Efficacy and Long-Term Adverse Effect Pattern of Lovastatin

Jonathan A. Tobert, MB, PhD

The efficacy of lovastatin, a potent inhibitor of HMG CoA reductase, has been established by numerous studies. At doses of 40 mg administered twice daily, lovastatin produces a mean reduction in total plasma cholesterol of 33%, attributable to a reduction in low-density lipoprotein cholesterol of 41%. The drug also produces a mean increase in high-density lipoprotein cholesterol of 9%, and a reduction in the high- and low-density lipoprotein cholesterol ratio of 44%.

The serious reported adverse effects of lovastatin are myopathy (0.5%) and asymptomatic but marked and persistent increases in transaminases (1.9%). Both are reversible when therapy is discontinued. Myopathy has occurred mainly in patients with complicated histories who were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil or niacin. In an ongoing long-term safety study, 744 patients have received lovastatin for an average duration of 2.5 years up to March 1988. Fifteen patients (2.0%) have been withdrawn because of drug-attributable adverse events: raised transaminases (9), skin rash (2), gastrointestinal symptoms (2), myopathy (1) and insomnia (1). No effect of the drug on the human lens has been observed up to the date mentioned above.

Lovastatin has been available in the United States since September 1987. By March 1988, the drug had been prescribed for approximately 250,000 patients. This clinical experience has confirmed the tolerability observed in clinical trials. The good adverse-effect profile of lovastatin is thus now supported both by a substantial body of data in patients treated for over 2 years in clinical trials, and by experience in clinical use with a large number of patients since the drug has been available for prescription.

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From the Department of Clinical Research, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey.

Address for reprints: Jonathan A. Tobert, MB, PhD, Department of Clinical Research, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065.

Lovastatin is a potent inhibitor of HMG CoA reductase,[1] which has been available in the United States since September 1987 for the treatment of primary hypercholesterolemia. The remarkable efficacy of lovastatin as a lipid-lowering drug was demonstrated initially in normocholesterolemic volunteers,[2] subsequently in small studies in patients with heterozygous familial hypercholesterolemia[3–6] and nonfamilial hypercholesterolemia[5,7] and later in 5 multicenter controlled studies involving over 1,000 patients. The first 2 large studies[8,9] used a double-blind placebo-controlled design; subsequently, lovastatin was compared with cholestyramine (open study),[10] probucol (double-blind study)[11] and later gemfibrozil (double-blind study).[12]

The efficacy and mechanism of action of lovastatin have been evaluated in detail in several recent reviews.[13–15] In brief, the effect of lovastatin on plasma cholesterol is similar in patients with familial and nonfamilial forms of hypercholesterolemia (Fig. 1). The mean percent reductions in total plasma and low-density lipoprotein (LDL) cholesterol in lovastatin-treated patients were approximately twice those in cholestyramine-treated patients when both drugs were administered at full dosage (Fig. 2). When data from approximately 200 patients who received dietary therapy plus lovastatin, 40 mg twice daily, in 4[8–11] of the multicenter studies were pooled, the following mean changes from baseline (dietary therapy alone) were obtained: total plasma cholesterol, −33%; total plasma triglycerides, −24% (median); LDL cholesterol, −41%; very low density lipoprotein (VLDL) cholesterol, −35% (median); high-density lipoprotein (HDL) cholesterol, +9%; LDL/HDL cholesterol ratio, −44%; apolipoprotein B, −29%; apolipoprotein A-I, +9%; and apolipoprotein A-II, +18%.

In his comprehensive 1988 review,[13] Grundy concluded that lovastatin and other HMG CoA reductase inhibitors are a promising new class of cholesterol-lowering drugs that should lower the risk of coronary heart disease by 50 to 60%, while appearing to be remarkably free of serious side effects, with the rare exception of rhabdomyolysis. Grundy also pointed out that there was insufficient long-term experience to rule out the possibility of new adverse events appearing during prolonged use in large patient populations. However, a substantial amount of data on long-term use has now been accumulated, much of which is unpublished. The purpose of this review is to summarize the published and unpublished data available on both the short- and long-term adverse effects of lovastatin as of March 1988. Lovastatin was first administered to patients with hypercholesterolemia in

1982.[16] The maximal duration of therapy in any patient up to March 1988 was therefore 5 years. Five years' experience is available in only a few patients, but 200 patients have reached 3 years with lovastatin therapy; 700, 2 years; and 1,000, 1 year. The total number of patients in clinical trials exceeded 4,000 in March 1988, and will exceed 8,000 by December 1988.

The clinical adverse events reported with an incidence of 1% or more in short-term (up to 6 months) controlled clinical studies are summarized in Table I.[17] In these studies, the participating clinics rated the adverse events reported by patients as definitely, probably, possibly, probably not or definitely not drug related.

The clinical adverse events that were thus reported as being possibly, probably or definitely drug related are shown in Table II. The adverse events were usually mild and transient, and as shown later, rarely caused the discontinuation of treatment. The most serious reported adverse effects of lovastatin are myopathy, and asymptomatic but marked and persistent increases in transaminases. Myopathy is not listed in either Tables I or II because it has been observed in only 1[10] of 756 patients participating in controlled (vs uncontrolled) studies. As will be described in detail, it usually occurred in patients with complicated medical histories who were receiving concomitant therapy with immunosuppressant drugs, gemfibrozil or niacin, which were not used during the controlled studies. Persistent increases in transaminases greater than 3 times the upper limit of normal were also not observed in the controlled studies, which is probably a consequence of the fact that this effect usually occurred after at least 3 months of therapy.

MYOPATHY

Myopathy, defined as muscle pain or weakness, or both, plus a creatine kinase (CK) value of at least 10 times the upper limit of normal, has been reported in 17 (<0.5%) of approximately 4,000 patients who had participated in clinical trials up to March 1988.[10,16,18-20] CK usually increased to between 8,000 and 30,000 U/liter, with the highest reported value at 223,000 U/liter. There is very little correlation between the magnitude of the CK elevation and the intensity of the symptoms. In 2 of the 17 patients, both of whom had a cardiac transplant and were receiving immunosuppressant therapy including cyclosporine, a frank rhabdomyolysis that precipitated renal failure occurred.[18-20] These 2 patients and the other 15 recovered promptly when therapy with lovastatin was discontinued. The duration of therapy before the onset of myopathy varied from a few weeks to over 2 years. Some of the late-appearing cases are probably related to changes in concomitant therapy.

The clinical features of these 17 patients with myopathy, and their concomitant therapy with cyclosporine, gemfibrozil and niacin are listed in Table III. It is evident that most of these patients have a variety of complicating factors, particularly cardiac transplantation with immunosuppressant therapy. However, the phenomenon has been observed in 4 patients with no particular complicating factors other than ischemic heart disease, 3 of whom were taking none of the 3 concomitant therapies in question. Most of the patients were women, whereas the patient population as a whole is about two-thirds men. Three patients had various biliary disorders that could have reduced biliary clearance, an important route of elimination for lovastatin.[17] Concomitant therapy with immunosuppressant drugs including cyclosporine with gemfibrozil or niacin, or a combination, appears to great-

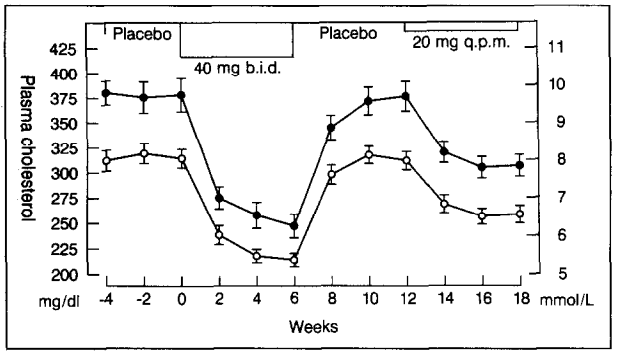

FIGURE 1. Effect of lovastatin on plasma cholesterol at minimal (20 mg/day) and maximal (80 mg/day) recommended doses.[8,9] *Filled circles*, study in familial hypercholesterolemia[9]; *open circles*, study in nonfamilial hypercholesterolemia.[8] Each point (± standard deviation) represents the mean of 15 to 21 observations. (Adapted with permission from *Ann Intern Med*[9] and *JAMA*.[8])

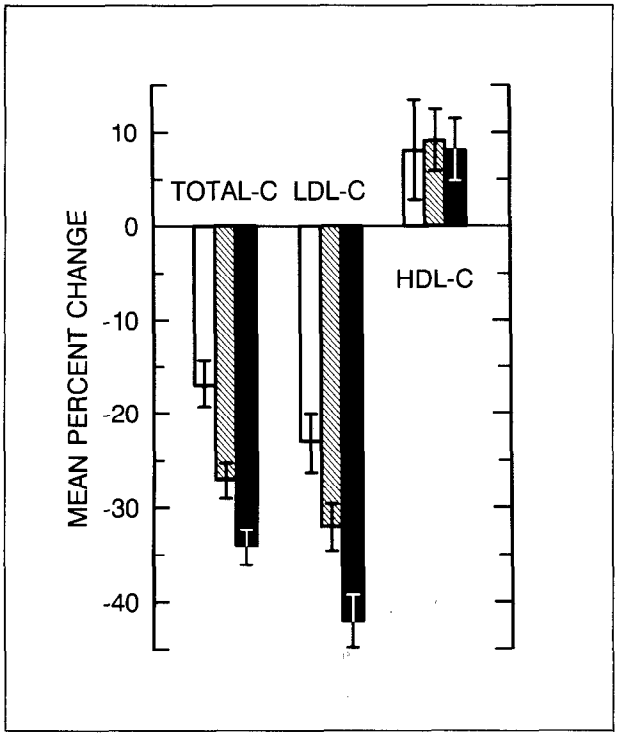

FIGURE 2. Mean percent changes with 95% confidence intervals in total cholesterol (C), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol.[10] Cholestyramine 12 g twice daily (n = 88) is represented by *clear bars*, lovastatin 20 mg twice daily (n = 85) by *hatched bars*, and lovastatin 40 mg twice daily (n = 88) by *black bars*. (Reproduced with permission from *JAMA*.[10])

ly increase the risk of myopathy (Table IV). When none of these concomitant therapies was present, the incidence of myopathy was less than 1 in 500. Although niacin was involved in only 3 patients, its role as a risk factor is supported by the fact that in all 3 cases myopathy occurred a few weeks after it had been added to the therapeutic regimen of patients taking lovastatin for several months.

It thus appears that myopathy occurring during therapy with lovastatin is usually the result of a complex interaction between drug, disease and concomitant therapy. In 6 of the 17 patients, plasma samples for drug assay were available at the time of the myopathy, and in all of these patients the concentrations of active metabolites of lovastatin (i.e., total plasma HMG CoA reductase inhibitory activity) were elevated to several times the expected level. Neither the mechanism of this elevation nor the mechanism of the ultimate effect of lovastatin on muscle cells is currently known. In some cases, the elevations may have been due to an interaction between cyclosporine and lovastatin: Both lovastatin[17] and cyclosporine[21] are excreted predominantly in the bile, and cyclosporine has been reported to produce cholestasis.[22] In 6 patients who had cardiac transplants, were receiving cyclosporine therapy and did not have myopathy, the plasma levels of active metabolites of lovastatin were also elevated to an average of about 4 times the expected value. On the other hand, the plasma concentrations of active metabolites of lovastatin were not usually elevated in patients receiving gemfibrozil or niacin. The apparent interaction with gemfibrozil may therefore be pharmacodynamic, as opposed to pharmacokinetic, in nature. Although not well documented for gemfibrozil, fibric acid derivatives can cause myopathy themselves.[23,24] Niacin, however, has not been reported to affect muscle and it is not clear why it should precipitate a myopathy in lovastatin-treated patients.

The risk of myopathy can be minimized by certain precautions. First, caution is indicated in patients taking immunosuppressive drugs, fibric acid derivatives or niacin (in lipid-lowering doses). In patients who have transplants, the option to discontinue immunosuppressive therapy does not exist, and these patients frequently have hypercholesterolemia[25,26] and accelerated atherosclerosis.[27,28] The use of bile acid sequestrants is not advisable because they may interfere with the absorption of the immunosuppressants. Therefore, the use of lovastatin may be justified; however, the maximal dosage should not exceed 20 mg/day. This low dosage appears to produce an increased therapeutic response, commensurate with the increase in plasma levels (Murphy F, personal communication). Fibrates and niacin produce marked reductions in VLDL cholesterol and triglycerides, but have smaller effects on LDL cholesterol,[29] whereas lovastatin markedly reduces LDL and VLDL cholesterol, while producing smaller reductions in triglycerides. Therefore, depending on which lipid abnormality is of most concern, it may be possible to eliminate one or the other drug from the therapeutic regimen. Second, all patients, whether receiving concomitant therapy or not, should be advised to report promptly any unexplained muscle pain or weakness. CK should then be measured to confirm the diagno-

TABLE I Clinical Adverse Events (%) with an Incidence of 1% or More in Patients Treated with Lovastatin in Controlled Clinical Studies[8–11,17]

	Lovastatin (n = 613)	Placebo (n =82)	Cholestyramine (n = 88)	Probucol (n = 97)
Duration of treatment (wks)	12–22	6	12–22	14
Nausea	5	4	9	6
Dyspepsia	4	—	14	3
Heartburn	2	—	8	—
Abdominal pain/cramps	6	2	6	5
Diarrhea	6	5	8	10
Constipation	5	—	34	2
Flatulence	6	2	22	2
Muscle cramps	1	—	1	—
Myalgia	2	1	—	—
Dizziness	2	1	—	1
Headache	9	5	5	8
Rash/pruritus	5	—	5	—
Blurred vision	2	—	1	3
Dysgeusia	1	—	1	—

TABLE II Clinical Adverse Events (%) with an Incidence of 1% or More for Lovastatin Reported as Possibly, Probably or Definitely Drug Related in Controlled Clinical Trials[8–11]

	Lovastatin (n = 613)	Placebo (n =82)	Cholestyramine (n = 88)	Probucol (n = 97)
Duration of treatment (wks)	12–22	6	12–22	14
Nausea	2	1	6	3
Dyspepsia	2	—	10	2
Abdominal pain	2	—	3	1
Diarrhea	3	2	6	8
Constipation	3	—	28	2
Flatulence	5	2	14	2
Headache	2	—	—	2
Rash	2	—	1	—

TABLE III Clinical Features of 17 Patients in Clinical Trials with Myopathy, and Their Concomitant Therapy with Immunosuppressive Drugs Including Cyclosporine, or with Gemfibrozil or Niacin

	F	M	Concomitant Therapy		
			Cyclosporine	Gemfibrozil	Niacin
Cardiac transplant	1	4	X (5)	X (2)	X (1)
Untreatable myxedema	1			X	
Primary biliary cirrhosis	1				
Acute cholelithiasis	1				
Gilbert's syndrome		1			X
Renal insufficiency	2			X (2)	
Sjogren's syndrome	1			X	
On LDL apheresis		1			
No particular features	4				X (1)
Total	11	6	5	6	3

LDL = low-density lipoprotein; X = drug taken concomitantly.

sis. If CK is markedly elevated, lovastatin should be discontinued. Third, therapy with lovastatin should be temporarily withheld in acute medical or surgical conditions predisposing to rhabdomyolysis or renal failure.

HEPATIC EFFECTS

Small increases in transaminases, particularly serum glutamic pyruvic transaminase (alanine transaminase), sometimes occur, often within 6 weeks of starting therapy.[8-10,16] Such increases are often transient and have not required withdrawal of therapy. The same phenomenon has been reported with most other lipid-lowering drugs.[29] In a large clinical trial comparing lovastatin and cholestyramine,[10] the 2 drugs raised transaminase levels equally. Because cholestyramine is not absorbed from the gastrointestinal tract, small increases in transaminases may be a response to changes in lipid metabolism, rather than a direct effect of lipid-lowering drugs on the liver. A more important finding is that 1.9% of the patients treated with lovastatin in clinical trials have had asymptomatic but marked and persistent transaminase increases, again particularly serum glutamic pyruvic transaminase.[15,17] When the drug was discontinued, transaminases returned to pretreatment levels, usually within a few weeks. In contrast to the small increases in transaminases that appear early in therapy, the larger increases have usually occurred between 3 and 12 months after starting therapy. Alkaline phosphatase remained essentially normal, indicating that the effect is most probably hepatocellular rather than cholestatic. A liver biopsy specimen was obtained in 1 of these patients, which showed areas of focal hepatitis.[17] Eleven patients have been rechallenged; 6 had a positive rechallenge, 2 had a positive rechallenge followed by a negative rechallenge, and 3 had a negative rechallenge. The increase in transaminase levels in the patients with positive rechallenges was delayed for at least 4 weeks. It is believed that a reduction of alcohol consumption may have been instrumental in producing some of the negative rechallenges. All the patients who have had increased transaminase levels have been asymptomatic throughout. The lack of symptoms, together with the delayed response on rechallenge, indicates that the effect is not a hypersensitivity phenomenon. As with myopathy, the mechanism is presently unknown. Although not seen in clinical trials, the possibility that symptomatic liver injury could occur if therapy were continued in the face of increasing serum transaminase levels requires the regular monitoring of these enzymes. They should be measured before therapy, at intervals of 4 to 6 weeks during the first 15 months of therapy, and periodically thereafter.[17]

TABLE IV Added Risk Effect of Concomitant Therapy with Immunosuppressive Drugs Including Cyclosporine, Gemfibrozil or Niacin, or a Combination

Concomitant Drugs	Patients with Myopathy	Patients at Risk	Incidence (%)
Cyclosporine	2		
Cyclosporine and gemfibrozil	2	18	28
Cyclosporine and niacin	1		
Gemfibrozil	4	80	5
Niacin	2	120	2
	11		
None of the above	6	4,000	0.15
Total	17	4,200	0.4

SPECIAL SAFETY STUDIES

Lovastatin has not been reported to have an effect on reported adrenal[2,6,8,9,30,31] or testicular[2,8,9,32] steroidogenesis, or on human spermatogenesis.[32] It has not been shown to increase biliary lithogenicity, and may reduce it.[33] Measurements of visual-evoked response and nerve

TABLE V Lovastatin Long-Term Adverse-Effect Study, Interim Data to March 1988: Patient Outcome

	No.	%
Entered study	744	100.0
Continuing	670	90.1
Lost to follow-up	43	5.8
Discontinued due to		
Drug-attributable adverse events	15	2.0
Other adverse events	15	2.0
Poor response	1	0.1
Total	744	100.0

TABLE VI Lovastatin Long-Term Adverse-Effect Study, Interim Data to March 1988—Patients Discontinued Because of Drug-Attributable Adverse Events

Adverse Event	No.	%
Raised transaminases	9	1.2
Rash	2	0.3
G.I. symptoms	2	0.3
Myopathy	1	0.1
Insomnia	1	0.1
Total	15	2.0

G.I. = gastrointestinal.

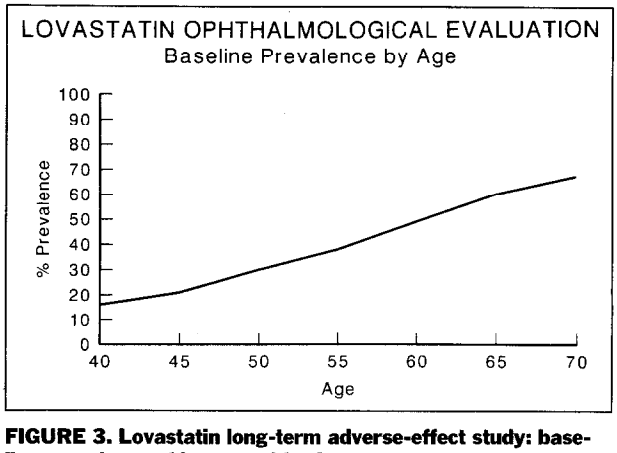

FIGURE 3. Lovastatin long-term adverse-effect study: baseline prevalence of lens opacities by age.

conduction velocity and electromyography have revealed no neurotoxic effects.[17] Because pediatric studies have not yet been performed, lovastatin is not currently recommended for use in children.[17]

LONG-TERM EXPERIENCE

Most of the long-term data on lovastatin has been provided by a long-term safety study, in which almost all the patients who participated in the original 4 multicenter controlled studies[8–11] have continued taking lovastatin. The 23 participating clinics (United States 17, Canada 5, Finland 1) are listed under Participants. The 744 patients in this study have been taking lovastatin for an average of 2.5 years up to March 1988. This population is at very high risk of coronary disease: 60% have familial hypercholesterolemia, accounting for the very high baseline plasma cholesterol of 359 mg/dl. Forty-eight percent have coronary or peripheral atherosclerosis, including 40% with a history of angina or myocardial infarction, or both, and 20% having undergone coronary bypass surgery or angioplasty. Seventy-two percent of these patients were titrated up to the maximal recommended dose of 80 mg/day, reflecting the severity of their hypercholesterolemia. For the same reason, approximately half have taken concomitant lipid-lowering agents, usually resins, temporarily or on a long-term basis. The outcome in these patients as of March 1988 is summarized in Table V. Therapy in 15 patients (2.0%) was discontinued because of drug-attributable adverse events and another 15 (2.0%), including 10 patients who died, discontinued the study because of adverse events unlikely to be related to lovastatin.

The drug-attributable adverse events (i.e., those adverse events considered to be probably causally related to lovastatin) are summarized in Table VI. Therapy in most of these patients was discontinued because of asymptomatic increases in transaminase levels that persisted over 3 times the upper limit of normal. Therapy in a very few patients was discontinued because of skin rashes or gastrointestinal symptoms, and in 1 patient because of insomnia and in another because of myopathy. (A second patient also had myopathy, but was able to continue taking lovastatin after concomitant therapy with gemfibrozil was discontinued.) All 15 of those withdrawn from therapy had no sequelae after lovastatin was stopped. All of these patients first experienced the relevant adverse event within the first 16 months of therapy. Thus, there is no evidence to date for new adverse events appearing after prolonged use. The 2.0% drug-attributable discontinuation rate is low by any standards, and demonstrates again the good tolerability and adverse-effect pattern of the drug.

Ten of the 15 patients who discontinued therapy because of adverse events unlikely to be related to lovastatin died. Nine of these deaths were caused by acute coronary events and 1 by carcinoma of the pancreas. Eight of the 9 who died from coronary disease had previous coronary disease. The coronary death rate (0.5/100 patient years) has thus been quite low to date, considering the high-risk nature of the study population. In the Lipid Research Clinics Program-Coronary Primary Prevention Trial study results,[34] the beneficial effect of cholestyramine on coronary risk was not seen until 2 years of therapy had elapsed. It will be interesting to see if coronary mortality becomes even lower in our study now that most patients are past the 2-year mark.

Therapy in the remaining 5 patients was discontinued because of breast cancer, peripheral neuropathy, depression, deep vein thrombosis and weight gain. Breast cancer was diagnosed in 1 patient after 4 months of therapy, and almost certainly was present at the time the patient entered the study. No other cause was discovered for the peripheral neuropathy, but this condition is not uncommon and frequently idiopathic. As indicated, a special study to detect neurotoxic effects yielded negative results. Therefore, the single case of peripheral neuropathy is probably a spontaneous event unrelated to lovastatin. Conditions that are not uncommon must be expected to occur occasionally in a large patient population followed for a prolonged period of time. Thus, there is no reason to attribute any of these single case events to lovastatin.

When given in doses greatly exceeding the maximal human therapeutic dose, lovastatin can cause cataracts in dogs.[35] In addition, MER-29 (triparanol), a late-stage cholesterol biosynthesis inhibitor developed by another laboratory, had to be withdrawn from clinical use in 1962 because it caused a syndrome consisting of cataracts, alopecia and ichthyosis.[36] For these reasons, ophthalmologic examinations formed an important part of the evaluation of the long-term safety of lovastatin in this study. As discussed elsewhere,[15] slit-lamp data from the earlier studies[8,9] are probably biased because the baseline ophthalmologic examinations were performed before lovastatin was found to produce cataracts in dogs. To avoid this problem, the analysis of lens opacities is confined to the 2 later studies[10,11] and their extensions; these started after the discovery of cataracts in dogs, and thus could not be subject to this bias. Figure 3 shows the baseline prevalence of lens opacities in this patient population. The baseline prevalence increases in an approximately linear manner with increasing age, so that by age 60 years, approximately half the patients in our population had lens opacities. Most of these opacities were small, peripheral and of no clinical significance. The baseline prevalence in these 470 patients was 35.2%. At the last available examination, these patients had been taking lovastatin for an average duration of 19 months, and the prevalence of lens opacities increased by 1.2 to 36.4%. On the basis of the aging of the study population, an increase in prevalence of 2.5% (1.6%/year) would be expected (calculated from the data shown in Figure 3). Therefore, these data do not indicate any effect of lovastatin on the human lens. Nevertheless, until this and other studies are completed, annual slit-lamp examinations are recommended as a precaution.[17]

EXPERIENCE OUTSIDE CLINICAL TRIALS

Lovastatin has been available for prescription in the United States since September 1987. By March 1988, physicians had prescribed the drug for approximately

250,000 patients. This clinical experience has confirmed the results of the clinical trials. There have been a few reports of bleeding or increased prothrombin time, or both, in patients taking warfarin.[17] Whether these events are caused by the drug is not clear, but in any event, prothrombin time should be closely monitored in patients taking coumarin anticoagulant therapy concomitantly with lovastatin.

CONCLUSIONS

In summary, lovastatin is a well-tolerated and very effective lipid-lowering agent. With the exception of rare cases of myopathy usually occurring in a complicated clinical setting, and asymptomatic increases in transaminases, lovastatin has caused very few clinical problems. The good adverse-effect profile of the drug is now supported both by a substantial body of data in patients treated for over 2 years in clinical trials and by experience with a large number of patients given lovastatin outside clinical trials.

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PARTICIPANTS

The clinics and principal investigators participating in the lovastatin long-term safety study are as follows: *United States*—Cardiovascular Research Institute, Cincinnati, Ohio (Evan A. Stein, MD, PhD); Heart Disease Prevention Clinic, Minneapolis, Minnesota (Donald B. Hunninghake, MD); New England Deaconess Hospital, Boston, Massachusetts (Robert S. Lees, MD); Oregon Health Sciences University, Portland, Oregon (D. Roger Illingworth, MD, PhD); The Methodist Hospital and Baylor College of Medicine, Houston, Texas (Antonio M. Gotto, MD, DPhil); University of Kansas Medical Center, Kansas City, Kansas (Carlos A. Dujovne, MD); George Washington University, Washington, DC (John C. LaRosa, MD, Valery T. Miller, MD); Medical Col-

lege of Georgia, Augusta, Georgia (Elaine B. Feldman, MD); Long Island Jewish Medical Center, Manhasset, New York (Paul Samuel, MD); Cardiovascular Research Institute, San Francisco, California (Richard J. Havel, MD); Northwest Lipid Research Clinic, University of Washington, Seattle, Washington (Robert H. Knopp, MD); Northwestern University School of Medicine, Chicago, Illinois (Neil J. Stone, MD); University of California Department of Medicine, La Jolla, California (Daniel Steinberg, MD, Joseph L. Witztum, MD); Washington University School of Medicine, St. Louis, Missouri (Gustav Schonfeld, MD); The Johns Hopkins Hospital, Baltimore, Maryland (Peter O. Kwiterovich, MD); Columbia University, New York, New York (Ira Goldberg, MD); University of Miami, Miami, Florida (Ronald B. Goldberg, MD). *Canada*—Shaughnessy Hospital, Vancouver, British Columbia (Jiri Frohlich, MD); McMaster University, Hamilton General Hospital, Hamilton, Ontario (Maurice A. Mishkel, MD); Clinical Research Institute of Montreal, Montreal, Quebec (Jean Davignon, MD); University of Western Ontario, London, Ontario (Bernard Wolfe, MD); Clinical Research Center, Dalhousie University, Halifax, Nova Scotia (Meng Tan, MD). *Finland*—Helsinki University Central Hospital, Helsinki, Finland (Matti J. Tikkanen, MD).