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Efficacy of Alternate-Day Dosing Versus Daily Dosing of Atorvastatin

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Background: Atorvastatin is a synthetic inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. In placebo-controlled trials, it has been shown to achieve significant dose-dependent reductions in low-density lipoprotein cholesterol, total cholesterol, and triglycerides. This trial compared the efficacy of daily atorvastatin administration with that of alternate-day dosing.

Methods: This was a randomized, prospective, nonblinded, controlled clinical trial. Fifty-four patients with low-density lipoprotein cholesterol of 100 to 200 mg/dL were enrolled. Baseline fasting lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), liver function tests (aspartate transaminase and alanine aminotransferase), and creatine kinase were drawn. Patients were randomized to three atorvastatin dose groups. Group I received 10 mg of atorvastatin every day, Group II received 10 mg every other day, and Group III received 20 mg every other day. After 6 weeks of treatment with atorvastatin, fasting lipid profiles, liver function tests, and creatine kinase concentrations were redrawn. Compliance to treatment was assessed at each visit.

Results: Of the 54 patients enrolled, 46 completed the study. All three regimens significantly reduced total cholesterol and low-density lipoprotein cholesterol compared to baseline. No statistically significant differences existed between the three groups in regards to total, or a percentage, decrease in total cholesterol and low-density lipoprotein cholesterol at 6 weeks compared to baseline. All regimens were well tolerated and none of the patients had a significant elevation of liver enzymes or creatine kinase during the course of the study.

Conclusion: Alternate-day dosing of atorvastatin is an efficacious and safe alternative to daily dosing.

Key words: atorvastatin, total cholesterol, low-density lipoprotein.

Atorvastatin, a synthetic inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, exhibits nonlinear pharmacokinetics, as reflected by a greater than proportional increase in maximum plasma concentrations (Cmax) and area under the concentration-time curves (AUC) (1). This is presumably due to saturation of the hepatic first-pass metabolism; however, this saturable process does not appear to alter the half-life of the drug, which is independent of the dose (1). Daily doses of atorvastatin (2.5–80 mg) produced a steady-state Cmax (1.95–252 μg/L) within 2 to 4 hours after administration. These plasma concentrations produced AUC values of 25.2 to 1293 μg/L/hr from time 0 to infinity (AUC∞). Due to this high, first-pass metabolism, the drug has an absolute bioavailability of 12% (2). Atorvastatin is 98% protein-bound in plasma and has a mean elimination half-life of approximately 14 hours with a range of 11 to 57.6 hours, which is longer than that of all the other available HMG-CoA reductase inhibitors (1,2).

Less than 2% of the parent drug and metabolites are excreted renally. Hepatic metabolism of atorvastatin

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produces orthohydroxylated and parahydroxylated derivatives, and various oxidation products (2). Atorvastatin is metabolized to at least two active, long-lasting metabolites with potencies similar to the parent compound. Accordingly, 70% of the HMG-CoA reductase inhibition with atorvastatin has been attributed to these active metabolites (2). Although atorvastatin has a half-life of 14 hours, due to its active metabolites, the half-life of its HMG-CoA reductase inhibition is as long as 20 to 30 hours (2). For that reason, this is an ideal agent for alternate-day dosing.

In the elderly, some accumulation of the drug and active metabolites is evident, without providing additional low-density lipoprotein cholesterol (LDL-C) reduction (3,4). Accordingly, alternate-day therapy may be better suited for such patients than the current daily dosing. Although it is expected that alternate-day dosing will reduce measures of systemic exposure (ie, Cmax, AUC), pharmacokinetic and pharmacodynamic studies have established that atorvastatin dose, rather than Cmax or AUC, is more likely a better index of hepatic exposure to the drug and its active metabolites (1). This is expected because all of the HMG-CoA reductase inhibitors are active primarily in the liver, the site of cholesterol synthesis.

All investigations of atorvastatin therapeutic efficacy have been conducted by the use of daily dosing. This investigation studied the therapeutic effects of alternate-day dosing and compared the efficacy and safety between alternate-day dosing and daily dosing of atorvastatin.

Methods

Informed consent was obtained from 54 patients to participate in a randomized, prospective, nonblinded, controlled clinical trial. Patients with LDL-C of 100 to 200 mg/dL were recruited from the general medicine, cardiology, and cholesterol clinics at the University of California, Irvine Medical Center. All patients enrolled in this study met NCEP guidelines for treatment. Patients with abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK) were excluded. Patients taking any cholesterol-lowering medications, or who were pregnant or breast-feeding, or had hypersensitivity or intolerance to any HMG Co-A reductase inhibitors were also excluded. Baseline fasting lipid profiles, liver function tests, and CK concentrations were drawn. Patients were randomized to three groups.

Table 1. Baseline and Changes from Baseline in Total Cholesterol, Triglycerides, LDL-C, and HDL-C after 6 Weeks

	Atorvastatin 10 mg Every Day (Group I)	Atorvastatin 10 mg Every Other Day (Group II)	Atorvastatin 20 mg Every Other Day (Group III)	*P*, *P**, *P*†, *P*‡
Baseline				
Total cholesterol (mg/dL)	228 ± 44	240 ± 44	224 ± 32	NS; NS; NS; NS
Triglycerides (mg/dL)	178 ± 106	179 ± 108	238 ± 240	NS; NS; NS; NS
LDL-C (mg/dL)	139 ± 29	153 ± 30	120 ± 38	.03; NS; NS; .008
HDL-C (mg/dL)	49 ± 14	49 ± 10	53 ± 19	NS; NS; NS; NS
After 6 weeks				
Total cholesterol (mg/dL)	189 ± 32	194 ± 42	164 ± 12	0.1; NS; .07; .04
Triglycerides (mg/dL)	156 ± 84	175 ± 122	220 ± 256	NS; NS; NS; NS
LDL-C (mg/dL)	110 ± 25	109 ± 37	78 ± 25	.03; NS; .01; .02
HDL-C (mg/dL)	51 ± 11	49 ± 12	48 ± 16	NS; NS; NS; NS
After 6 weeks (change from baseline)				
Total cholesterol (mg/dL)	(40 ± 45)	(47 ± 51)	(66 ± 27)	NS; NS; NS; NS
Triglycerides (mg/dL)	(27 ± 74)	(10 ± 65)	(39 ± 39)	NS; NS; NS; NS
LDL-C (mg/dL)	(30 ± 40)	(44 ± 47)	(41 ± 23)	NS; NS; NS; NS
HDL-C (mg/dL)	2 ± 10	(1 ± 9)	8 ± 11	.09; NS; NS; .03
After 6 weeks (percent change from baseline)				
Total cholesterol (%)	(15 ± 21)	(18 ± 22)	(28 ± 9)	NS; NS; NS; NS
Triglycerides (%)	(3 ± 44)	(1 ± 75)	(19 ± 19)	NS; NS; NS; NS
LDL-C (%)	(17 ± 32)	(26 ± 30)	(32 ± 12)	NS; NS; NS; NS
HDL-C (%)	5 ± 28	(4 ± 19)	11 ± 26	NS; NS; NS; NS

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; *P* value is a comparison amongst groups I, II and III. *P** value is for a comparison between groups I and II. *P*† value is for a comparison between groups I and III. *P*‡ value is for a comparison between groups II and III.

Group I received 10 mg of atorvastatin every day; Group II received 10 mg every other day, and Group III received 20 mg every other day. After 6 weeks of treatment with atorvastatin, the fasting lipid profiles, liver function tests, and CK concentrations were redrawn. Compliance to treatment was assessed at each visit.

Differences between the three groups were compared using two-way analysis of variance (ANOVA), repeated measures. Data are presented as mean ± standard deviation. A P value of $<.05$ was considered statistically significant.

Results

Of the 54 patients enrolled in the three groups, 46 completed the study: Group I, 23 patients enrolled, 19 completed; Group II, 20 patients enrolled, 18 completed; and Group III, 11 patients enrolled, 9 completed. No statistically significant differences existed in the groups in regards to age (56 ± 10 vs. 56 ± 11 vs. 59 ± 12 years, respectively), gender, or baseline weight in pounds. The six patients that did not complete the study did not keep their 6-week follow-up appointments. Since we were not able to perform post-treatment lipoprotein analysis in these 6 patients, they were considered as dropouts.

Patients in Group III had a lower LDL-C concentration at baseline compared to Group II (Table 1). All three regimens significantly reduced total cholesterol and LDL-C compared to baseline (Table 1; Fig. 1). Atorvastatin, at 20 mg every other day, resulted in a significantly higher increase in HDL-C (Table 1; Fig. 1). Group III had the lowest LDL-C at 6 weeks compared to Groups I and II. This was expected, as Group III had the lowest baseline LDL-C. No statistically significant differences existed among the groups in regards to total or a percentage decrease in total and LDL-C at 6 weeks compared to baseline. Nine patients (two in Group I, five in Group II, and two in Group III) had diabetes mellitus. No statistically significant differences existed among the groups in regards to the incidence of diabetes mellitus.

All regimens were well tolerated, and none of the patients had a significant elevation of liver enzymes or creatine kinase (Table 2). There were no complaints of musculoskeletal pain, and all patients complied with the study therapy.

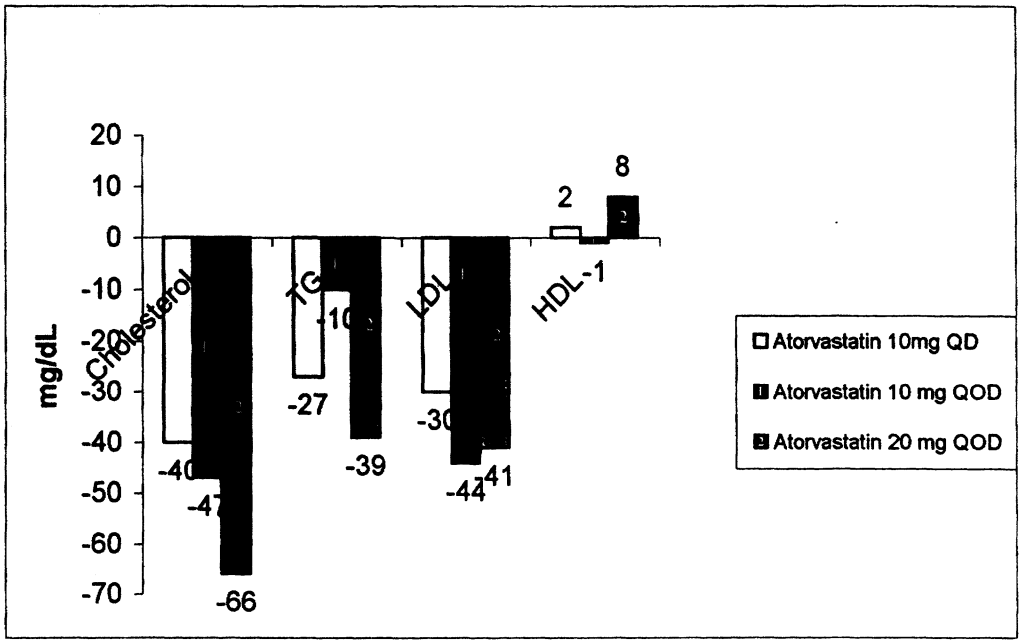

Fig. 1. Graph shows 6-week change in baseline in cholesterol, triglycerides, LDL, and HDL in the three groups after administration of atorvastatin. TG, triglycerides; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; QD, every day; QOD, every other day.

Table 2. Laboratory Values to Assess Safety of Three Different Regimens of Atorvastatin

	Atorvastatin 10 mg Every Day (Group I)	Atorvastatin 10 mg Every Other Day (Group II)	Atorvastatin 20 mg Every Other Day (Group III)	*P*
Baseline				
AST (U/L)	24 ± 13	30 ± 25	24 ± 10	NS
ALT (U/L)	16 ± 5	39 ± 23	NA	NS
CK (U/L)	96 ± 69	99 ± 23	NA	NS
After 6 weeks				
AST (U/L)	23 ± 6	21 ± 3	24 ± 8	NS
ALT (U/L)	44 ± 26	24 ± 15	13 ± 0	NS
CK (U/L)	154 ± 104	111 ± 44	NA	NS

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatine kinase; NA, not available; NS, not significant.

Discussion

Therapeutic Consideration

Based on the results of this study, atorvastatin, 10 mg or 20 mg every other day, is as efficacious and safe as 10 mg every day in reducing total cholesterol and LDL-C. However, a valid concern with alternate-day dosing is patient adherence to the dosing regimen and to our knowledge, no systematic studies have assessed patient adherence to alternate-day dosing (5). This was a 6-week study, and the staff made a great effort to ensure patient compliance. Assuming suboptimal compliance with dosing every other day, a lower response rate with this regimen might be expected; however, our results did not indicate this.

The patients who participated in this study had a mild baseline elevation of LDL-C (120–139 mg/dL). Although this level of severity is common and is within the range that requires treatment, especially in secondary prevention or in the presence of other risk factors, the results of this study cannot be projected beyond the level of severity present in this patient group.

Cost

Although the primary purpose of this study was to evaluate the clinical efficacy of alternate-day dosing with atorvastatin, study results show that this change in the prescribing pattern of atorvastatin may result in a significant cost reduction for consumers and third-party payers. The cost of 10 mg of atorvastatin every day is $56.40 per month. Taking 10 mg of atorvastatin every other day would save the patient about $28.20 monthly, or $338.40 annually. This is based on an average wholesale price, not including other mark-ups (6).

Conclusion

Atorvastatin administered every other day is effective in reducing LDL-C in patients with hypercholesterolemia. Alternate-day dosing with atorvastatin neither results in diminished therapeutic outcomes nor in an increase in toxicity.

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