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Reduction of LDL Cholesterol by 25% to 60% in Patients With Primary Hypercholesterolemia by Atorvastatin, a New HMG-CoA Reductase Inhibitor

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Abstract

Abstract This 6-week, double-blind clinical trial evaluated lipid parameter responses to different dosages of atorvastatin in patients with primary hypercholesterolemia. Atorvastatin is a new 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor under development. After completing an 8-week placebo-baseline dietary phase, 81 patients were randomly assigned to receive either placebo or 2.5, 5, 10, 20, 40, or 80 mg atorvastatin once daily for 6 weeks. Plasma LDL cholesterol reductions from baseline were dose related, with 25% to 61% reduction from the minimum dose to the maximum dose of 80 mg atorvastatin once a day. Plasma total cholesterol and apo B reductions were also dose related. Previously, reductions in LDL cholesterol of the magnitude observed in this study have been seen only with combination drug therapy. In this study, atorvastatin was well tolerated by hyperlipidemic patients, had an acceptable safety profile, and provided greater reduction in cholesterol than other previously reported HMG-CoA reductase inhibitors.

Key Words:

- atorvastatin
- coronary disease
- LDL cholesterol
- hydroxymethylglutaryl CoA reductase
- hypercholesterolemia

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The risk for coronary heart disease (CHD), the number one cause of death in Western societies, is increased in individuals with elevated concentrations of plasma LDL cholesterol.[1] National Cholesterol Education Program (NCEP) and European Atherosclerosis Society (EAS) guidelines for prevention of CHD emphasize the importance of reducing LDL cholesterol levels in patients at risk for CHD as well as in the general population.[1,2,3] If dietary and lifestyle changes are unsuccessful in

bringing plasma cholesterol concentrations down to acceptable ranges, drug therapy is often warranted. Although several types of lipid-regulating drugs are available, combination drug therapy may be necessary in some patients to achieve target plasma cholesterol levels.[4]

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors effectively reduce plasma cholesterol levels in patients with hypercholesterolemia.[5,6] These drugs decrease cholesterol synthesis by competitively inhibiting HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in the cholesterol biosynthetic pathway. Doses of 20 mg/d lovastatin or pravastatin or 10 mg/d simvastatin generally reduce plasma LDL cholesterol levels by about 20% to 30%.[5,7,8,9] Higher doses of these drugs can reduce LDL cholesterol levels by as much as 40%.[5] Treatment with HMG-CoA reductase inhibitors also produces increases of about 5% to 10% in plasma HDL cholesterol and reductions of about 10% to 20% in triglycerides.[5] Millions of patients have taken HMG-CoA reductase inhibitors to lower plasma cholesterol levels over the past 10 years.

Atorvastatin, a recently synthesized member of the HMG-CoA reductase inhibitor class of lipid-modifying drugs, is currently being evaluated in clinical trials. Atorvastatin is a chiral, calcium salt of a pentasubstituted pyrrole.[10] In laboratory animals, atorvastatin effectively lowers plasma LDL cholesterol as well as VLDL cholesterol and triglyceride levels.[11] Acute- and multiple-dose (13-week) toxicology evaluations indicate that atorvastatin has an acceptable margin of safety between doses causing little or no toxicity at the anticipated human dose.[12] In early clinical dose-ranging studies with healthy human volunteers, atorvastatin in a single dose or 2-week multiple doses was well tolerated.[13] The dose-ranging study reported here is the first study of atorvastatin in patients with primary hypercholesterolemia.

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Methods

Patients

Outpatients with elevated LDL cholesterol (>4.14 but <6.21 mmol/L) and normal levels of triglycerides (<3.39 mmol/L) entered an 8-week, dietary, placebo-baseline phase at one Canadian and five US centers. Eligible patients were aged 18 to 70 years with a body mass index ≤30 kg/m^2. Patients were ineligible if they had uncontrolled hypertension (diastolic blood pressure >95 mm Hg), diabetes mellitus and/or other metabolic endocrine disease, active liver disease, or hepatic or renal dysfunction. Women of childbearing potential were also ineligible. Study participants could consume no more than 14 oz/wk of ethanol equivalents and could not concurrently take drugs known to affect lipid levels or known to interact with the study medication.

Informed Consent

Identical protocols were submitted to and approved by an institutional review board for each center. Prior to entering the study, each patient provided witnessed, written informed consent.

Dietary Counseling and Monitoring

Upon entering the baseline phase and continuing throughout the double-blind phase of the study, patients were counseled on the use of the National Institutes of Health (NIH) NCEP Step 1 Diet.[1] This diet limits dietary cholesterol to <300 mg/d and total fats to <30% of total calories, with <10% of total calories from saturated fats, 10% from polyunsaturated fats, and 10% to 15% from monounsaturated fats. During the week before selected clinic visits, patients recorded their daily food and drink intakes in a diary for 3 consecutive days. Food record rating (FRR) scores[14] were determined from these patient diaries at weeks −8, −2, 2, and 6 to evaluate dietary compliance. Analysis of the average American diet yields an FRR score of >20, whereas a score of <10 is expected for Step 1 diets. The Chicago Center for Clinical Research, Chicago, Ill, coordinated the dietary aspects of the study. At weeks −2 and 6, the Chicago Center performed a Nutritional Data System dietary constituent analysis using information from the 3-day dietary diary.

Baseline Phase

Upon entering the placebo-baseline phase, patients were instructed to take two placebo capsules once daily at bedtime. Each patient's plasma lipid profile was determined at weeks −4, −2, and −1. To qualify for randomization into the double-

blind period at week 0, patients had to have LDL cholesterol values >4.14 and <5.69 mmol/L at both weeks −2 and −1, with the lower value within 15% of the higher value; triglyceride values <3.39 mmol/L at both visits; and an FRR score <15 at week −2 or −1.

Double-blind Treatment Phase

At the end of the 8-week, placebo-baseline phase, eligible patients were randomly assigned to receive placebo or 2.5-, 5-, 10-, 20-, 40-, or 80-mg doses of atorvastatin once daily for 6 weeks. Patients were assigned to treatment according to a randomization code prepared by the Parke-Davis Biometrics Department. Patients received either one bottle containing 2.5-, 5-, 10-, 20-, or 40-mg atorvastatin capsules and one bottle with matching placebo capsules; two bottles with atorvastatin 40-mg capsules; or two bottles with placebo capsules. Patients were instructed to take one capsule from each bottle once a day at bedtime. The appearance of the capsules did not change throughout the baseline and double-blind phases of the study. Compliance with the study medication was judged by a capsule count at each clinic visit. During the active treatment phase, both patients and investigators were blinded to the study medication and to plasma lipid concentrations.

Clinic visits took place at 2-week intervals during the double-blind phase, and patient lipid profiles were determined at each visit. Patients prepared dietary diaries for visits at weeks 2 and 6. Complete clinical laboratory determinations were done at the randomization visit and at the final visit at week 6. To monitor safety, clinical laboratory tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], creatine phosphokinase [CPK], alkaline phosphatase, and total bilirubin) were performed at every visit. Because there was no extension to the treatment period, investigators could return patients to their standard therapy at study completion.

Laboratory Analyses

Using standardized procedures, Medical Research Laboratories, Cincinnati, Ohio, performed lipid and clinical laboratory measurements for all sites. This laboratory was certified for standardization of lipid analyses during this study, as specified by the Standardization Program of the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute.[15] After the patients fasted overnight for a minimum of 12 hours, blood was drawn for lipid profiles and collected in evacuated tubes (Vacutainers) containing EDTA. Total plasma cholesterol and triglycerides were determined enzymatically with the Hitachi 737 analyzer.[16]Plasma HDL cholesterol was determined enzymatically after LDL cholesterol and VLDL cholesterol were selectively removed from the plasma sample by heparin and magnesium chloride precipitation.[17] LDL cholesterol concentration was estimated by the Friedewald formula (LDL cholesterol=total cholesterol−HDL cholesterol−triglycerides/5).[18] Direct LDL cholesterol was determined by ultracentrifugation (β-quantification) at weeks −1 and 6.[19] Long-term precision was monitored by using a stabilized plasma pool, and the coefficient of variation (CV) was 2.5% during this study. Apo A-I and apo B were determined at weeks −1 and 6 by fixed-rate nephelometry.[20] [21] The precision for both assays was measured by using two frozen serum pools. For apo A-I the between-run CVs were approximately 3.4% and 3.2% for the high and low pools, respectively. For apo B, the CVs were 3.2% and 2.6%, respectively. Lp(a) was qualitatively assessed at weeks −1 and 6 by competitive enzyme-linked immunosorbent assay,[22] and long-term precision was monitored with two frozen serum pools. The CV of the low pool was 7%, whereas the high pool had a CV of 8.5%.

Safety Evaluation

Before entering the placebo-baseline phase, patients received a complete physical examination and clinical laboratory evaluation. At each visit, patients were asked about their health status and adverse events. Each patient's blood pressure and weight were determined, and clinical laboratory data were evaluated.

Data Analysis

The sample size for this study was chosen to detect a significant linear dose effect for a 25% difference between the mean percent changes of placebo and the highest dose of atorvastatin. Statistical analyses were performed with the SAS statistical package.[23] Analyses included data from all randomized patients, with at least one baseline and one double-blind measurement of the parameter of interest regardless of patient compliance with the protocol. ANOVA was used to evaluate the effect of atorvastatin on the percent change from baseline in LDL cholesterol, the primary efficacy parameter. Baseline was defined as the mean of each patient's LDL cholesterol values at weeks −2, −1, and 0, with the analysis of percent change from baseline being performed at the last visit of the double-blind period. On the basis of this model, a sequential, "step-down" trend test was performed to determine the significance of the drug effect. Dunnett's test was used to compare each atorvastatin dose group to placebo when the percent change was not monotonic across the dose levels. An additional model for LDL cholesterol by ANCOVA added baseline LDL cholesterol as a covariate and tested the interaction of the treatment group and covariate. All analyses were done using a two-sided significance level of 5%.

The same analyses were performed for secondary efficacy parameters except that the baseline value for apo A-I, apo B, and Lp(a) was the mean of measurements at weeks −1 and 0 and that for LDL cholesterol, as measured by β-quantification, was the measurement at week −1.

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Results

Patient Characteristics and Disposition

Although overall patient characteristics were similar for the seven treatment groups, the small number of patients randomized to each treatment group resulted in some differences. Median patient body mass index was 26 kg/m^2, with a range of treatment group median values from 25 to 28 kg/m^2. Treatment group median age ranged from 49 to 63 years with an overall patient median age of 54 years. Neither the placebo nor the 40-mg treatment group included patients aged 65 years or older compared with two or three in each of the other treatment groups. Sixteen of the 81 patients were women. All treatment groups included two or three women except the 80-mg treatment group that contained only men. Most patients (95%) in the study were white. Mean baseline LDL and total cholesterol levels were 4.86 and 6.98 mmol/L, respectively.

Of the 81 patients randomized to double-blind treatment, 78 (96%) completed the study. One patient who was receiving 2.5 mg atorvastatin withdrew on day 13 due to indigestion and flu (not thought by the investigator to be related to the study drug), and two patients were withdrawn after 2 days because they had been incorrectly entered. The efficacy analyses included data from the 79 patients with double-blind data. No patients were excluded from the efficacy evaluations because of protocol variations. Most patients (97%) were judged to have been compliant with the study medication, as determined by capsule counts at clinic visits. Dietary compliance as judged by FRR scores was acceptable. Treatment group FRR scores were relatively constant from week −2 to week 6 except in the 20-mg atorvastatin treatment group, whose mean FRR score increased from 7.3 at week −2 to 12.1 at week 6.

Plasma Lipids, Lipoproteins, and Apolipoproteins

Mean percent reductions from baseline in LDL cholesterol increased with increasing doses of atorvastatin. Patients treated with 2.5 mg atorvastatin had mean reductions of 25%; those treated with 80 mg atorvastatin had mean reductions of 61% (Table 1⇓). Approximately 90% of the maximum reduction in plasma LDL cholesterol levels was achieved by week 2 of the double-blind phase in atorvastatin-treated patients (Figure⇓).

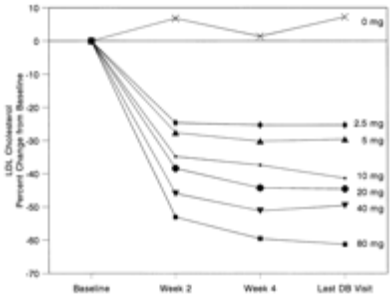

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Figure 1.

Line plot of reductions in LDL cholesterol by atorvastatin as a function of dose and time.

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Table 1.

Adjusted Mean Percent Changes From Baseline in Lipid and Apolipoprotein Values at Last Visit of Double-blind Phase

Table 1.

Adjusted Mean Percent Changes From Baseline in Lipid and Apolipoprotein Values at Last Visit of Double-blind Phase

Parameter	Placebo (n=12)	Atorvastatin Treatment Group, mg					
		2.5 (n=11)	5 (n=13)	10 (n=11)	20 (n=10)	40 (n=11)	80 (n=11)
LDL cholesterol							
Percent change	7.6	−25.0[1]	−29.0[1]	−41.0[1]	−44.3[1]	−49.7[1]	−61.0[1]
SE	2.7	2.8	2.6	2.8	2.9	2.8	2.8
Total cholesterol							
Percent change	4.8	−17.3[1]	−21.8[1]	−30.3[1]	−34.5[1]	−37.8[1]	−45.7[1]
SE	2.3	2.4	2.2	2.4	2.5	2.4	2.4
HDL cholesterol							
Percent change	−2.5	5.4	8.0	4.5	12.1[2]	−2.6	3.4
SE	3.4	3.6	3.3	3.5	3.7	3.6	3.5
Triglycerides							
Percent change	−0.7	−9.9	−24.6[2]	−14.2	−33.2[2]	−24.9[2]	−27.2[2]
SE	6.3	6.6	6.1	6.6	6.9	6.7	6.6
Apo A-I							
Percent	−3.5	2.8	7.1[2]	4.6	6.8[2]	−2.2	0.8

Parameter	Placebo (n=12)	Atorvastatin Treatment Group, mg					
		2.5 (n=11)	5 (n=13)	10 (n=11)	20 (n=10)	40 (n=11)	80 (n=11)
change							
SE	2.4	2.6	2.3	2.6	2.7	2.6	2.6
Apo B							
Percent change	5.8	−16.6[1]	−21.9[1]	−34.4[1]	−36.3[1]	−40.9[1]	−50.3[1]
SE	2.8	2.9	2.7	2.9	3.1	3.0	2.9
Lp(a)							
Percent change	7.1	4.9	−4.0	4.3	−7.9	2.8	−14.2[2]
SE	5.4	5.7	5.2	5.6	5.9	5.7	5.6

- SE indicates standard error.

- 1 Significantly different than placebo by sequential, step-down, dose-response trend test, $P<.05$.
- 2 Significantly different than placebo by Dunnett's test, $P<.05$.

Values of LDL cholesterol as estimated by the Friedewald formula were generally in agreement with those determined by ultracentrifugation. At the last visit of the double-blind phase, mean percent changes from baseline in LDL cholesterol for patients treated with 2.5, 5, 10, 20, 40, or 80 mg atorvastatin or placebo were −22%, −28%, −37%, −45%, −48%, −59%, and 3%, respectively, as determined by ultracentrifugation, compared with −25%, −29%, −41%, −44%, −50%, −61%, and 8%, respectively, as estimated with the Friedewald formula.

Atorvastatin-treated patients had dose-related reductions from baseline in total plasma cholesterol and apo B (Table 1⇑). Patients treated with 2.5 and 80 mg atorvastatin had reductions in total cholesterol of 17% and 46%, respectively, and reductions in apo B of 17% and 50%, respectively. Atorvastatin reduced plasma triglyceride concentrations at every dose level, but without any consistent dose trend. Reductions in triglycerides from baseline values were 25% or greater for patients treated with 5, 20, 40, and 80 mg atorvastatin. There was no consistent pattern in the percent changes from baseline for HDL cholesterol, apo A-I, or Lp(a).

Safety

The study treatments were well tolerated. All patients who entered the double-blind phase were included in the safety evaluations. Thirty-four (42%) of the 81 patients (4 [33%] on placebo; 30 [43%] on atorvastatin) had adverse events. Of these patients, 85% reported adverse events of mild or moderate intensity. For patients treated with atorvastatin, the most frequent adverse event was the common cold (5.8%), followed by headache (4.3%) (Table 2⇓). There was no consistent atorvastatin dose relationship for adverse events. One patient who was receiving 2.5 mg atorvastatin had a serious adverse event (broken ankle) that was not considered drug related. In addition, one patient who was also in the 2.5-mg treatment group withdrew from the study at week 2 due to adverse events (mild indigestion and moderate flu symptoms) not attributed to the study drug.

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Table 2.

Most Frequent Adverse Events, by Number of Patients

Clinically significant changes in laboratory parameters were not dose related. One patient in each of the atorvastatin-treatment groups had bilirubin values one to two times the upper limit of the reference range (1.1 mg/dL) at week 4 or 6; prior to randomization, three of these patients had levels in this elevated range. No patients had clinically significant elevations of CPK. One patient treated with 40 mg atorvastatin had elevations of three to four times the upper limit of the reference range (22 U/L for AST; 25 U/L for ALT) in AST and ALT values that returned to normal 2 to 3 weeks after the end of the study.

There was a dose-related increase in the number of patients with mild elevations of ALT and AST. At week 6, ALT elevations of one to two times the upper limit of the reference range were observed for 1 patient in both the 5- and 10-mg treatment groups, for 3 in the 20-mg treatment group, for 4 in the 40-mg treatment group, and for 6 in the 80-mg group. While fewer patients had AST elevations, the trend was similar. No other dose-related changes in laboratory parameters were seen.

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Discussion

Atorvastatin has a rapid onset of action; approximately 90% of the LDL cholesterol reduction from baseline occurred within the first 2 weeks of treatment (Figure⇑). Increasing doses of atorvastatin produced progressive increases in efficacy. Reductions of 25% to 61% in LDL cholesterol were achieved with once-daily doses of 2.5 to 80 mg atorvastatin.

In addition to LDL cholesterol, apo B, the major protein component of LDL cholesterol, was reduced from baseline by 18% to 51% in a dose-related manner. As with other drugs in this class, there were no clinically important changes in HDL cholesterol, apo A-I, or Lp(a). Although the patients who were selected for this study had elevated LDL cholesterol levels, most patients had normal plasma triglyceride concentrations (<3.39 mmol/L) at randomization. Triglycerides were reduced from baseline by 9% to 32%, but with no apparent dose trend.

Atorvastatin was well tolerated in this study. Of 81 patients randomized to treatment, 78 completed the study. No drug-related serious adverse events were reported. There was a dose-related increase in the number of patients with mild elevations (one to two times the reference range) of AST and ALT. Similar transaminase elevations have been reported with other HMG-CoA reductase inhibitors[5] and lipid-lowering drugs such as cholestyramine[24] and may result from changes in hepatic lipid metabolism. In this study, one atorvastatin-treated patient had clinically significant AST and ALT elevations of three to four times the reference range, but these values returned to normal at study follow-up.
The recently released NCEP II recommendations include reducing LDL cholesterol to <3.36 or <2.59 mmol/L for patients with elevated LDL cholesterol and two other risk factors or with elevated LDL cholesterol and preexisting CHD, respectively. Adequate treatment often requires combination therapy, with the associated risk of increased side effects. In this clinical trial, greater reductions from baseline in LDL cholesterol levels were observed in atorvastatin-treated patients than have been previously reported in patients treated with other lipid-regulating drugs.[25] At the end of this study (week 6), patients treated with 80 mg atorvastatin achieved a 61% mean reduction from baseline in LDL cholesterol. Although a 50% to 60% reduction in LDL cholesterol can be achieved by combining several lipid-modifying drugs,[25] no single agent has been reported to produce this result. This study suggests that atorvastatin, with its enhanced efficacy, may provide adequate therapy for a large number of dyslipidemic patients, including those previously treated with multiple therapies.

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Acknowledgments

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