An Overview of the Clinical Safety Profile of Atorvastatin (Lipitor), a New HMG-CoA Reductase Inhibitor

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Background: Statins (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] reductase inhibitors) have been used for a decade to lower low-density lipoprotein (LDL) cholesterol levels and to improve cardiovascular disease and clinical outcomes.

Objective: To evaluate the safety profile of atorvastatin (Lipitor).

Methods: Data were pooled for 21 completed (2502 patients) and 23 ongoing (1769 patients) clinical trials of atorvastatin conducted in US and international community- and university-based research centers. In these trials, patients with lipid disorders received atorvastatin at dosages of 10 to 80 mg/d. The majority of patients had moderate to severe hypercholesterolemia and were treated from 4 weeks to more than 24 months.

Main Outcome Measures: Transaminase and creatine phosphokinase levels and adverse events were recorded.

Results: Atorvastatin was well tolerated; fewer than 2% of the atorvastatin-treated patients withdrew due to drugattributable adverse events. The overall adverse event profile for atorvastatin was similar to that observed with other statins. The most common adverse events with atorvastatin as well as with other statins tested were constipation, flatulence, dyspepsia, and abdominal pain. Approximately 5% of atorvastatin-treated patients had serious adverse events; only 2 of these events were possibly associated with treatment. Thirty patients (0.7%) had confirmed transaminase elevations greater than 3 times the upper limit of the normal range. Most elevations occurred within 16 weeks of beginning treatment. No patients had a conclusive characterization of druginduced myopathy.

Conclusions: The safety profile of atorvastatin was consistent with that of all statins tested and was similar to that seen in all compounds of this class.

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TORVASTATIN (Lipitor), a highly effective 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statin), suppresses hepatic cholesterol synthesis, thereby promoting an increase in hepatic lowdensity lipoprotein (LDL) receptors and altering the formation of very-low-density lipoprotein (VLDL) particles.1-3 Dosedependent reductions in LDL cholesterol levels ranging from 41% to 61% have been reported for the dosage range of 10 to 80 mg/d.4,5 In addition, serum triglyceride levels have been reduced up to 43% in patients with hypertriglyceridemia.6

Overall, statins have consistent and acceptable safety profiles, as evidenced by widespread exposure in currently marketed compounds: lovastatin, pravastatin, simvastatin, and fluvastatin.⁷⁻³¹ Data from individual studies in patients with hyperlipidemias of various phenotypes indicate

that atorvastatin has a more significant effect on LDL cholesterol reduction than other statins while maintaining a safety profile comparable to those of marketed compounds in its class. 4-6,32-49 The present analysis combines the safety information collected from 21 completed studies to evaluate the clinical safety of atorvastatin within an integrated database. Twenty-three ongoing trials contributed additional information concerning elevations in transaminase or creatine phosphokinase levels. In an effort to determine if atorvastatin's increased efficacy is associated with an increase in adverse events compared with other drugs in its class, we evaluated the relationship, if any, among treatment, dose, and duration of treatment and the development of adverse events. Most patients enrolled in these trials had moderate to severe hypercholesterolemia and represented a sample of patients likely to be treated with a cholesterol-lowering drug.

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METHODS

CONTRIBUTING STUDIES

Patients were randomly assigned in each of 21 studies conducted in the United States, Canada, Europe, South Africa, and Australia (1 study remained unpublished at the time of this report). 4,6,32-49 The data from all 21 studies were combined into a large, integrated safety database for analysis. Most studies (15/21) began with a single-blind placebo baseline period of 4 to 6 weeks during which patients followed the National Cholesterol Education Program Step 1 Diet. 50 The baseline period allowed lipid levels to stabilize during dietary intervention and enabled the exclusion of patients whose lipid levels could be successfully managed by diet alone. Eligible patients were then randomized to active treatment with atorvastatin lasting from 4 weeks to 24 months. Ninety-nine percent of study participants received 10 to 80 mg/d. Eleven studies were parallel group trials during which patients maintained a single dosage level of treatment throughout the study. Ten studies were dose-titration or treatmentchange studies in which patients received a fixed dosage of treatment during the first 4 to 16 weeks of the study, after which the study medication dosage was doubled or treatment was changed. Six of the dosetitration studies were 1-year studies designed to acquire safety information over long-term treatment in comparison with other statins (lovastatin, pravastatin, simvastatin).

All studies were conducted in patients with varied forms of hyperlipidemia, including primary hypercholesterolemia (Fredrickson type IIa), with LDL cholesterol levels greater than 3.48 mmol/L (135 mg/dL) and triglyceride levels lower than 2.26 mmol/L (200 mg/dL); and mixed hyperlipidemia (Fredrickson type IIb), with LDL cholesterol levels greater than 3.48 mmol/L (135 mg/dL) and triglyceride levels of 2.26 mmol/L (200 mg/dL) or greater.

Seven studies designed to select a population of patients with a particular form of hyperlipidemia included one 8-week, uncontrolled study in patients with documented

homozygous familial hypercholesterolemia. Three studies included patients with hypertriglyceridemia, most of whom had combined dyslipidemia; 2 of these patients had noninsulin-dependent diabetes mellitus, as determined by criteria established by the National Diabetes Data Group in the United States.⁵¹ Two studies (1 of 6-week duration and 1 of 1-year duration) were in patients with severe hypercholesterolemia (LDL cholesterol level >5.68 mmol/L [>220 mg/dL]), either heterozygous familial hypercholesterolemia (defined by the presence of tendon xanthomas and evidence of inheritance or confirmed LDL receptor defect) or nonfamilial hypercholesterolemia (all other hyperlipidemias). One study was completed in postmenopausal women.

The primary focus of comparison was other statins (simvastatin, 10-40 mg/d; lovastatin, 20-40 mg/d; and pravastatin, 20-40 mg/d), since these compounds have demonstrated similarities in their safety profiles. Within each study, the length of exposure and number of follow-up visits with these compounds were similar to those with atorvastatin. In 23 additional ongoing studies, information on transaminase and creatine phosphokinase levels was collected, providing most of the data on exposure at the higher dosages of atorvastatin. Many of the ongoing trials were extensions of the 21 completed studies.

PATIENT POPULATION

In general, study participants in both completed and ongoing studies were men and women (postmenopausal or practicing an acceptable form of birth control) of any race, aged 18 through 80 years, with no history of hypersensitivity to statins, no evidence of severe liver or renal disease, no evidence of uncontrolled hypertension, and in some studies, no medical history of myocardial infarction, coronary angioplasty, coronary artery bypass graft, or unstable angina pectoris within 3 months of study entry. Excluded were patients who consumed excessive amounts of alcohol for the culture in which the study was conducted or who were taking prohibited lipid-lowering medications or medications associated with rhabdomyolysis, including erythromycin, cyclosporine, and gemfibrozil. In general, participants had baseline plasma LDL cholesterol levels greater than 4.13 mmol/L (160 mg/dL) and triglyceride levels lower than 4.52 to 6.79 mmol/L (400-600 mg/dL), consistent with a population of patients with hyperlipidemia.

SAFETY MEASURES

Of the 21 integrated studies, 17 were multicenter trials that used central laboratories; the remaining 4 studies were single-center trials that used local laboratory facilities. The designated laboratory for each study determined the normal range for each laboratory parameter. Evaluations were performed on fasting (12-hour minimum) venous blood samples drawn 6 to 18 hours after dosing. Full clinical laboratory evaluations (routine hematology and blood chemistry testing) were completed for each patient at each visit or at designated visits. Additional safety evaluations (including but not limited to measurement of plasma aspartate aminotransferase, alanine aminotransferase, and creatine phosphokinase levels) were performed at intervening visits. Physical examinations and electrocardiograms were done at baseline and at the end of the studies. At each visit, patients were queried about adverse experiences. Investigators rated adverse experiences as definitely, probably, possibly, probably not, or definitely not drug related. Adverse events recorded in investigators' terms were converted to preferred terms and body systems using version IV of the COSTART dictionary. 52 All randomized patients were included in the safety evaluation. All information collected was included, and missing data were not imputed.

Only persistent (2 consecutive) transaminase values more than 3 times the upper limit of the normal range or creatine phosphokinase values more than 10 times the upper limit of the normal range with concurrent muscle pain, tenderness, or weakness were summarized from the 23 ongoing trials. This safety evaluation is consistent with clinical practice.

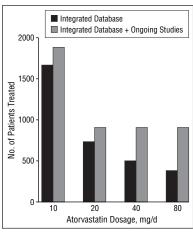


Figure 1. Number of patients treated with atorvastatin by dosage. Patients were counted more than once if they had received more than 1 doce

STATISTICAL METHODS

The sample size was not based on considerations of power but was judged to provide sufficient data to evaluate the safety of atorvastatin. The presentation of all safety information is descriptive, without statistical testing. Considering the low rate of adverse events with reductase inhibitors, the number of patients in the integrated database was not sufficient to provide meaningful statistical testing.

RESULTS

PATIENT EXPOSURE

Patients from the integrated database received atorvastatin for a total of 1845 patient-years of exposure. A total of 2502 patients received at least 1 dose of atorvastatin, 1721 (69%) had at least 6 months of exposure, and 1253 (50%) had at least 12 months of exposure. Although most studies allowed for the titration of dosage to achieve National Cholesterol Education Program target levels, more than two thirds of all patients were adequately treated with the 10-mg/d starting dosage (1083 patient-years). Consequently, most of the safety data come from patients receiving the 10-mg/d dosage. The primary focus of comparison was with other statins (simvastatin, lovastatin, and pravastatin) examined in the clinical trials (601 patient-years of exposure), as well as colestipol and

Table 1. Patient Demographic and Baseline Characteristics for Completed Studies

	Placebo (n = 110)	Atorvastatin (n = 2502)*	Other Statins† (n = 742)‡	Colestipol (n = 44)	Fenofibrate (n = 52)
Sex, No.(%)					
Men	70 (64)	1386 (55)	374 (50)	24 (55)	35 (67)
Women	40 (36)	1116 (45)	368 (50)	20 (45)	17 (33)
Race, No. (%)	, ,	. ,	, ,	, ,	, ,
White	101 (92)	2346 (94)	698 (94)	38 (86)	50 (96)
Other	9 (8)	156 (6)	44 (6)	6 (14)	2 (4)
Age, y		. ,	, ,	, ,	, ,
Median [mean (SE)]	55 [54 (1.1)]	57 [55 (0.2)]	58 [57 (0.4)]	58 [57 (1.8)]	53 [54 (1.2)]
No. (%)					
<70 y	104 (95)	2243 (90)	661 (89)	37 (84)	50 (96)
≥70 y	6 (5)	259 (10)	81 (11)	7 (16)	2 (4)
Body mass index, kg/m², median [mean (SE)]	26 [26 (0.3)]	27 [27 (0.1)]	27 [27 (0.1)]	26 [26 (0.4)]	27 [27 (0.4)]

^{*}Includes 93 patients who received placebo for 16 weeks and then atorvastatin for 36 weeks.

fenofibrate. When we included patients from the ongoing trials, a total of 4271 patients received atorvastatin, with more than 900 patients treated for at least 24 months (>3000 patient-years). Patient exposure is summarized in **Figure 1** for the 10-to 80-mg/d dosage range.

DEMOGRAPHIC CHARACTERISTICS

Patient characteristics at screening were similar across treatment groups (**Table 1**). Similar percentages of men (55%) and women (45%) were treated with atorvastatin. Approximately 10% of patients were 70 years of age or older. Participants were primarily white, with a mean age ranging from 54 to 57 years. As with the individual studies, overall mean baseline lipid values were generally well balanced across treatment groups and any differences did not appear to influence safety evaluations.

OVERALL SAFETY

Atorvastatin was well tolerated; fewer than 2% of the 2502 patients treated withdrew due to adverse effects related to treatment. Similarly, about 3% of patients treated with other statins withdrew due to adverse effects related to treatment. The adverse effects that most often led to withdrawal in atorvastatin-treated (as well as other statin-treated) patients were nausea, pain, depression, myalgia, abdominal pain, and abnor-

Table 2. Adverse Events Associated With Treatment Experienced by 2% or More of Patients Treated With Atorvastatin or Other Statins

	No. (%) of Patients			
Adverse Event	Atorvastatin (n = 2502)*	Other Statins† (n = 742)‡		
Constipation	73 (3)	39 (5)		
Flatulence	58 (2)	24 (3)		
Dyspepsia	56 (2)	14 (2)		
Abdominal pain	41 (2)	13 (2)		
Headache	37 (1)	14 (2)		
Myalgia	34 (1)	12 (2)		
Any event	508 (20)	179 (24)		

*Includes 93 patients who received placebo for 16 weeks and then atorvastatin for 36 weeks. †Simvastatin, lovastatin, and pravastatin. ‡Includes 67 patients who received placebo for 16 weeks and then lovastatin for 36 weeks.

mal liver function test results. These specific events occurred in fewer than 0.3% of atorvastatin-treated patients, with a similar distribution in patients treated with other statins. The withdrawal rate was not dosedependent.

In general, the overall adverse event profile for atorvastatin was similar to that observed with other statins. Approximately 20% of patients treated with atorvastatin and other statins had adverse events related to treatment. Specific adverse events associated with study medication occurred infrequently (≤5% of patients) in the groups treated with atorvastatin or other statins and are listed in **Table 2**. The placebo-

[†]Simvastatin, lovastatin, and pravastatin. ‡Includes 67 patients who received placebo for 16 weeks and then lovastatin for 36 weeks.

Table 3. Adverse Events Associated With Treatment Experienced by 1% or More of Atorvastatin-Treated Patients in Placebo-Controlled Studies

		Atorvastatin					
	Placebo (n = 270)	10 mg/d (n = 863)	20 mg/d (n = 36)	40 mg/d (n = 79)	80 mg/d (n = 94)	Combined Dosages (n = 1122)*	
Flatulence	6 (2)	11 (1)	1 (3)	1 (1)	1 (1)	15 (1)	
Myalgia	2 (1)	10 (1)	2 (6)	1 (1)	0 (0)	14 (1)	
Constipation	4 (1)	9 (1)	0 (0)	2 (3)	1 (1)	13 (1)	
Pain	1 (<1)	10 (1)	0 (0)	1 (1)	0 (0)	11 (1)	
Diarrhea	2 (1)	6 (1)	0 (0)	1 (1)	2 (2)	10 (1)	
Asthenia	1 (<1)	8 (1)	0 (0)	1 (1)	0 (0)	10 (1)	
Headache	5 (2)	7 (1)	0 (0)	0 (0)	2 (2)	9 (1)	
Dyspepsia	5 (2)	7 (1)	1 (3)	0 (0)	1 (1)	9 (1)	
Nausea	0 (0)	5 (1)	1 (3)	0 (0)	1 (1)	7 (1)	
Breast pain	0 (0)	6 (1)	0 (0)	0 (0)	0 (0)	6 (1)	
Any event	48 (18)	159 (18)	4 (11)	13 (16)	17 (18)	198 (18)	

^{*}Includes patients who received atorvastatin dosages of 2.5, 5, or 60 mg/d.

Table 4. One- vs Two-Year Overview of Safety				
	Incidence, %			
	First Year Second Year of Exposure			
	Atorvastatin	Lovastatin	Atorvastatin	Lovastatin
Deaths	<1	0	<1	0
Serious adverse events	8	7	10	14
Adverse events Withdrawals	6	7	3	2
Elevated alanine aminotransferase and aspartate aminotransferase levels*	<1	1	<1	1
Elevated creatine phosphokinose levels†	0	0	0	<1

^{*}More than 3 times the upper limit of the normal range at 2 consecutive time points.

Table 5. Drug-Associated* Adverse Events Occurring in 2% or More of Patients

	No. (%) of Patients				
	First Year o	f Exposure	Second Year of Exposure		
	Atorvastatin (n = 719)	Lovastatin (n = 193)	Atorvastatin (n = 623)	Lovastatin (n = 164)	
Digestive system	62† (9)	18 (9)	34 (5)	11 (7)	
Dyspepsia	17 (2)	2 (1)	5 (1)	2 (1)	
Flatulence	18 (3)	5 (3)	9 (1)	4 (2)	
Constipation	16 (2)	3 (2)	14 (2)	2 (1)	
Body as a whole	37† (5)	14† (7)	9 (1)	7 (4)	
Pain	13 (2)	3 (2)	3 (<1)	3 (2)	
Nervous system	22 (3)	6† (3)	12 (2)	3 (2)	
Musculoskeletal system	21 (3)	8 (4)	12 (2)	6 (4)	
Myalgia	14 (2)	4 (2)	7 (1)	4 (2)	
Skin and appendages	19† (3)	6 (3)	12 (2)	0 (0)	
Any event	139 (19)	40 (21)	76 (12)	24 (15)	

^{*}Possibly, probably, or definitely related to the study drug, or insufficient information. †Some patients had more than 1 type of event within this body system.

controlled phase II studies, a subset of the integrated database, captured adverse events by dosage. As shown in **Table 3**, no dosage-

related increase in adverse events was observed in these studies.

Adverse events within a given study were not captured in a man-

fore, the effect of length of exposure on the safety profile was determined by comparing the results of a 1-year safety study and its 1-year extension. This large safety study contributed 719 atorvastatintreated patients and 193 lovastatintreated patients to the integrated database. Patients were treated for 1 year (with all safety parameters analyzed at the end of the year) and then enrolled in a 1-year extension study (with safety parameters again analyzed at the end of the second year). The overall safety profile of atorvastatin was similar for years 1 and 2 and was similar to that seen with lovastatin (Table 4). In addition, rates of adverse events related to drug treatment were similar for years 1 and 2 of exposure to atorvastatin and were similar to those seen with lovastatin (Table 5).

ner that would allow for their analysis by discrete units of time. There-

Serious adverse events (hospitalization, cancer, overdose, and death) were reported by approximately 5% of the patients treated with atorvastatin and by approximately 7% of the patients treated with other statins in these studies. Only 2 patients (<1%) treated with atorvastatin had serious events possibly associated with treatment. One patient was admitted to the hospital with acute pancreatitis. He had received atorvastatin, 10 mg/d, for approximately 20 weeks. The patient recovered without sequelae. Cholestatic jaundice was reported in a patient with a history of diabetes mellitus and icterus after approxi-

[†]More than 10 times the upper limit of the normal range at 2 consecutive time points, with concurrent muscle pain, tenderness, or weakness.

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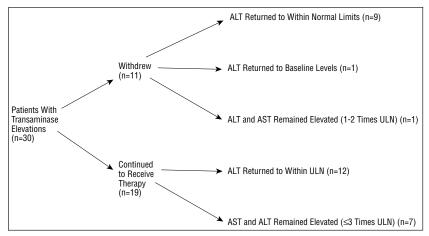


Figure 2. Disposition of patients with clinically important transaminase elevations. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; and ULN, upper limit of normal range.

mately 36 weeks of treatment with atorvastatin, 10 mg/d. This patient had markedly elevated transaminase levels and a positive result on a hepatitis A (IgG/IgM) antibody test. The hepatitis A (IgM) antibody test result was negative, indicating a previous hepatitis A infection. This patient's liver function test results returned to normal approximately 14 weeks after atorvastatin treatment was stopped, and he recovered without sequelae.

There were no significant changes in results of physical examinations, electrocardiograms, systolic and diastolic blood pressure evaluations, and urinalysis parameters in patients treated with atorvastatin.

LIVER

Among the more than 4000 patients treated with atorvastatin in both the integrated database of completed studies and all ongoing studies, persistent transaminase elevations greater than 3 times the upper limit of the normal range were reported for 30 patients (0.7%). Only 1 patient had a persistent elevation in aspartate aminotransferase level independent of an elevation in alanine aminotransferase level. Six additional patients in other statin and placebo control groups had persistent elevations. The only symptomatic patient was the patient with cholestatic jaundice described above. Of the 30 atorvastatin-treated patients with persistent transaminase elevations, only 11 (<0.3%) withdrew because of elevated hepatic enzyme

levels (Figure 2). Although the incidence of persistent elevations more than 3 times the upper limit of the normal range may be interpreted as dose-dependent, the incidence associated with dosages of 10 to 40 mg/d, which produced a reduction in LDL cholesterol levels of 41% to 55%, was similar to that seen with placebo (Table 6). Whether patients started receiving low or high dosages of atorvastatin, the majority of elevations occurred within 16 weeks of initiation of treatment with atorvastatin. Only about 3% of patients with an early, minor transaminase elevation experienced a subsequent persistent elevation greater than 3 times the upper limit of the normal range. Furthermore, in a long-term study with atorvastatin in which all patients were treated for a comparable period, no dosagerelated increase in minor elevations was observed.36

Single alanine aminotransferase elevations greater than 3 times the upper limit of the normal range were examined according to stratification by age ($<70 \text{ vs} \ge 70 \text{ years}$), sex, height (as an index of liver size; <169.4 vs ≥169.4 cm), alcohol consumption (none vs \geq 10 drinks per week), body mass index ($<27 \text{ vs} \ge 27 \text{ kg/m}^2$), and final LDL cholesterol level. None of these variables was related to the incidence of alanine aminotransferase elevations greater than 3 times the upper limit of the normal range. In addition, the impact of atorvastatin's LDL cholesterol lowering on these elevations was evaluated with LDL cholesterol lowering categorized as 15% or greater, 30% or greater, and 40% or

Table 6. Incide Transaminase by Atorvastati	Elevations	sistent*
	No. of Patients Treated	No. (%) o Patients With Elevations

	No. of Patients Treated	Patients With Elevations
Placebo	270	1 (0.4)
Atorvastatin by		
dosage, mg/d		
10	1843	3 (0.2)
20	892	2 (0.2)
40	811	5 (0.6)
80	888	20 (2.3)
Total	4271†	30 (0.7)

*Greater than 3 times the upper limit of the normal range at 2 or more consecutive visits. †Some patients received more than 1 dosage.

greater. No differences in the incidence of a single transaminase elevation greater than 3 times the upper limit of the normal range were noted at any level of efficacy.

MUSCLE

The rate of occurrence of all myalgia, arthralgia, and muscle disorders was similar among patients treated with placebo, atorvastatin, and other statins.

No patient experienced myoglobinuria or acute renal failure. Muscle symptoms with a single episode of a creatine phosphokinase elevation greater than 10 times the upper limit of the normal range were observed in only 3 patients treated with atorvastatin (2 receiving 10 mg/d and 1 receiving 20 mg/d) and occurred between 5 and 7 months of treatment. One patient, concurrent with the creatine phosphokinase elevation, had sore legs attributable to a marathon run. All 3 patients had a history of muscle pain, elevated baseline creatine phosphokinase values, and hyperthyroidism or hypothyroidism, the last a condition associated with elevated creatine phosphokinase values.⁵³ One patient treated with lovastatin, 80 mg/d, had received concurrent erythromycin treatment unintentionally and had persistent elevations in creatine phosphokinase levels greater than 10 times the upper limit of the normal range with concurrent muscle soreness. Lovastatin therapy was interrupted and creatine phosphokinase levels returned to normal within 2 weeks.

OTHER SERUM CHEMISTRY AND HEMATOLOGIC DETERMINATIONS

Median values for change from baseline for patients with at least 1 baseline measurement and 1 measurement during treatment were similar among patients treated with atorvastatin and other statins for fasting glucose level, creatinine level, hemoglobin level, total white blood cell count, differential cell count, and platelet count.

OTHER SAFETY EXPERIENCES

LDL Cholesterol Level

Twenty atorvastatin-treated patients had LDL cholesterol levels of 1.29 mmol/L (50 mg/dL) or lower for up to 24 months. No differences were noted in the adverse event profile of these patients, and no patient experienced transaminase elevations greater than 3 times the upper limit of the normal range.

Elderly

The safety profiles of 1365 patients younger than 70 years and 180 patients 70 years or older who had received atorvastatin for 1 year were compared. Approximately 20% in each age category experienced adverse events associated with drug treatment. The incidence of specific types of adverse events in each category was low (1% to 4%), with differences in frequencies between age categories of 2-fold or less. No age-related differences were noted in any other safety parameters.

Sex

The safety profiles of 832 men and 713 women who had received atorvastatin for 1 year were compared. Approximately 20% in each category experienced adverse events associated with drug treatment. Differences in the types of adverse events experienced varied by 1% to 2%. No sex-related difference were noted in any other safety parameters.

Pediatric

Very limited safety information on children was collected. The safety of atorvastatin was evaluated in 9 children (<14 years of age) with homozygous familial hypercholesterolemia at dosages up to 80 mg/d for 8 weeks. These patients had no unusual side effects. No significant laboratory-related abnormalities or serious adverse events were reported.

COMMENT

The superior efficacy of atorvastatin in patients with hypercholesterolemia has been reported elsewhere.4-6,32-37 Because the riskbenefit ratio of a more effective drug should be carefully considered. it was of interest to summarize the adverse event experience in a large number of patients, including data from ongoing trials. There were no adverse events reported in these studies that have not been previously reported with other statins. The incidence of drug-associated adverse events was not related to dosage or length of exposure to atorvastatin. The incidence rates of these adverse events and of withdrawals due to adverse events were similar to rates in previously published reports and were similar to rates associated with other drugs in the present report.7-31 Toxicology studies with atorvastatin have not described any new findings, and results are consistent with reports of other statins.54

The probable mechanism of atorvastatin's greater efficacy lies in a high first-pass effect in the liver, with a long half-life of 3-hydroxy-3-methoxyglutaryl-coenzyme A reductase inhibition.5 Therefore, we focused on the liver for the analysis of safety. The incidence of confirmed transaminase elevations greater than 3 times the upper limit of the normal range for atorvastatin throughout its entire dosage range was 0.7%. While direct comparison to other statins in large numbers of patients is not possible, this incidence is similar to those reported for other drugs of the class: 1% for simvastatin, 1.1% for fluvastatin, 1.9% for lovastatin, and 1.3% for pravastatin. 10,19,55,56 The

2.3% incidence associated with atorvastatin, 80 mg/d, is similar to that seen with lovastatin, 80 mg/d (1.9%). 10 The comparison of lipid reduction and changes on liver function test results indicates that, compared with other statins, atorvastatin produces a greater level of LDL cholesterol reduction with fewer persistent elevations in liver function test results. For example, a 40% reduction in LDL cholesterol level produced by lovastatin was associated with alanine aminotransferase elevations in 1.9% of patients, while a 40% reduction in LDL cholesterol level produced by atorvastatin was associated with alanine transaminase elevations in 0.2% of patients. 10,56 Most of the persistent elevations experienced in this program were self-limiting or resolved with dosage adjustments.

Monitoring of elevations did not identify possible liver damage (hepatitis, hepatic steatosis, etc). Cholestatic jaundice, an adverse event reported with other statins, occurred in only 1 patient who received atorvastatin; it was identified by the jaundice in a patient whose antibody test results indicated previous hepatitis infection.^{57,58} As with other statins, liver function test results should be monitored. In patients with persistent elevations in transaminase levels greater than 3 times the upper limit of the normal range, the dosage should be reduced or atorvastatin treatment should be discontinued.

As stated in a 1995 review of drug-associated transaminase elevations, some tests used to assess liver function are nonspecific, and abnormal results may sometimes indicate a harmless interaction between a drug and hepatic cells or may be caused by other maladies not related to the drug, such as nonspecific systemic infections.⁵⁹ An underlying low rate of elevations may indeed be present in this population, as evidenced by a 0.4% incidence of persistent alanine aminotransferase elevations greater than 3 times the upper limit of the normal range in placebo-treated patients. Since early minor transaminase elevations did not predict a subsequent greater risk of persistent elevations greater than 3 times the upper limit of the normal range, physicians should not be discouraged from using these drugs in patients with minor transaminase changes, although patients should be closely monitored and/or the dosage should be adjusted if transaminase values exceed 3 times the upper limit of the normal range.

No conclusive characterization of a drug-induced myopathy was evident in the current safety database for atorvastatin. The incidence of patients with a single creatine phosphokinase level greater than 10 times the upper limit of the normal range with concurrent muscle pain was consistent with rates reported for currently marketed statins.55 Patients participating in our evaluation of atorvastatin were excluded if they were receiving some medications known to interact with statins (cyclosporine, erythromycin, fibrates, nicotinic acid, and azole antifungal agents), thereby reducing the factors associated with an increased risk of the development of myopathy. The cause of drug-induced myopathy is unknown, perhaps the result of complex interactions associated with concurrently administered compounds, underlying disease, or genetic predisposition. 60 Consistent with prescribed practice established for other statins, atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of myopathy.

Although it is of benefit to decrease LDL cholesterol levels below 2.58 mmol/L (100 mg/dL) in patients with coronary artery disease, one concern was whether cholesterol levels could be reduced too far. No differences from controls in adverse events were noted in 20 patients maintaining LDL cholesterol levels below 1.29 mmol/L (50 mg/dL) for up to 24 months.

Statins have consistent and acceptable safety profiles, as evidenced by widespread exposure with currently marketed compounds: lovastatin, pravastatin, simvastatin, and fluvastatin. ⁷⁻³¹ Atorvastatin has superior lipid-lowering effects dosage to dosage, with results from 44 studies indicating that atorvastatin has a safety profile comparable to

other drugs of this class. Because of its superior efficacy profile and equivalent safety, atorvastatin has the most favorable risk-benefit ratio among the statin class.

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REFERENCES

- Ma PTS, Gil G, Sudhf TC, Bilheimer DW, Goldstein JL, Brown MS. Mevinolin, an inhibitor of cholesterol synthesis, induces mRNA for low density lipoprotein receptor in livers of hamsters and rabbits. Proc Natl Acad Sci U S A. 1986;83:8370-8374
- Naoumova RP, Marais AD, Mountney J, et al. Plasma mevalonic acid, an index of cholesterol synthesis in vivo, and responsiveness to HMG-CoA reductase inhibitors in familial hypercholesterolemia. Atherosclerosis. 1996;119:203-213.
- Kasim SE, LeBoeuf RC, Khilnani S, Tallapaka L, Dayananda D, Jen KL. Mechanisms of triglyceridelowering effect of HMG-CoA reductase inhibitor in a hypertriglyceridemic model, the Zucker obese rat. J Lipid Res. 1992;33:1-7.
- Nawrocki JW, Weiss SR, Davidson MH, et al. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor.
 Arterioscler Thromb Vasc Biol. 1995;15:678-689
- Bakker-Arkema RG, Best J, Fayyad R, et al. A brief review paper of the efficacy and safety of atorvastatin in early clinical trials. *Atherosclerosis*. 1997:131:17-23.
- Bakker-Arkema RG, Davidson MH, Goldstein RJ, et al. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA*. 1996;275:128-133.
- Dujovne CA, Chremos AN, Pool JL, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results, IV: additional perspectives on the tolerability of lovastatin. Am J Med. 1991;91 (suppl 1B):25S-30S.
- Mantell G, Burke T, Staggers J. Extended clinical safety profile of lovastatin. Am J Cardiol. 1990; 66:11B-15B.
- Bradford RH, Shear CL, Chremos AN, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results, I: efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. *Arch Intern Med.* 1991;151:43-49.
- Bradford RH, Shear CL, Chremos AN, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results: 2-year efficacy and safety follow-up. Am J Cardiol. 1994;74:667-673.
- Lovastatin Study Groups I-IV. Lovastatin 5-year safety and efficacy study. Arch Intern Med. 1993; 153:1079-1087.

- Hunninghake DB, Mellies MJ, Goldberg AC, et al. Efficacy and safety of pravastatin in patients with primary hypercholesterolemia, II: once-daily versus twice-daily dosing. Atherosclerosis. 1990;85: 219-227
- Hunninghake DB, Knopp RH, Schonfeld G, et al. Efficacy and safety of pravastatin in patients with primary hypercholesterolemia, I: a doseresponse study. Atherosclerosis. 1990;85:81-89.
- Hoogerbrugge N, Mol MJ, Van Dormaal JJ, et al.
 The efficacy and safety of pravastatin, compared to and in combination with bile acid binding resins, in familial hypercholesterolaemia. J Intern Med. 1990;228:261-266.
- Beigel Y, Brook G, Eisenberg S, et al. Efficacy and safety of pravastatin once daily in primary moderate hypercholesterolemia: the Israeli experience. Isr J Med Sci. 1993;2:272-277.
- Pravastatin Multicenter Study Group II. Comparative efficacy and safety of pravastatin and cholestyramine alone and combined in patients with hypercholesterolemia. Arch Intern Med. 1993; 153:1321-1329.
- Simons LA, Nestel PJ, Clifton P, Janus ED, Simons J, Parfitt A. Treatment of primary hyper-cholesterolaemia with pravastatin: efficacy and safety over 3 years. *Med J Aust.* 1992;157:584-589.
- Simons LA. Simvastatin in severe primary hypercholesterolemia: efficacy, safety, and tolerability in 595 patients over 18 weeks. *Clin Cardiol.* 1993; 16:317-322.
- Pedersen TR, Berg K, Cook TJ, et al. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. Arch Intern Med. 1996;156: 2085-2092.
- Emmerick J, Aubert I, Bauduceau B, et al. Efficacy and safety of simvastatin (alone or in association with colestyramine): a 1-year study in 66 patients with type II hyperlipoproteinaemia. Eur Heart J. 1990;11:149-155.
- Keech A, Collins R, MacMahon S, et al. Threeyear follow-up of the Oxford Cholesterol Study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. Eur Heart J. 1994;15:255-269.
- Farnier M, Bonnefous F, Debbas N, Irvine A. Comparative efficacy and safety of micronized fenofibrate and simvastatin in patients with primary type IIa or IIb hyperlipidemia. *Arch Intern Med.* 1994; 154:441-449.
- Molgaard J, Lundh BL, von Schenck H, Olsson AG. Long-term efficacy and safety of simvastatin alone and in combination therapy in treatment of hypercholesterolaemia. *Atherosclerosis*. 1991;91 (suppl):S21-S28.
- Boccuzzi SJ, Bocanegra TS, Walker JF, Shapiro DR, Keegan ME. Long-term safety and efficacy profile of simvastatin. Am J Cardiol. 1991;68:1127-1131.
- Stalenhoef AF, Lansberg PJ, Kroon AA, et al. Treatment of primary hypercholesterolaemia: short-term efficacy and safety of increasing doses of simvastatin and pravastatin: a double-blind comparative study. *J Intern Med.* 1993;234:77-82.
- The Simvastatin Pravastatin Study Group. Comparison of the efficacy, safety and tolerability of simvastatin and pravastatin for hypercholesterolemia. Am J Cardiol. 1993;71:1408-1414.
- 27. Peters TK. Safety profile of fluvastatin. *Br J Clin Pract Symp Suppl.* 1996;77A:20-23.
- 28. Davidson MH. Fluvastatin Long-term Extension

- Trial (FLUENT): summary of efficacy and safety. *Am J Med.* 1994;96(suppl 6A):41S-44S.
- Hsu I, Spinler SA, Johnson NE. Comparative evaluation of the safety and efficacy of HMG-CoA reductase inhibitor monotherapy in the treatment of primary hypercholesterolemia. *Ann Pharma*cother. 1995;29:743-759.
- Shepherd J. Fibrates and statins in the treatment of hyperlipidaemia: an appraisal of their efficacy and safety. Eur Heart J. 1995;16:5-13.
- Walker JF, Tobert JA. The clinical efficacy and safety of lovastatin and MK-733: an overview. Eur Heart J. 1987;8(suppl E):93-96.
- Bertolini S, Bittolo Bon G, Campbell LM, et al. The efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. Atherosclerosis. 1997;130:191-197.
- Heinonen TM, Schrott JH, McKenney JM, et al. Atorvastatin, a new HMG-CoA reductase inhibitor as monotherapy and combined with colestipol. J Cardiovasc Pharmacol Ther. 1996;1:117-122
- Dart A, Jerums G, Nicholson G, et al. A multicenter, double-blind, 1-year study comparing the safety and efficacy of once-daily atorvastatin with that of simvastatin in patients with hypercholesterolemia. Am J Cardiol. 1997;80:39-44.
- Heinonen TM, Stein E, Weiss SR, et al. The lipidlowering effects of atorvastatin, a new HMG-CoA reductase inhibitor: results of a randomized, double-blind study. Clin Ther. 1996;18:853-863.
- Davidson M, McKenney J, Stein E, et al. Comparison of 1-year efficacy and safety of atorvastatin-versus-lovastatin in primary hypercholesterolemia: Atorvastatin Study Group I. Am J Cardiol. 1997;79:1475-1481.
- Ooi TC, Heinonen T, Alaupovic P, et al. Efficacy and safety of a new hydroxymethylglutarylcoenzyme A reductase inhibitor, atorvastatin, in patients with combined hyperlipidemia: comparison with fenofibrate. *Arterioscler Thromb Vasc Biol.* 1997;17:1793-1799.
- Heinonen TM, Schrott H, Broyles F, Shurzinske L, Black DM. An evaluation of estrogen and atorvasatin, a new HMGRI, in hypercholesterolemic postmenopausal women. Presented at the 66th Congress of the European Atherosclerosis Society; July 13, 1996; Florence, Italy.
- Gmerek A, Yang R, Bays H, et al. Atorvastatin causes a dose-dependent reduction in LDL-C and

- triglycerides. Presented at the 66th Congress of the European Atherosclerosis Society; July 13, 1996: Florence, Italy.
- Seiler K-U, Wolffenbuttel BHR, Mahla G, et al. Comparison of atorvastatin, a new HMG-CoA reductase inhibitor, with pravastatin and simvastatin. *Atherosclerosis*. 1994;109(special issue):314.
- Best JD, Nicholson GC, O'Neal DN, Kotowicz MA, Tebbutt NC, Chan K-W, Sanders KM. Atorvastatin and simvastatin reduce elevated cholesterol in non-insulin dependent diabetes. *Diab Nutr Metab.* 1996;9:74-80.
- Reckless JPD, Stirling CA, Cole D, Sethi S, Williams C, Gould B. Influence of 2 hydroxymethylgluteryl coenzyme-A reductase inhibitors on postprandial lipoprotein and apo B-48 metabolism. Presented at the 66th Congress of the European Atherosclerosis Society; July 13, 1996; Florence, Italy.
- McCormick L, Black D. A 12-week study comparing atorvastatin with niacin patients with hypertriglyceridemia with or without hypercholesterolemia. Presented at the 66th Congress of the European Atherosclerosis Society; July 13, 1996; Florence, Italy.
- 44. Nawrocki J, Schwartz S, Fayyad R, Simunovic L. Atorvastatin, a new HMG-CoA reductase inhibitor is safe and effective in NIDDM patients with hyperlipidemia. Presented at the 66th Congress of the European Atherosclerosis Society; July 13, 1996; Florence, Italy.
- Heinonen T, Black D. Atorvasatin monotherapy and combination therapy in the treatment of severe hypercholesterolemia. *Atherosclerosis*. 1995;115 (suppl):S20.
- 46. Wagner B, Huwel D, Rehorst D, Smilde JG, Wunderlich J, Black D. A 1-year treat-to-target study of atorvastatin vs pravastatin in risk-stratified hypercholesterolemic patients. Presented at the 66th Congress of the European Atheroslcerosis Society; July 13,1996; Florence, Italy.
- Marais AD, Firth JC, Bateman M, Byrnes P, Martens C, Mountney J. Atorvastatin: an effective lipid-modifying agent in familial hypercholesterolaemia. Arterioscler Thromb Vasc Biol. 1997;17: 1527-1531.
- Dujovne CA, Harris WS, Altman R, Overhiser RW, Cunningham JJ, Black DM. Changes in hemorheology and atherothrombotic parameters by improving serum lipids in atorvastatin. Presented at

- the 66th Congress of the European Atherosclerosis Society; July 13,1996; Florence, Italy.
- Marais D, Naoumova RP, Firth JC, Penny C, Neuwirth CKY, Thompson GR. Decreased production of low density lipoprotein by atorvastatin after apheresis in homozygous familial hypercholesterolemia. J Lipid Res. 1997;38:2071-2078
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA. 1993;269:3015-3023.
- National Diabetes Data Group. Classification and diagnosis of diabetes and other areas of glucose intolerance. *Diabetes*. 1979;28:139-157.
- COSTART: Coding Symbols for Thesaurus of Adverse Reaction Terms. 4th ed. Washington, DC: Food and Drug Administration, Dept of Health and Human Services; 1993.
- Goldman J, Matz R, Mortimer R, Freeman R. High elevations of creatine phosphokinase in hypothyroidism: an isoenzyme analysis. *JAMA*. 1977;238: 325-326
- Ciaravino V, Kropko ML, Rothwell CE, Hovey CA, Theiss JC. The genotoxicity profile of atorvastatin, a new drug in the treatment of hypercholesterolemia. *Mutat Res.* 1995;343:95-107.
- 1996 Physicians' Desk Reference.
 Montvale, NJ: Medical Economics Co; 1996:765-769, 1699-1703, 1775-1779, 2267-2269.
- Lipitor [package insert]. Ann Arbor, Mich: Parke-Davis Pharmaceutical Research Division, Warner-Lambert Co: 1997.
- Ballare M, Campanini M, Catania E, Bordin G, Zaccala G, Monteverde A. Acute cholestatic hepatitis during simvastatin administration. *Recenti Prog Med.* 1991;82:233-235.
- Tobert JA, Shear CL, Chremos AN, Mantell GE. Clinical experience with lovastatin. Am J Cardiol. 1990:65:23F-26F.
- Jick H. Drug-associated asymptomatic elevations of transaminase in drug safety assessments. *Pharmacotherapy*. 1995;15:23-25.
- Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatingemfibrozil combination therapy. *JAMA*. 1990; 264:71-75.