Safety of *Atorvastatin* Derived from Analysis of 44 Completed Trials in 9,416 Patients

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This analysis assessed the safety of atorvastatin in the 10- to 80-mg dose range using pooled data from 44 completed trials comprising 16,495 dyslipidemic patients treated with atorvastatin (n = 9,416), placebo (n = 1,789), and other statins (n = 5,290). A retrospective analysis was conducted and included treatment-associated adverse events, serious adverse events, and musculoskeletal and hepatic adverse events. Only 3% (n = 241) of atorvastatin-treated patients withdrew from studies due to treatment-associated adverse events, compared with 1% of those (n = 16) on placebo and 4% of those (n = 188) receiving other statins; the most frequently reported treatment-associated adverse events were related to the digestive system. Serious adverse events were rare and seldom led to withdrawal. Persistent elevations in hepatic transaminases to >3 times the upper limit of normal (ULN) were experienced by 0.5% (n = 47) of atorvastatin-treated patients. A persistent elevation in creatine phosphokinase (CPK) (>10 × ULN) was observed in only 1 atorvastatin-treated patient and was not associated with myopathy. The incidence of treatment-associated myalgia was low in the atorvastatin (1.9% [n = 181]), placebo (0.8% [n = 14]), and other statin (2.0% [n = 105]) groups, and was not related to the atorvastatin dose. No cases of rhabdomyolysis or myopathy were reported. Thus, the overall incidence of treatment-associated adverse events observed with atorvastatin did not increase in the 10- to 80-mg dose range, and was similar to that observed with placebo and in patients treated with other statins. Specific analysis of musculoskeletal and hepatic adverse events showed that these occurred infrequently and rarely resulted in treatment discontinuation. ©2003 by Excerpta Medica, Inc.

(Am J Cardiol 2003;92:670–676)

The withdrawal of cerivastatin from the market after reports of an association with fatal rhabdomyolysis[1] caused the safety of many long-term medications to be scrutinized. A comprehensive assessment of the clinical trial safety data for atorvastatin seems particularly relevant at this time. In addition, studies have suggested that despite guidelines for cholesterol management, physicians have not effectively implemented these guidelines; many patients remain untreated or undertreated.[2–4] Providing the medical community with additional information on the side effects of atorvastatin is the purpose of this study.

METHODS

Pooled studies database: Data from 44 clinical trials of atorvastatin, completed as of November 1, 2001, were pooled into a single database for analysis (Table 1). In these trials, atorvastatin was administered as atorvastatin calcium.

Eighteen of the trials began with a baseline period of 4 to 8 weeks' duration, during which patients received placebo once daily and followed the National Cholesterol Education Program Step 1 Diet. This baseline period permitted lipid levels to stabilize during dietary intervention. After the baseline period, eligible patients were randomly assigned to treatment. For most studies, active treatment phases ranged from 2 weeks to 18 months, with atorvastatin doses ranging from 10 to 80 mg once daily.

Twenty-three trials had a fixed-dose parallel group design in which patients maintained a single dose throughout the study. Twenty-one trials were either dose-titration or treatment-change studies in which patients received a fixed dosage of treatment for the first 4 to 16 weeks, after which the medication dosage was increased or treatment was changed from placebo to active treatment or from a single active treatment to combination treatment. Six of the dose-titration studies were 1 year in duration and designed to acquire safety information over longer term treatment in comparison with other statins.

In 17 studies, patients received other statins, including fluvastatin 20 to 80 mg, lovastatin 20 to 80 mg, pravastatin 10 to 40 mg, and simvastatin 10 to 80 mg. Within each trial, the length of exposure and number of follow-up visits with these comparator statins were similar to those with atorvastatin.

Database groupings: Two separate database groupings were analyzed. The All Completed Studies Data Grouping contained data from all portions of all studies and allowed a comprehensive analysis of safety. Data for patients treated with currently marketed sta-

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0002-9149/03/$–see front matter
doi:10.1016/S0002-9149(03)00820-8

TABLE 1 Summary of All Completed Trials in Patients Treated With Atorvastatin (n = 9,416), Placebo (n = 1,789), and other statins (n = 5,290) as of November 1, 2001

Patient Population	No. of Trials	Treatment Duration (wks)	Atorvastatin Dose Range (mg)
Hypercholesterolemia, (LDL-C ≥160 mg/dl [4.1 mmol/L]; triglycerides ≤400 mg/dl [4.5 mmol/L])*	23[22–29]	2–52	10–80
Mixed dyslipidemia (triglycerides ≥200 mg/dl [2.3 mmol/L])†	6[30]	4–52	10–80
Hypercholesterolemic patients with CHD	4[7]	26–78	10–80
Heterozygous familial hypercholesterolemia	3	6–52	20–80
Homozygous familial hypercholesterolemia	2	8–52	40–80
Children and adolescents with hypercholesterolemia (familial or severe)	1	52	10–20
Hyperlipoproteinemia‡	1	12	80
Dyslipidemic patients with type 2 diabetes mellitus	2	4–26	10–20
Dyslipidemic patients with nephrotic syndrome	1	4	10
Acute coronary syndrome	1[6]	16	80

*Inclusion criteria for LDL-C were ≥130 mg/dl [3.4 mmol/L] for 1 trial, and ≥110 mg/dl [2.8 mmol/L] for 1 trial.
†Inclusion criteria for triglycerides were ≥350 mg/dl [4.0 mmol/L] for 3 trials.
‡Types II a, II b, IV.
CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol

TABLE 2 All Completed Studies Data Grouping: Patient Demographics and Baseline Characteristics

	Placebo (n = 1,789)	Atorvastatin (all doses) (n = 9,416)	Other Statins (n = 5,290)
Men	1,191 (67%)	5,618 (60%)	3,070 (58%)
Women	598 (33%)	3,798 (40%)	2,220 (42%)
Age (yrs)			
Median	64	60	61
Range	10–94	2–93	18–82
Mean ± SE	63 ± 0.3	58 ± 0.1	60 ± 0.2
Race*			
White	1,543 (86%)	8,524 (91%)	4,810 (91%)
Black	54 (3%)	415 (4%)	280 (5%)
Asian	61 (3%)	117 (1%)	54 (1%)
Other	131 (7%)	311 (3%)	110 (2%)
Body mass index (kg/m^2)			
Median	27	27	27
Mean ± SE	27 ± 0.1	27 ± 0.1	27 ± 0.1
Mean plasma lipids (mg/dl) (mean ± SE)			
LDL cholesterol	132 ± 1.0	186 ± 0.7	185 ± 0.6
VLDL cholesterol	59 ± 6.7	39 ± 0.5	38 ± 0.5
Total cholesterol	215 ± 1.1	272 ± 0.8	273 ± 0.6
Triglycerides	185 ± 2.4	197 ± 1.5	206 ± 1.4
HDL cholesterol	46 ± 0.3	47 ± 0.1	46 ± 0.2
Non-HDL cholesterol/HDL cholesterol ratio	4 ± 0.0	5 ± 0.0	5 ± 0.0

*Total percentage may not equal 100% due to rounding.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

tins other than atorvastatin were pooled and presented as a combined "other statin group." Data from 236 patients treated with cerivastatin were excluded from this analysis. The Fixed-Dose Data Grouping consisted of data from the entire duration of treatment in 23 parallel-group studies and from before treatment or any dose change in 21 titration or treatment-change studies. This grouping provided a means of evaluating the safety of atorvastatin across dose ranges.

Patient population: Study participants were men and women (women were postmenopausal or practicing a reliable method of birth control) of different ethnic backgrounds. Eligibility criteria in many postapproval studies allowed enrollment of patients with established coronary heart disease, including high-risk cardiovascular patients. Patients were excluded if they consumed excessive amounts of alcohol or were taking prohibited lipid-lowering agents, such as niacin, probucol, psyllium, fibrates, bile-acid-sequestering resins, fish oils, or other statins at study entry. Most participants had baseline plasma low-density lipoprotein (LDL) cholesterol levels of ≥160 mg/dl (4.1 mmol/L) and triglyceride levels of ≤600 mg/dl (6.8 mmol/L).

Safety analysis: Multicenter trials used central laboratories and single-center trials used local laboratories to evaluate safety parameters. The designated laboratory determined the normal range for each parameter. Evaluations were performed on fasting (minimum of 12 hours) venous blood samples, drawn 6 to 18 hours after dosing. Full clinical laboratory evaluations were conducted for each patient at each visit or designated visits. Additional safety evaluations, including, but not limited to, measurement of plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were also performed. Physical examinations and electrocardiograms were performed at baseline and at trial end.

Adverse events were recorded throughout the treatment phase of each trial and up to 30 days after treatment was discontinued. Adverse events recorded in investigator's terms were converted to preferred terms and body systems using Version IV of the *Coding Symbols for Thesaurus of Adverse Reaction Terms* dictionary.[5]

Adverse events were classified based on their intensity and relation to study drug. Events that began during treatment, or increased in intensity or frequency from initiation of therapy or from the placebo–baseline phase, were defined as treatment-emergent signs or symptoms. For each patient, a particular adverse event was counted only once. The severity of the adverse event was defaulted to the most severe outcome. The intensity (mild, moderate, or severe) of the adverse event and its relation to study medication (definitely not, un-

TABLE 3 All Completed Studies Data Grouping: Overview of Safety, Comparing Atorvastatin With Other Statins and Placebo

	Placebo (n = 1,789)	Atorvastatin (all doses) (n = 9,416)	Other Statins (n = 5,290)
Patients experiencing ≥1 adverse event			
All	45%	65%	67%
Treatment-associated	15%	18%	19%
Withdrawals due to adverse events (no. of patients (%))			
All	25 (1%)	398 (4%)	297 (6%)
Treatment-associated	16 (1%)	241 (3%)	188 (4%)
Serious, nonfatal adverse events (no. of patients (%))			
All	137 (8%)	963 (10%)	590 (11%)
Treatment-associated	114 (6%)	19 (<1%)	6 (<1%)
Deaths (no. of patients (%))	12 (1%)	66 (1%)	30 (1%)

TABLE 4 All Completed Studies Data Grouping: Treatment-associated Adverse Events Experienced by ≥1% of Atorvastatin-treated Patients, by Body System

Body System	Placebo (n = 1,789)	Atorvastatin (all doses) (n = 9,416)	Other Statins (n = 5,290)
Digestive	78 (4%)	732 (8%)	455 (9%)
Body as a whole	87 (5%)	483 (5%)	291 (6%)
Musculoskeletal	18 (1%)	299 (3%)	186 (4%)
Nervous	31 (2%)	248 (3%)	154 (3%)
Skin/appendages	15 (1%)	166 (2%)	88 (2%)
Metabolic/nutritional	18 (1%)	136 (1%)	46 (1%)
Special senses	3 (<1%)	51 (1%)	20 (<1%)
Urogenital	11 (1%)	51 (1%)	30 (1%)
Cardiovascular	32 (2%)	49 (1%)	30 (1%)

Data are presented as numbers (percentages).

likely, possibly, probably, or definitely related, or insufficient information) was determined by the investigator. If there was insufficient information, or no relation was designated on the case report form to make a judgment, then the event was considered related to study drug. Serious adverse events were defined according to Food and Drug Administration criteria and included all of the following: cancer, death, life-threatening events, permanently disabling events, congenital anomalies, events requiring or prolonging hospitalization, and accidental or intentional overdose. From April 1, 1998, criteria for defining serious adverse events were modified by the Food and Drug Administration. This modification excluded cancer and overdose. Serious adverse events for some trials were collected under the previous criteria.

In 2 clinical trials, cardiac-related serious adverse events were not summarized, as they were deemed end points and thus considered efficacy rather than safety data.[6,7]

Musculoskeletal and hepatic safety analysis: Persistent elevations in creatine phosphokinase (CPK) were defined as 2 consecutive values >10 × upper limit of normal (ULN). If judged appropriate by the investigator, muscle symptoms were also assessed using standard clinical measures of functional capacity and muscle strength.

To allow direct comparison with the atorvastatin new drug application, (1996) persistent, clinically relevant elevations in ALT/AST were characterized as 2 consecutive values >3 × ULN obtained within a 14-day period. Additionally, any other elevations in ALT or AST were noted: 2 consecutive measurements >3 × ULN regardless of time interval; 1 post-baseline ALT or AST value >3 × ULN with no repeat laboratory measurements; and 1 baseline ALT/AST measurement >3 × ULN and post-baseline measurements greater than baseline. Although not clinically relevant, these definitions provide a broader estimate of the incidence of hepatic transaminase elevations within this analysis.

These conventions are consistent with the advisory on the use and safety of statins published by the American College of Cardiology, the American Heart Association, and the National Heart, Lung, and Blood Institute.[8]

Statistical analyses: Descriptive statistics are displayed. Because the goal of the analysis was only to summarize the safety of atorvastatin in the 44 completed clinical trials, no inferential statistical analyses were performed.

RESULTS

Patient characteristics: The All Completed Studies Data Grouping included data from 16,495 patients. Of these, 9,416 received atorvastatin, 5,290 received other statins (simvastatin, 2,771 patients; pravastatin, 807 patients; lovastatin, 968 patients; fluvastatin, 744 patients), and 1,789 received placebo. Patient demographics at screening are listed in Table 2.

The Fixed-Dose Data Grouping included data from 11,065 patients, who were distributed by treatment as follows: placebo, 1,949 patients; atorvastatin 10 mg, 6,343 patients; atorvastatin 20 mg, 242 patients; atorvastatin 40 mg, 186 patients; and atorvastatin 80 mg, 2,345 patients. Overall, patient characteristics for the Fixed-Dose Data Grouping and the All Completed Studies Data Grouping were comparable.

Patient exposure: For the All Completed Studies Data Grouping, total exposure for placebo, atorvastatin, and other statins was 506, 7,812, and 4,064 patient-years, respectively. For atorvastatin, this represents an approximately threefold increase in exposure (from 1,845 patient-years) since the new drug application in 1996. Almost half of the patients (47%) were exposed to atorvastatin for ≥1 year.

For the Fixed-Dose Data Grouping, greatest exposure was at the 10-mg dose (6,074 patient-years for

atorvastatin 10 mg compared with 138, 65, and 1,144 patient-years for atorvastatin 20, 40, and 80 mg, respectively). This reflects the fact that most studies initiated treatment with atorvastatin 10 mg before titrating to a higher dose. The level of exposure for the 80-mg dose group represents a 13-fold increase since 1996.

Safety: Analysis of the All Completed Studies Data Grouping showed that the overall adverse event profiles for the atorvastatin and other statins groups were similar (Table 3). Although the percentage of patients experiencing any adverse event in the placebo group was lower compared with the atorvastatin group, this can be explained in part by the fact that the total duration of exposure for atorvastatin-treated patients was markedly longer than for patients who received placebo, thereby increasing the reporting period. Across all groups, treatment-associated adverse events were most frequently reported for the digestive system, the body as a whole, the musculoskeletal system, and the nervous system (Table 4). Specific treatment-associated adverse events in the atorvastatin and other statins groups occurred infrequently.

Atorvastatin was found to be well tolerated overall. Among those patients receiving atorvastatin, the incidence of withdrawal due to any specific type of adverse event was low (0.01% to 0.4%). The most common adverse events leading to withdrawal among atorvastatin-treated patients were myalgia (0.4%), followed by pain (0.3%) and abdominal pain (0.2%). The most common adverse events leading to withdrawal among patients receiving other statins were myalgia (0.7%), pain (0.4%), and dyspepsia (0.4%). For placebo-treated patients, adverse events that most often led to withdrawal were abdominal pain (0.3%), nausea (0.3%), and diarrhea (0.2%). Only 3% of atorvastatin-treated patients, compared with 1% of patients on placebo and 4% of those receiving other statins, withdrew from studies due to treatment-associated adverse events (Table 3).

Serious, nonfatal adverse events were reported for a similar proportion of patients in each treatment group (Table 3). In the atorvastatin group, serious adverse events were primarily related to the cardiovascular system (4%), body as a whole (2%), and digestive system (2%). Comparative values for these body systems in the other statins group were 5%, 3%, and 1%, respectively. For both the atorvastatin and other statin groups, the incidence of specific serious adverse events was infrequent ($\leq$2%); specific cardiovascular serious adverse events included angina pectoris, myocardial infarction, and coronary artery disorder. Cardiovascular serious adverse events were anticipated, as many of the studies enrolled patients at high risk for cardiovascular disease. Treatment-associated serious adverse events were rare and reported in $<$1% of both the atorvastatin and other statins groups. Across all treatment groups, the incidence of death was low, and no deaths were considered related to treatment.

Analysis of adverse event data for the Fixed-Dose Data Grouping showed that the proportion of patients

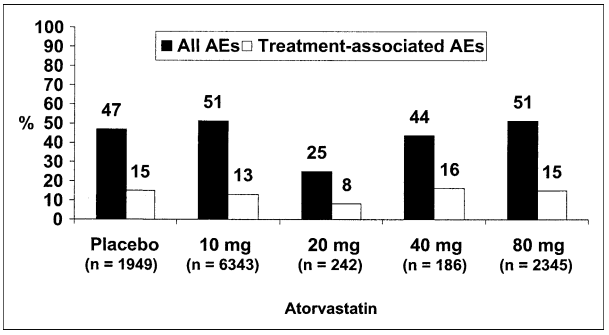

FIGURE 1. Percent of patients experiencing ≥1 adverse event (AE) (all and treatment-associated) in the Fixed-Dose Data Grouping.

experiencing ≥1 adverse event or ≥1 treatment-associated adverse event was similar to placebo at each atorvastatin dose (Figure 1). When the incidence of specific treatment-associated adverse events experienced by ≥1% of patients were summarized by body system, values were low and no consistent dose-related trends were evident (Table 5). Clinical laboratory abnormalities were generally more frequently reported in atorvastatin-treated patients than in those who received either placebo or other statins. However, as with the adverse event data, this finding may be due to differences in total patient exposure.

Musculoskeletal and hepatic safety parameters: Across the 44 studies analyzed, none of the atorvastatin-treated patients experienced myopathy or rhabdomyolysis. For both the atorvastatin and other statin groups, the most common musculoskeletal adverse event was myalgia; in both groups all-cause myalgia was recorded in 4% of patients. Analysis of the Fixed-Dose Data Grouping showed that the frequency of myalgia did not increase across the atorvastatin dose range, and at each dose the proportion of patients experiencing the event was low (Figure 2).

Only 1 patient receiving atorvastatin experienced persistent CPK elevations $>10 \times$ ULN. The elevated levels of CPK were not accompanied by muscle symptoms. The patient was a 16-year-old male with severe hypercholesterolemia and a history of xanthomas, hypertension, headache, and slightly elevated CPK levels, who received treatment with atorvastatin 40 mg/day for 28 days, followed by treatment with atorvastatin 80 mg/day for 479 days. Study medication was continued and by the end of the study the elevated levels of CPK had returned to baseline.

Elevations in hepatic transaminases were similar for both the atorvastatin and the other statin treatment groups relative to the placebo group. Persistent, clinically relevant elevations in ALT/AST were recorded in 47 patients (0.5%) who received atorvastatin at any dose in the All Completed Studies Data Grouping, compared with 5 placebo-treated patients (0.3%). Of the 47 atorvastatin-treated patients, 18 continued with their treatment. Analysis by atorvastatin dose showed that at any given dose, $<$1% of patients experienced persistent transaminase elevations (Table 6).

Musculoskeletal and hepatic nonfatal serious ad-

TABLE 5 Fixed-dose Data Grouping: Treatment-associated Adverse Events Experienced by ≥1% of Atorvastatin-treated Patients, by Body System

Body System	Placebo (n = 1,949)	Atorvastatin 10 mg (n = 6,343)	Atorvastatin 20 mg (n = 242)	Atorvastatin 40 mg (n = 186)	Atorvastatin 80 mg (n = 2,345)
Digestive	93 (5%)	340 (5%)	8 (3%)	12 (6%)	174 (7%)
Body as a whole	94 (5%)	252 (4%)	5 (2%)	8 (4%)	84 (4%)
Musculoskeletal	22 (1%)	139 (2%)	6 (2%)	8 (4%)	40 (2%)
Nervous	37 (2%)	126 (2%)	2 (1%)	5 (3%)	42 (2%)
Skin/appendages	18 (1%)	87 (1%)	1 (<1%)	2 (1%)	25 (1%)
Metabolic/nutritional	19 (1%)	52 (1%)	1 (<1%)	3 (2%)	36 (2%)
Urogenital	11 (1%)	34 (1%)	0 (0%)	1 (1%)	7 (<1%)
Special senses	4 (<1%)	27 (<1%)	0 (0%)	4 (2%)	8 (<1%)
Cardiovascular	33 (2%)	26 (<1%)	1 (<1%)	2 (1%)	5 (<1%)
Respiratory	22 (1%)	12 (<1%)	0 (0%)	1 (1%)	6 (<1%)

Data are presented as numbers (percentages).

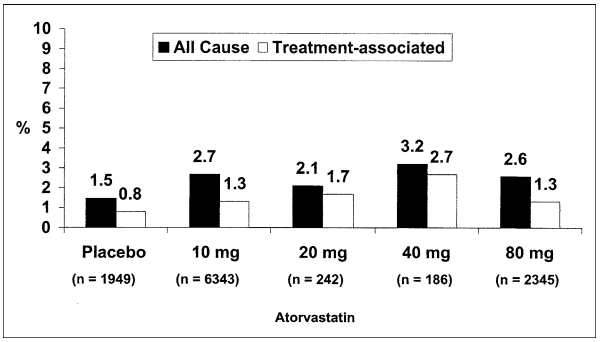

FIGURE 2. Fixed-Dose Data Grouping: incidence of myalgia across the dose range of atorvastatin compared with placebo.

verse events were rare (<0.5% for any specific adverse event) in both the atorvastatin and other statins groups. The most common musculoskeletal serious adverse event was arthritis, with an incidence of 0.15% in patients who received atorvastatin and 0.21% in patients treated with other statins. Myalgia was recorded as a serious adverse event for only 3 atorvastatin patients (0.03%) and for only 1 patient receiving other statins (0.02%). Cholecystitis and cholelithiasis were the only hepatic serious adverse events reported in >10 patients in the atorvastatin group (17 patients [0.18%] and 15 patients [0.17%], respectively) and the other statin groups (13 patients [0.25%] and 9 patients [0.16%], respectively). Other hepatic serious adverse events reported for atorvastatin-treated patients included abnormal liver function tests (6 patients [0.06%]), hepatitis (5 patients [0.05%]), cholestatic jaundice (2 patients [0.02%]), enzymatic abnormality (1 patient [0.01%]), and increases in ALT (2 patients [0.02%]) and AST (1 patient [0.01%]).

Discontinuations considered related to hepatic and musculoskeletal adverse events were rare (<1%).

DISCUSSION

The present review, based on 44 completed trials, represents an almost threefold increase in patient exposure to atorvastatin since 1996. Much of the data reflects use of the lowest and highest approved doses of atorvastatin. Substantial numbers of patients were treated with 10- and 80-mg atorvastatin, permitting assessment of the relation of dose to adverse events.

Overall, the incidence of adverse events for atorvastatin-treated patients, patients receiving other statins, and patients receiving placebo was low, and for the atorvastatin group, the incidence of these events was lower than that reported in the original new drug application. When treatment-associated adverse events were analyzed by body system, the most frequent treatment-associated adverse event for both the atorvastatin and the other statin groups was related to the digestive system. Among atorvastatin patients, serious adverse events were rare and seldom led to study withdrawal, and laboratory abnormalities occurred infrequently.

One of the issues raised with respect to a potent statin such as atorvastatin is the possibility that low LDL cholesterol levels associated with treatment might cause adverse effects. A previous analysis of data pooled from 21 of these 44 clinical trials found that the frequency of treatment-associated adverse events in 319 atorvastatin-treated patients with ≥1 LDL cholesterol value ≤80 mg/dl was comparable to the frequencies associated with all atorvastatin-treated patients and for patients receiving other statins.[9]

Statins decrease intracellular cholesterol production in the liver by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme for cholesterol biosynthesis,[10] and by increasing the number of hepatic LDL receptors on the cell surface to increase the uptake and catabolism of LDL cholesterol.[11] As such, the potential for statins to cause elevated liver enzymes has always been recognized. Previous clinical trials with statins have demonstrated that the incidence of hepatic transaminase increases greater than threefold was approximately 1%.[12–15]

The incidence of persistent elevations in hepatic transaminases reported in the atorvastatin new drug application in 1996 was low: 0.2%, 0.2%, 0.6%, and 2.3% for atorvastatin 10, 20, 40, and 80 mg, respectively, and 0.7% for all atorvastatin doses combined.[16]

TABLE 6 All Completed Studies Data Grouping: Incidence of Hepatic Transaminase Elevations by Atorvastatin Dose

Atorvastatin (mg/d)	1996 New Drug Application*		2001 Summary Any Elevation†		2001 Summary Clinically Relevant‡	
	Patients Exposed	Patients With Elevation	Patients Exposed	Patients With Elevation	Patients Exposed	Patients With Elevation
10	1,843	3 (0.20%)	6,046	12 (0.20%)	6,093	8 (0.13%)
20	892	2 (0.20%)	2,542	3 (0.12%)	2,542	3 (0.12%)
40	811	5 (0.60%)	1,983	17 (0.86%)	1,983	8 (0.40%)
80	888	20 (2.30%)	3,123	57 (1.83%)	3,131	28 (0.89%)
Any dose	4,271	30 (0.70%)	9,360	90 (0.96%)	9,416	47 (0.50%)
Placebo	110	1 (0.91%)	1,776	8 (0.45%)	1,789	5 (0.28%)

*ALT/AST >3 × ULN for 2 consecutive measurements taken within 7 to 10 days of each other.[16]

†ALT/AST >3 × ULN for 2 consecutive measurements obtained at >14 days, or post-baseline ALT/AST >3 × ULN with no repeat laboratory measurement, or baseline ALT/AST >3 × ULN and post-baseline greater than baseline with ≥1 laboratory measurement.

‡ALT/AST >3 × ULN for 2 consecutive measurements obtained within a 14-day period.

The present study confirms earlier analysis of atorvastatin's safety (Table 6). Hepatic adverse events occurred infrequently and persistent elevations in hepatic transaminases were rare, with a range of incidence similar to that reported for other statins. In the 10- to 80-mg dose range, <1% of atorvastatin-treated patients experienced persistent elevations. After dose reduction or discontinuation of treatment, the elevated levels usually returned to normal. As with other statins, liver function tests should be conducted in all patients receiving atorvastatin. In cases of persistent elevations in transaminase levels to >3 × ULN, the dosage should be reduced or treatment discontinued.

Myopathy, generally defined clinically as CPK levels >10 × ULN with accompanying muscle pain or weakness, is rare (approximately 1 in 1,000 patients) but is considered an important adverse effect of statins.[8] The precise mechanism of statin-induced myopathy is unknown. However, it is more likely to occur in subjects who have complex medical problems and/or those who are receiving several concomitant drug therapies.[8] Combining some statins with drugs that are potent inhibitors of CYP3A4 may increase the risk of myopathy. Such agents include cyclosporine, erythromycin, clarithromycin, nefazodone, and azole antifungals.[8,17] Other lipid-lowering drugs (e.g., niacin and fibrates) that can cause myopathy, if given alone, may also increase the risk of statin-induced myopathy.[8,17]

If statin-induced myopathy is undetected and therapy continues, acute rhabdomyolysis and irreversible renal failure can occur.[18] Because of this, large-scale clinical trials of some statins (lovastatin, pravastatin, and simvastatin) included specific safety assessments designed to detect myotoxicity; however, no evidence of increased rates of rhabdomyolysis or persistent elevations in CPK >10 × ULN compared with placebo were observed.[19] More recently, a pooled analysis by Benghozi and colleagues[20] demonstrated that the frequency of significant CPK elevations among a large population of patients treated with fluvastatin 20, 40, and 80 mg was low and not different from placebo-treated patients.

In the present analysis, there were no reports of myopathy or rhabdomyolysis in the atorvastatin treatment group and only 1 atorvastatin-treated patient experienced a persistent elevation in CPK, which was not associated with muscle symptoms. Thus, the present analysis provides no evidence to suggest that atorvastatin therapy is associated with an increased incidence of myopathy across its therapeutic dose range. However, it should be noted that the data in this study are derived from controlled clinical trials in which other concomitant lipid-lowering medications (such as fibrates) were often excluded medications. In postmarketing experience, myopathy has been rarely reported with atorvastatin, and the atorvastatin package insert clearly states that, as with other statins, atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of myopathy.

The incidence of myalgia was low (≤3%) in atorvastatin- and placebo-treated patients, and did not appear to be related to the dose of atorvastatin. Discontinuation rates due to myalgia were low and comparable among the atorvastatin and other statins groups (0.4% and 0.7%, respectively). Review of serious adverse events related to musculoskeletal problems revealed that these events were infrequent.

The recently published Anglo-Scandinavian Cardiac Outcomes Study (ASCOT) further supports the safety of atorvastatin.[21] In ASCOT, 10,305 patients with mild to moderate elevations of total cholesterol were randomized to atorvastatin 10 mg (n = 5,168) or placebo (n = 5,137) for a median treatment duration of 3.3 years. Only 1 nonfatal case of rhabdomyolysis was reported in an atorvastatin-treated man who had a very high alcohol intake and a recent febrile illness. The number of serious adverse events and rates of elevations in hepatic transaminases did not differ between placebo- and atorvastatin-treated patients.[21] Other clinical trials of atorvastatin in a variety of patient populations are ongoing and will provide additional safety information in the future.

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