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Efficacy of alternate day dosing of atorvastatin

Research Article

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Abstract: Atorvastatin is a synthetic inhibitor of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. It has a longer half life and longer duration of action than that of all other available HMG-CoA inhibitors. We evaluated the efficacy of alternate-day dosing of atorvastatin in comparison with the standard one-daily dose on total cholesterol, low and High-density lipoprotein (LDL and HDL) and triglycerides. This study is a randomized, blinded, and controlled clinical trial. Sixty-six patients with LDL cholesterol of more than 100 mg/dl were enrolled. Baseline fasting lipid profile (total cholesterol, LDL, HDL and triglyceride), liver function tests 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 20 mg of atorvastatin every 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 re-taken. Compliance to treatment was assessed at each visit. Of the sixty-six patients enrolled, sixty completed the study. All three regimens significantly reduced total cholesterol and LDL compared to baseline. No statistically significant difference existed between the three groups in regards to total or a percentage decrease in total cholesterol and LDL cholesterol at 6 weeks compared to baseline. All regimens were well tolerated and none of the patients showed significant elevation of liver enzyme or creatine kinase during the course of the study. In conclusions the alternate-day dosing of atorvastatin is an efficacious and safe alternate to daily dosing and yet inexpensive.

Keywords: *Atorvastatin • Cholesterol • Dosing • Lipoprotein*

1. Introduction

Despite a continuing decline in the incidence of atherosclerosis related death in the past 35 years, death from coronary artery disease (CAD), cardiovascular accidents and peripheral vascular disease accounted for 30% of the 2.3 million deaths in the United States alone in 1997. Among those dying of sudden cardiac death in 1997, 50% of the men and 63% of the women had been previously asymptomatic. These statistics illustrate the importance of identifying the modifiable risk factors for (CAD). Control of the modifiable risk factors accounts for 85% of excess risk for premature CAD [1,2]. When total cholesterol levels are below 160 mg/dl, CAD risk is markedly attenuated, even in the presence of additional risk factors [3]. The pivotal role of hypercholesterolemia in atherogenesis gave rise to the almost universally accepted cholesterol-diet-CAD hypothesis [4] which states that elevated plasma cholesterol levels cause CAD, that diets rich in saturated (animal) fat and cholesterol raise cholesterol levels, and that the lowering of cholesterol levels reduce CAD risk [3]. The statins (competitive inhibitors of HMG-CoA reductase, an early rate limiting step cholesterol biosynthesis catalyser) are the most effective and best tolerated agents for treating Dyslipidemia [5]. Atorvastatin has a long half-life (approximately 14 hours) allowing its administration at any time of day [6], with active metabolites effective for 20-30 hours [5,6]. This makes it an ideal candidate for alternate-day dosing [7,8]. In addition to many helpful effects of statins, they are among the more expensive drugs. Patients in lower socioeconomic status may discontinue statin therapy due to prohibitive costs. Alternate-day dosing, therefore may solve the problem of statin underutilization. The aim of this study is to compare the safety and efficacy of alternate-day dosing and the routine daily dosing of atorvastatin.

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Table 1. Baseline clinical and paraclinical characteristics of patients and controls.

	Group I (n=20) 10 mg QD	Group II (n=20) 20 mg QD	Group III (n=20) 20 mg QOD	p value
Age (years)	60±9	55±12	61±11	NS
Male	10 (50%)	10 (50%)	11 (55%)	NS
Smoking	11 (55%)	10 (50%)	10 (50%)	NS
Hypertension	10 (50%)	11 (55%)	10 (50%)	NS
Diabetes	2 (10%)	3 (15%)	2 (10%)	NS
Mean weight (kg)	69±10	72±13	70±8	NS
Mean TC (mg/dl)	220±40	226±55	228±31	NS
Mean LDL-C (mg/dl)	143±34	152±50	152±31	NS
Mean HDL-C	38±9	38±8	37±7	NS
Mean TG (mg/dl)	187±74	176±85	189±46	NS

QD: once daily; QOD: alternate daily dose; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglyceride; NS: not significant

2. Material and Methods

2.1. Patients and Controls

After informed consent, sixty-six patients participated in this randomized, blinded case- control clinical trial study that was conducted in our cardiology outpatient clinic. None of the patients were alcohol users. Patients with hypercholesterolemia met the criteria for pharmacologic treatment according to the national cholesterol education program (NCEP) adult treatment panel III (ATPIII) guidelines [9]. Patients were randomly grouped into three groups: group I received 10 mg atorvastatin daily, group II received 20 mg atorvastatin daily and group III received 20 mg atorvastatin every other day. Baseline fasting lipid profile (total cholesterol, LDL, HDL and triglyceride), liver function tests (Aspartate transaminase [AST] and alanin aminotransferase [ALT]), and creatine kinase (CK) were drawn. LDL was directly measured by *Cholesterol Sterification Technique*. All sera were frozen at 70 degrees below zero Celsius (-70◦C) and all were thawed at the same time, and the tests performed within the same laboratory standards and techniques. The drug was administered for six weeks in all groups, after which fasting lipid profiles, AST, ALT, and CK concentrations were redrawn. Compliance to treatment was assessed at each visit. Prior to treatment, a complete medical history and physical exam, including height and weight of the patients were done. Subjects were on concurrent diet regimen according to NCEP step II diet [3]. They were also educated on the potential side effects of atorvastatin, especially of hepatic and musculo-skeletal toxicities. The patients were instructed to call the investigator if they experienced muscle pain, cramp, malaise, pale stools or dark urine. Drug compliance and toxicity were assessed at each visit (every 3 weeks). Atorvastatin used for all patients came from the same producer (LIPITOR). This study was approved and monitored by the ethics committee of the Shiraz University of Medical Sciences.

2.2. Exclusion Criteria

Exclusion criteria were: 1) significant hypertriglyceridemia (> 400 mg/dl); 2) abnormal ALT, AST or creatine kinase; 3) concurrent cholesterol-lowering medication, immune suppressants or Azole antifungal agents; 4) hypothyroidism, 5) pregnancy/lactation; and, 6) prior hypersensitivity/intolerance to any HMG-Co A reductase inhibitor.

2.3. Statistical Analysis

Data from the three groups was compared using the ANOVA and Bonferroni procedures, and are presented as mean (± SD). The SPSS version 11.5 statistical software program was used in data analysis, and a P value of less than 0.05 was considered significant.

3. Results

Six patients did not complete the study, as they did not keep their 6 weeks of follow-up appointments and they had not post treatment lipoprotein analysis, therefore they were considered dropouts. Sixty patients completed the study, with 20 subjects in each group. There was no significant difference in age, gender, BMI and baseline lipid profiles of the three groups (Table 1). The mean age was 60±9, 55±12 and 61±11 years old for groups I, II and III, respectively. All three regimens significantly reduced

Table 2. Baseline and change from baseline in total cholesterol, triglycerides, LDL and HDL after 6 weeks.

	Atorvastatin 10 mg daily (group I)	Atorvastatin 20 mg daily (group II)	Atorvastatin 20 mg every other day (group III)	p, p* p¸ p+
Baseline				
TC (mg/dl)	220±40	226±55	228±31	NS;NS;NS;NS;
TG (mg/dl)	187±74	176±85	189±46	NSNS;NS;NS;
LDL-C(mg/dl)	143±36	152±50	152±31	NSNS;NS;NS;
HDL-C(mg/dl)	38±9	38±8	37±7	NSNS;NS;NS;
After 6 week				
TC (mg/dl)	172±35	168±46	166±27	0.3,0.7,0.4,1.0
TG (mg/dl)	165±66	158±67	161±60	0.6,1.0,1.0,1.0
LDL-C(mg/dl)	100±25	96±41	68±28	0.3,0.6,0.6,1.0
HDL-C(mg/dl)	38±10	40±10	37±7	0.7,1.0,1.0,1.0

LDL-C: low density lipoprotein; HDL-C: high-density lipoprotein cholesterol; TG: Triglyceride, total cholesterol; p value is comparison among groups I, II, III; p value is for a comparison between group I and II; p* value is for a comparison between group I, III; p+ value is for a comparison between group II and III; NS: not significant*

total cholesterol and LDL-C within the group at the end of the study compared to baseline (Table 2). However, there was no significant difference noted between the 3 groups in total or percentage decrease of either total cholesterol or LDL-C after 6 weeks compared to baseline. Likewise, there was no significant difference between the groups regarding the total or percentage decrease of triglyceride levels. Atorvastatin at 20 mg/day resulted in higher increases in HDL-C, but these were not significant (Table 2). All regimens were well tolerated, and none of the patients had a significant elevation of liver enzymes (≥ 2 times the base line) or creatine kinase (Table 3). No patients complained of any musculo-skeletal pain. All the sixty patients had fully complied with therapy.

Table 3. Laboratory tests to assess safety of three different regimen of atorvastatin.

	Group I	Group II	Group III	p value
Baseline				
AST (U/L)	17±6	16±4	19±5	NS
ALT (U/L)	13±5	12±3	15±5	NS
CK (U/L)	66±13	60±15	66±24	NS
After 6 week				
AST (U/L)	18±5	18±3	19±4	1.01.01.0
ALT (U/L)	16±6	16±6	19±5	
CK (U/L)	67±14	63±26	68±18	

AST, Aspartate aminotransferase, ALT, Alanin aminotransferase; CK, Creatine kinase; NS, not significant

4. Discussion

The results of this study show that atorvastatin 20 mg every other day has an efficacy and safety at par with the routine 20 mg daily dosage in reducing total cholesterol and LDL-C. However, a valid concern with the alternate day dosing is the patients adherence to medication and to our knowledge, no systematic studies have assessed patient adherence to alternate-day dosing. Assuming a suboptimal compliance with the alternate-day dosing, a lower response rate with this regimen might be expected. None the less, our study did not indicate this.

The patients who participated in this study had a mild to moderate baseline elevations of LDL-C. Although such levels are common and are within the ranges that require treatment, especially in secondary prevention or in the presence of co-morbid risk factors, the results of this study can not be justifiably generalized to incorporate the level of severity beyond that present in this patients group.

Although the primary scope of this study was to evaluate the clinical efficacy of the alternate-day dosing with atorvastatin, the study results show that such change in atorvastatin prescription pattern may result in a significant cost reduction for both the consumers and third party payers.

The statins have other benefits which were not investigated in this study, as the main focus here was the lipid profile changes. Statin therapy reverses endothelial dysfunction [10], affect plaque stability [11], modulate the cellularity of the artery wall by inhibiting proliferation of smooth muscle cells and enhancing apoptotic cell death [12], play an anti-inflammatory role [12], reduce the susceptibility of lipoproteins to oxidation [13], stabilize or increase the plasma level of paraoxinase, the anti-oxidation

enzyme associated with plasma HDL, and reduce platelet aggregation and deposition of platelet thrombi [14]. These heterotropic effects are seen with daily dosing of statins, and whether the alternate day dosing method is be effective in offering such advantages needs further investigations.

In conclusions atorvastatin administered every other day is as effective as the current daily dosage in reducing LDL-C in patients with mild to moderate hypercholesterolemia. Alternate-day dosing with this drug neither diminish therapeutic outcome nor does it causes an increase in toxicity rates or patient incompliance.

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