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EFFECTIVE ANALYSIS OF ATORVASTATIN VERSUS IN SIMVASTATIN PATIENTS WITH HYPERLIPIDEMIA

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Abstract

We directly evaluate the safety and dose efficacy of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor atorvastatin (X-tor) and simvastatin (Zocor) in hypercholesterolemic patients. Fifty hyperlipidemia patients between the ages of 20 and 75 years with baseline of low-density-lipoprotein (LDL) cholesterol (>160 mg/dl) and triglycerides (>400 mg/dl) received once-daily dosing with atorvastatin 10, 20 mg or simvastatin 10, 20 mg. The efficacy end points were mean percent change in plasma LDL cholesterol, total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) concentrations from baseline to the end of treatment (week 8). Atorvastatin 10, 20 mg caused significantly greater reductions in total cholesterol, LDL cholesterol and apolipoprotein B, respectively, than the milligram equivalent doses of simvastatin. On the other hand Atorvastatin 10 mg caused triglycerides and HDL cholesterol were not different between atorvastatin and the other reductase inhibitors except at the 20-mg dose when atorvastatin produced significant changes in triglycerides and HDL cholesterol than simvastatin. No patient in either treatment group had clinically important elevations in creatine phosphokinase (CPK), alanine aminotransaminase (ALT), or aspartate aminotransaminase (AST). No serious adverse events were considered associated with treatment. In summary, there is a need for more effective total cholesterol and LDL lowering agents to improve treatment aimed at reducing risk of coronary heart diseases (CHD). In this trial, atorvastatin was more effective than simvastatin. Atorvastatin should constitute an important therapeutic option for patients with hyperlipidemia.

Keywords: HMG-CoA reductase inhibitors, atorvastatin, simvastatin, LDL-C, coronary heart disease

Introduction

Various genetic and environmental factors contribute to the development and progression of atherosclerotic disease. Aberrant plasma cholesterol, lipoprotein, and apolipoprotein levels play significant roles in this disease and reductions in LDL cholesterol are consistently related to reductions in vascular disease and improved outcomes [1,2]. The Adult Treatment Panel of the National Cholesterol Education Program has established guidelines for the evaluation and treatment of elevated cholesterol concentrations based on an individual's risk factors for coronary artery disease (CAD) [3]. The LDL cholesterol treatment goals are (1) LDL cholesterol ≤100 mg/dl for patients with CAD; (2) LDL cholesterol <130 mg/dl in patients with ≥2 risk factors for CAD;

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(3) LDL cholesterol <160 mg/dl in patients with <2 risk factors for CAD.

Simvastatin lower LDL cholesterol from 18% to 41% over the most commonly used recommended dose range of each agent [4-14]. A recently approved synthetic HMG-CoA reductase inhibitor, atorvastatin, reduces LDL cholesterol from 35% to 61% over the dose range of 10 to 80 mg [1,15]. The present multicenter study was designed to evaluate the comparative dose efficacy of the HMG-CoA reductase inhibitor, atorvastatin, with equivalent dose strengths of simvastatin in hyperlipidemia patients after 8 weeks of treatment.

Materials and Methods

This study was a open-label, randomized, parallel-group, 8-week comparative study evaluating the efficacy of once-daily doses of atorvastatin 10 and 20mg compared with once-daily doses of simvastatin 10 and 20mg. Male and female patients 20 to 75 years old with plasma LDL cholesterol concentrations >160 mg/dl as calculated by the Friedewald formula, and triglyceride concentrations >400 mg/dl at 2 consecutive visits (weeks -6 and -2) were eligible for inclusion [16]. Patients with any of the following conditions were excluded: primary hypothyroidism; nephrotic syndrome; type 1 or uncontrolled type 2 diabetes mellitus; hepatic dysfunction; serum creatine phosphokinase levels >3 times the upper limit of normal; body mass index >32 kg/m^2; uncontrolled hypertension; myocardial infarction, coronary angioplasty, coronary artery bypass graft, or severe or unstable angina pectoris within the 3 months before the study; known hypersensitivities to HMG-CoA reductase inhibitors; or significant abnormalities that the investigator believed could compromise the patient's safety or successful participation in the study. Medications known to effect lipid levels interact with study medications, or effect clinical laboratory parameters (erythromycin, anticoagulants, isotretinoin, immune suppressive agents, lipid-regulating drugs, systemic steroids) were not allowed during the study.

Eligible patients were instructed to follow the step 1 diet for 6 weeks before randomization and throughout the duration of the study. After dietary stabilization, patients who qualified were randomized to 1 of 15 treatment groups, as described above, and were treated for 8 weeks. All study medication was taken according to recommended dosing. The study was performed using a common protocol at 34 sites. An appropriate institutional review board at all sites approved the protocol and all patients signed written informed consent.

Estimation of Biochemical Parameters

The laboratory was certified for standardization of lipid analyses as specified by the Standardization Program of the Centers for Disease Control and Prevention [17] and BIO-RAD External Quality Assurance Services (EQAS). After patients fasted overnight, blood was drawn in vacationers and immediately determined the level of total cholesterol, triglycerides, HDL, LDL, CK, ALT and AST by fully automated clinical chemistry analyzer (Hitachi 912, Boehringer Mannheim, Germany). VLDL level was calculated according to Friedewald *et al*. [16].

To monitor safety, complete clinical laboratory determinations were obtained at screening, randomization, and the end of the active treatment period. Physical

examinations were performed at the beginning and end of the study. Adverse events were recorded at each clinic visit. Serum AST and ALT and CPK concentrations were determined at every study visit and as deemed necessary by the investigator.

Statistical analysis

All data were expressed as mean ± SD. The statistical significance was evaluated by Student's t test using Statistical Package for the Social Sciences (SPSS Cary, NC, USA) version 10.0.

Results

Information about the demographic characteristics of the study population is shown in Table 1. Of the 75 patients randomized to treatment, 50 patients completed the study. Sixteen patients withdrew before the end of the study: 4 because of adverse events, 3 for personal reasons, and 2 who were lost to follow-up. Thirty-five patients (35) were men and 15 were women. Mean age was 45.6± 9.0 years (range 20 to 75), 30 patients had hypertension and 20 patients had established CAD.

The summary of mean baseline characteristics (all patients randomized to treatment) in hyperlipidemia patients is shown Table 2. When given once daily in equivalent (mg) doses, atorvastatin 10 and 20mg produced greater reductions in total cholesterol, LDL cholesterol and triglyceride than simvastatin. As with LDL cholesterol, atorvastatin 10 and 20 mg produced greater reductions in total cholesterol than simvastatin at milligram-equivalent doses. The effects on triglycerides were not different between atorvastatin and the other reductase inhibitors except at the 20-mg dose when atorvastatin produced greater reductions in triglycerides than the 20-mg doses of simvastatin. Effects on HDL cholesterol were not different between atorvastatin and the other reductase inhibitors except at the 20-mg dose when atorvastatin produced greater elevations in HDL cholesterol than simvastatin. There were no incidences of persistent (2 measurements within 1 week) elevations in serum transaminases (AST and ALT) >3 times the upper limit of normal. There were no incidences of elevations in CPK >3 times the upper limit of normal or reports of myopathy in any treatment group.

The overall frequency of adverse events was similar between treatment groups Table 3. Four patients reported adverse events that were judged by the investigator to be possibly, probably, or definitely associated with treatment, most of which were mild to moderate in intensity. Of these, the most commonly reported events were abdominal pain (1%), diarrhea (1%), flatulence (1%), and nausea (1%). The adverse events leading to withdrawal included gastrointestinal complaints, dizziness, depression, myalgia, hypertonia, angina, and back pain.

Table 1: **Demographic characteristics of hyperlipidemia patients**

Parameter	Hyperlipidemia patients
Total number of subjects (n)	75
Completed the study	50
Withdrew before the end of the study	16
Adverse events	4
Personal reasons	3
Lost to follow-up	2
Age range (Years)	20 to 75
Age (Mean ±S.D) years	45.6± 9.0
Body mass index (Mean ± SD), kg/m^2	27.7 ± 2.0
Systolic blood pressure (mm of Hg)	128 ± 10
Diastolic blood pressure (mm of Hg)	90 ± 7
Risk factors, %	
Hypertensive	30
Cardiovascular disease	20

Table 2. Summary of mean baseline characteristics (all patients randomized to treatment)

Parameters	Patients with hyperlipidemia groups			
	Simvastatin	Simvastatin	Atorvastatin	Atorvastatin
(mg/dl)	Dose 10mg	20mg	10mg	20mg
Total Cholesterol	272 ± 15.7	234 ± 11.3	240 ± 10.8†	200 ± 13.8***$^{\infty\infty}$
Triglycerides	205 ± 13.3	180 ± 14.3	179 ± 14.8^{NS}	175 ± 15.6 **^{NS}
HDL-C	39 ± 1.5	41 ± 1.0	40 ± 1.2^{NS}	42 ± 1.1* ^{NS}
LDL-C	217 ± 10.3	175 ± 10.1	179 ± 9.3 ^{NS}	150 ± 12.2***$^{\delta}$
VLDL-C	37 ± 2.3	32 ± 2.0	31 ± 2.2 ^{NS}	28 ± 2.1***$^{\delta}$
Apolipoprotein-B	196 ±10.0	180 ± 9.5	181 ± 9.5 ^{NS}	172 ± 8.1***$^{\infty\infty}$
Apolipoprotein-A-1	140 ± 7.9	150 ± 8.0	156 ± 7.7†	163 ± 7.7***$^{\infty\infty}$
Lipoprotein (a)	42 ±7.4	41 ±7.9	40 ±7.5 ^{NS}	38 ±7.1**$^{\infty\infty}$

Values are given as mean ± S.D from fifty subjects in each group.
Atorvastatin 20mg compared with simvastatin10 mg (*p<0.05, **p<0.01, ***p<0.001)
Atorvastatin 20mg compared with simvastatin 20 mg ($^{\delta}$p<0.05, $^{\infty}$p<0.01)
Atorvastatin 10mg compared with simvastatin 20mg (†p<0.05) NS-Not significant

Discussion

The study is the first trial to compare the lipid-lowering efficacy of all marketed HMG-CoA reductase inhibitors, including the recently approved synthetic HMG-CoA reductase, atorvastatin, across their dose ranges. An open-label design was chosen for this study because of the impracticality of blinding 15 treatment arms. Efficacy end points were based on objective

laboratory measurements. Atorvastatin 10 and 20mg produced greater reductions in total and LDL cholesterol than the other reductase inhibitors studied at milligram-equivalent doses. Atorvastatin 10 mg produced greater reductions in LDL cholesterol than to simvastatin 10 mg. An HMG-CoA reductase inhibitor's efficacy is measured by its ability to lower LDL cholesterol regardless of the amount of drug substance needed to accomplish this result [9,18, 19]. The present study in conjunction with previous comparative studies that have included atorvastatin, have clearly established atorvastatin as the most efficacious HMG-CoA reductase inhibitor for lowering total cholesterol and LDL cholesterol [20].

This study was not powered to detect differences in effects on triglycerides. The patient population studied consisted mostly of patients with elevated cholesterol without elevated triglycerides (mean baseline triglycerides ranged from 147 to 200 mg/dl. Atorvastatin 10 and 20mg produced numerically, but not statistically, greater reductions in triglycerides than the other reductase inhibitors at milligram-equivalent doses, and statistically greater reductions in triglycerides at the 20 mg dose. As with LDL cholesterol, the reductions in triglycerides seen in all of the treatment groups in the present study are consistent with those reported in previous studies [21].

In addition to providing greater reduction in LDL, atorvastatin treatment

Table 3. Withdrawals due to adverse events

Treatment	Dose (mg)	No of patients	No of adverse Events	Event(s)	Relation to Therapy*
Atorvastatin	10mg	25	0	Abdominal Pain/diarrhea	Possibly
Atorvastatin	20mg	25	1	Myalgia	Definitely not
Simvastatin	10mg	25	1	Depression/dizziness	Possibly
Simvastatin	20mg	25	2	Hypertonia /nausea, Abdominal Pain/flatulence	Possibly

*The investigator judged relation to therapy.

was associated with beneficial changes in LDL/HDL and total cholesterol/HDL ratios, variables that are garnering increasing attention as markers of CHD risk [22]. The rosuvastatin 10-mg group also achieved a modest but statistically significant increase in HDL compared with the atorvastatin group over 6 weeks. In addition, the rosuvastatin 10-mg group maintained a significantly greater reduction in Apo B level and Apo B/Apo A-I ratio compared with atorvastatin treatment over 6 weeks; these variables have recently been identified as important predictors of risk, [23,24] including risk for first CHD event during statin treatment.

In the present study, no patient in any treatment arm experienced persistent clinically significant increases in serum transaminases. Most cases of significant elevations in serum transaminases have been reported to occur within the first 2 to 3 months of treatment, and the duration of this study (8 weeks) may not have been long enough to detect such cases [25]. In rare instances, severe creatine phosphokinase elevations and myositis have been associated with the use of reductase inhibitors.

In summary, there is a need for more effective total cholesterol and LDL-Cholesterol lowering agents to improve treatment aimed at reducing risk of CHD. In the present study, atorvastatin was more effective and exhibited a similar safety profile than simvastatin. Therefore, atorvastatin should constitute an important therapeutic option for patients with hyperlipidemia.

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