patients). Only 1 death (auto accident) was not cardiovascular in nature. None of these fatal or nonfatal cardiovascular events were considered related to simvastatin therapy by the study investigators.

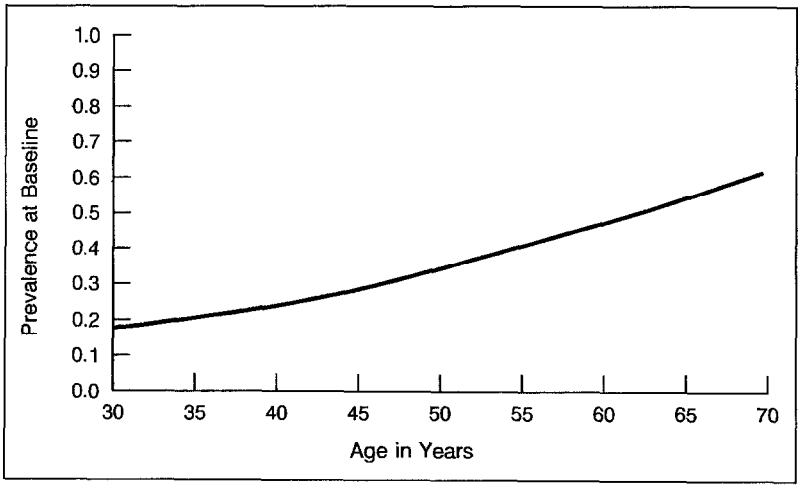

FIGURE 1. Pretreatment prevalence of lens opacities in the simvastatin population versus age.

TABLE V Clinical Adverse Events Occurring in ≥1% of the Elderly (>65 years) and Nonelderly Populations Related to Simvastatin Therapy

Adverse Event	Elderly Patients (n = 349) No. (%)	Nonelderly Patients (n = 2,012) No. (%)
Constipation	7 (2.0)	53 (2.6)
Dyspepsia	4 (1.1)	11 (0.5)
Flatulence	6 (1.7)	41 (2.0)
Insomnia	5 (1.4)	5 (0.2)
Nausea	3 (0.9)	23 (1.1)
Abdominal pain	2 (0.6)	50 (2.5)
Headache	3 (0.9)	20 (1.0)

Clinical and laboratory safety in the elderly: There were 349 (15%) elderly patients (≥65 years) in this cohort (131 men and 218 women, mean age 68 years). Of these patients, 142 (41%) received simvastatin therapy for a period of ≥1 year, 62 (18%) for ≥1.5 years and 17 (5%) for ≥2 years.

The incidence of clinical and laboratory adverse events in the elderly (>65 years) was similar to that seen in the nonelderly population, suggesting that the elderly do not experience an increased frequency of adverse experiences (Table V). The trend for a slightly higher incidence of insomnia in the elderly must be viewed in light of the increased prevalence of sleep disturbances associated with this age group.[14]

Efficacy: An analysis of long-term efficacy (2 years) in patients taking simvastatin (10 to 40 mg/day) revealed that the reductions in total cholesterol, LDL cholesterol and triglycerides and the elevation of high-density lipoprotein (HDL) cholesterol observed initially were maintained with chronic administration. Over a 2-year period, mean decreases in total cholesterol ranged from 29 to 31%, LDL cholesterol from 37 to 40%, triglycerides from 14 to 16%, with HDL cholesterol ranging from 11 to 14%. These data are summarized in Figure 2.

DISCUSSION

The overall prevalence and type of adverse experiences observed in this long-term evaluation of simvastatin-treated patients has not changed since the initial controlled clinical trials.[12] Clinical adverse events related to simvastatin are generally low in frequency, mild and gastrointestinal in nature, rarely requiring a discontinuation of therapy. The discontinuation rate for this population was extremely low considering that half of the patients included in these studies were treated for a period of >1 year. Concomitant therapy with other major classes of medications (cardiovascular, anti-inflammatory, lipid-lowering and anticoagulants) also failed to suggest any increase in the incidence of adverse experiences independent of the medical conditions for which they were prescribed.

The small number of patients having persistent elevations of serum transaminases has not been associated with any clinical syndrome and in most instances resolved either spontaneously or with interruption or discontinuation of therapy. Based on these data, the hepatic effects of simvastatin appear to be similar to those of lovastatin.[15] Monitoring of liver enzymes is therefore recommended.

The incidence of myopathy was also low (0.08%) with no reports of myoglobinuria. Although myopathy has been reported with the use of other HMG-CoA reductase inhibitors[16,17] administered with and without fibrates, niacin and cyclosporine, the number of patients taking simvastatin and these agents concomitantly was too small to make any clinical conclusions. Patients who develop unexplained muscle pain or tenderness associated with a marked elevation of creatine kinase should have therapy with HMG-CoA reductase inhibitors discontinued. Although, to date, reports of clinical myopathy have been rare with simvastatin, caution should be exercised when using cyclosporine, fibrates or niacin concomitantly with simvastatin.[15] The

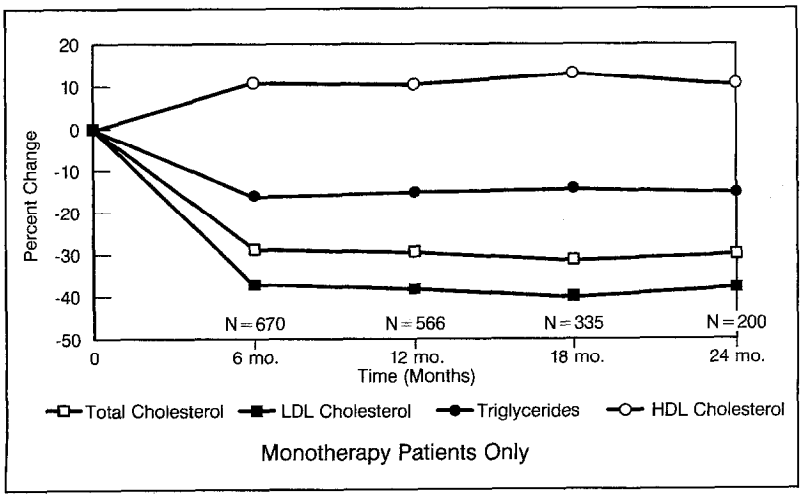

FIGURE 2. Long-term lipid response to simvastatin 10 to 40 mg/day (mean change [%] over time). HDL = high-density lipoprotein; LDL = low-density lipoprotein.

dose of simvastatin used with cyclosporine should probably not exceed 10 mg/day.

Ophthalmologic examinations in simvastatin-treated patients demonstrated only minimal increases in the prevalence of lens opacities, consistent with normal aging. These data provide no evidence for an adverse effect of simvastatin on the human lens.

The data presented for the elderly subpopulation demonstrated a safety profile very similar to nonelderly persons. Simvastatin therapy is not associated with an increased risk of adverse events when administered to elderly patients. Despite a claim of sleep disturbance with simvastatin therapy,[18] no patient in this large cohort has required discontinuation of simvastatin because of any sleep-related disturbance.

Chronic administration of simvastatin is associated with persistent reduction in total cholesterol, LDL cholesterol and triglycerides and an increase in HDL cholesterol similar to that observed with initial administration.

In addition to these clinical studies, simvastatin has been administered to over 20,000 patients in compassionate use and postmarketing clinical studies, and to approximately 900,000 patients since marketing of the drug in 22 countries worldwide. The safety profile in this larger population continues to be consistent with the data from the population presented in this report and appears very similar to the safety profile of lovastatin.[19]

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