A Randomized, Double-blind, Placebo-controlled, 8-week Study to Evaluate the Efficacy and Safety of Once Daily Atorvastatin (10 mg) in Patients with Elevated LDL-cholesterol

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SUMMARY

Lowering of serum cholesterol levels by pharmacologic intervention with statins reduces the incidence of cardiovascular events in subjects with and without atherosclerotic manifestations. In an 8-week, randomized, double-blind study we compared the efficacy and safety of the new compound atorvastatin for reducing LDL-cholesterol (LDL-C) with placebo in an Asian patient cohort. Patients with LDL-C between 160 mg/dl and 250 mg/dl were randomly assigned to treatment with 10 mg atorvastatin or placebo once daily for 8 weeks. At the end of weeks 4 and 8 of the randomized phase, the serum concentrations of lipid parameters as well as safety parameters were determined. Fifty-four patients (32 males and 22 females) were enrolled. Twenty-six patients were assigned to the treatment group. The primary end-point, LDL-C, was reduced by 40% and 42% after 4 and 8 weeks of treatment in the atorvastatin treated patients ($p < 0.001$). The reductions in total cholesterol and triglycerides were up to 31% and 23%, respectively. The HDL-C levels increased up to 11% ($p = 0.043$). There were no significant adverse events. Transient increases in CPK levels (10 times) without myalgia were identified in 1 patient. Atorvastatin, 10 mg/day produced significant reductions in LDL-C, total cholesterol and triglycerides and an elevation of HDL-C levels when used as an adjunct to diet in hyperlipidemic patients. The majority of the clinical effects could be attained by week 4. The overall safety profile of atorvastatin was similar to that of placebo. Atorvastatin was considered to be well tolerated in this patient cohort. (Jpn Heart J 2001; 42: 725-738)

Key words: Low density lipoprotein, High density lipoprotein, Cholesterol, Triglycerides

THE relationship between the risk of atherosclerotic heart disease and serum lipoproteins is well established.¹⁾ Elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), and low levels of high-density lipoprotein cholesterol (HDL-C),^{2,3)} are associated with increased risk of coronary heart disease (CHD). Epidemiological data have demonstrated that the risk for

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CHD is directly related to the level of blood cholesterol. The Multiple Risk Factor Intervention Trial (MRFIT) reported an escalating curve relating CHD mortality to TC serum levels.⁴⁾

Evidence of the beneficial effects of reductions in serum TC and LDL-C has led to the development of guidelines from the United States National Cholesterol Education Program (NCEP) for the detection, evaluation, and treatment of high blood cholesterol levels in adults.^{5,6)}

Dietary manipulation recommended by the American Heart Association and NCEP guideline is the first step in the treatment of patients with high risk (>160 mg/dl) or moderate risk (130-159 mg/dl) elevations in the LDL-C level. A diet which emphasizes reductions in total fat, saturated fat and cholesterol and a long term exercise program have been shown to lower plasma LDL-C and triglyceride (TG) levels, increase HDL-C levels, aid in weight control, and to reduce cardiovascular mortality rates. If after 3-6 months, diet plus exercise has failed to normalize (<130 mg/dl) or reduce LDL-C levels to an adequate level (<160 mg/dl), drug therapy should be considered.

Large clinical trials have demonstrated that statin lipid lowering agents have been the first line treatment strategy in reducing the incidence of cardiovascular events in hypercholesterolemic subjects with and without atherosclerotic manifestations.⁷⁻¹¹⁾ A recently approved synthetic HMG-CoA reductase inhibitor atorvastatin has exhibited greater reductions in serum TC, LDL-C and TG levels.¹²⁾ Atorvastatin is effective in the treatment of primary hypercholesterolemia, mixed lipidemias, and homozygous familial hypercholesterolemia.¹²⁻¹⁵⁾ Atorvastatin impedes the formation of mevalonic acid, which is the rate limiting step in the biosynthesis of cholesterol, resulting in endogenous cholesterol synthesis reduction.

In placebo-controlled clinical trials, atorvastatin 10-80 mg/day lowered LDL-C by 35-61% and TG concentrations by 14-45%.¹⁶⁾ In comparative trials, atorvastatin 10-80 mg/day showed a greater reduction in serum TC, LDL-C, and TG concentrations, and apolipoprotein B-100 (apo B) compared with pravastatin, simvastatin, or lovastatin.¹⁷⁾ Atorvastatin has been well tolerated in clinical studies of up to 52 weeks in duration.¹⁸⁾ Like other HMG-CoA reductase inhibitors, gastrointestinal effects (including flatulence, dyspepsia, constipation and abdominal pain) are the most frequently reported adverse events associated with atorvastatin.

This single institute study was designed to evaluate the clinical efficacy and safety profile of atorvastatin in an Asian hypercholesterolemic patient cohort after 4 to 8 weeks of treatment.

METHODS

Study design: This study was a randomized, double-blind, placebo-controlled, 8-week study to evaluate the efficacy and safety of atorvastatin 10 mg once daily. Male and female participants from the Outpatients Department of the Cardiovascular Division were enrolled. Patients provided written informed consent prior to entering the study. All participants, including the control group, were counseled to follow the NCEP step 1 diet (TC <300 mg/day, calories from fat <30%, and saturated fat <10%) throughout the study. Patients between 18 and 80 years old with a plasma LDL-C concentration >160 mg/dl (4.2 mmol/l) and <250 mg/dl (6.5 mmol/l) as calculated by the Friedewald formula ($LDL-C = TC - HDL-C - TG \times 0.2$) and a TG concentration <400 mg/dl (4.5 mmol/l) were eligible for inclusion. Patients with any of the following conditions were excluded: pregnant or breast feeding women; primary hypothyroidism with TSH >5.5 μ l U/ml; nephrotic syndrome or renal function impairment with creatinine/BUN >2.0/30 mg/dl; poor controlled type II DM with HbA1c >10%; Type I DM; Liver disease with AST or ALT >1.5 times normal; serum creatine phosphokinase >3 times normal; body mass index >30; blood pressure >160/95 mmHg; history of alcohol or drug abuse; history of myocardial infarction, s/p percutaneous coronary intervention, s/p coronary artery bypass graft, and unstable angina <3 months; participated in another trial within less than 30 days; compliance rate <80%; known hypersensitivity to statins; use of any lipid-regulating agents; drugs known to affect lipid levels; associated with any unstable systemic diseases such as congestive heart failure, chronic lung diseases, dementia, cerebral vascular disease, or active malignancy. The study design is illustrated in Figure 1.

Efficacy: The primary endpoint was to evaluate the percent change from baseline to week 8 of serum LDL-C. The secondary analysis included the percent change from baseline to week 4 of serum LDL-C and percent change from baseline to week 4 and to week 8 of serum TC, TG, and HDL-C.

Safety variables: All adverse events were collected and reported at each clinic visit. This class of drug has been associated with 2 important side effects: elevated transaminase levels and the occurrence of myopathy. Accordingly, the corresponding safety assessments were performed throughout the study in order to fully describe and document any deleterious findings.

A physical examination was performed at screening, baseline, and at termination from double-blind or at the end of the active treatment period following the completion of the study. Significant adverse changes were recorded as adverse events.

A clinical laboratory determination of safety parameters was performed by a local laboratory during the screening period and at week 8. An abbreviated clin-

Figure 1. Study diagram.

Figure 2. Percent change of lipid profile-atorvastatin TC=total cholesterol; LDL=low density lipoprotein; TG=triglyceride; HDL=high density lipoprotein.

ical laboratory examination of key safety parameters (ALT, AST, and CPK) was done at screening (week 5), week 0, week 4, and week 8 and was performed at any time during the study. A clinically significant laboratory abnormality, preferably verified by a repeat measurement, occurring during the study was reported as an adverse event and followed until the abnormality had resolved or a satisfactory explanation had been obtained.

Statistical methods: The primary analysis of efficacy parameters for TC, LDL-C, HDL-C, and TG, was performed based on the intent-to-treat (ITT) population. The statistical analysis of safety data for vital signs, physical examinations, adverse events, and laboratory evaluations was performed based on safety population. Patients in both the ITT population and safety population who were randomized into the study, and had taken at least one dose of study medication recorded and at least one efficacy or safety evaluation after receiving randomized study medication were included in the analysis. The last-observation-carried-forward (LOCF) approach was used to evaluate missing data for both the ITT population and safety populations.

Descriptive statistics such as mean, median, standard deviations, minimum, maximum, and 95% confidence interval were used to summarize the continuous data. Frequency and proportion were used to summarize the categorical data. Differences between two treatment groups were compared. For continuous data, the Wilcoxon rank sum test or analysis of covariance (ANCOVA) was performed.

For categorical data, Fisher's exact test or the chi-square test was performed. All available data and tabulation of results are displayed by treatment group. All statistical tests were two-sided which evaluated at the 0.05 level of significance.

Frequency of dropouts, premature termination of study medication and withdrawal were provided and summarized by treatment groups.

For demographic data and baseline characteristics, the comparability between two treatment groups was examined using the Wilcoxon rank sum test for continuous data, and Fisher's exact test and the chi-square test for categorical data.

For the efficacy parameters, the baseline was defined as the average of the measurements taken at week 1 and week 0. The percent change from baseline was compared between two treatment groups using an ANCOVA model with treatment as the factor and the CHD risk factor category as the covariate since the CHD risk factor category was statistically significant between two treatment groups. The within treatment group comparison was carried out using the Wilcoxon signed rank test.

For the safety parameters, vital signs such as weight, pulse, respiratory rate, and blood pressure were calculated base on the mean change from baseline using the Wilcoxon signed rank test for within treatment groups and the Wilcoxon rank-sum test for between treatment groups. All adverse events were provided by the treatment groups, body systems, and COSTART terms. The hematology and blood biochemistry laboratory data were compared with their normal range. Transition tables from baseline were performed using the Wilcoxon signed rank test for within treatment groups and the Wilcoxon rank-sum test for between treatment groups.

RESULTS

Demographic data: Fifty-four patients (32 males and 22 females, mean age: 66 years old) were randomly assigned to treatment groups. The mean values of the demographics and baseline characteristics of the patients are summarized in Table I. There were no significant differences in demographic data or baseline mean lipid values between the two groups. However, CHD risk factor category designation showed a statistically significant difference between the two groups. More atorvastatin treated patients (58%) were classified as Category B (2 or more risk factors for CHD) than placebo (21%), while more patients in the placebo group (68%) had Category C (established CHD) than the atorvastatin group (38%).

Efficacy results: The results of primary endpoint analysis showed that the LDL-C was significantly reduced by 42% compared with baseline after 8 weeks of

Table I. Demographic and Baseline Characteristics

General data	Atorvastatin <i>n</i> =26 (%)	Placebo <i>n</i> =28 (%)	Difference
Sex (M/F)	14(54%)/12(46%)	18(64%)/10(46%)	0.435*
Age, years	66.8±8.6	65.4±9.0	1.4
Height, cm	160.1±8.6	159.6±8.1	0.50
Weight, kg	62.4±7.2	63.0±9.2	-0.6
BMI, kg/m ²	24.4±2.0	24.7±2.5	-0.4
PR, minutes	65.2±8.2	67.1±8.2	-1.9
RR, minutes	17.7±3.2	17.5±4.0	0.2
SBP, mmHg	138.6±12.5	135.2±11.0	3.4
DBP, mmHg	81.7±6.6	78.7±7.3	3.0
CHD risk factors			
Family history of CHD	1 (4%)	1 (4%)	0.506*
Diabetes	1 (4%)	2 (7%)	0.597*
Smoking	10 (39%)	12 (43%)	0.120*
Hypertension HDL	23 (88%)	26 (93%)	0.578*
<35 mg/dl	4 (15%)	5 (18%)	0.970*
>60 mg/dl	2 (8%)	2 (7%)	
30-60 mg/dl	20 (77%)	21 (75%)	
CHD risk factors category			0.023*
A (<2)	1 (4%)	3 (11%)	
B (≥2)	15 (58%)	6 (21%)	
C (Established CHD)	10 (38%)	19 (68%)	

*: Chi-square test. PR=pulse rate; PR=respiratory rate.

Table II. Mean Change/Percent Reduction in Serum Lipoprotein Concentrations

Lipid Profile (mean±SD)	Atorvastatin (10 mg/QD) <i>n</i> =26	Placebo ^a <i>n</i> =28	<i>p</i> -value
LDL-C			
Baseline	192.70±20.00	187.29±18.31	0.277*
Week 4	116.18±23.11/-40±7.8	187.59±22.07/0.53±11.1	0.000**
Week 8	112.83±23.00/-41.6±9.1	187.19±24.32/0.3±11.6	0.000**
Total cholesterol			
Baseline	267.0±24.9	260.1±21.9	0.221*
Week 4	185.6±28.3/-30.8±5.6	257.9±23.7/-0.6±8.2	0.000**
Week 8	183.7±27.1/-31.3±6.8	261.4±28.0/0.6±8.7	0.000**
Triglyceride			
Baseline	144.8±45.3	138.5±50.1	0.776*
Week 4	106.7±40.6/24.5±20.3	129.6±57.6/-5.9±28.1	0.009**
Week 8	104.7±28.5/22.6±26	139.4±60.0/3.7±34.6	0.004**
HDL-C			
Baseline	45.4±92.1	45.11±10.6	0.654*
Week 4	48.1±10.6/6.4±12.6	44.4±9.5/-0.9±9.7	0.030**
Week 8	49.9±9.6/11.2±16	46.3±10.4/3.1±10.4	0.043**

^aWilcoxon rank-sum test, **ANOVA model with treatment as the fixed factor and CHD risk factor as the covariate.

treatment in the atorvastatin treated patients. This LDL-C lowering effect of atorvastatin was demonstrated by a 40% decrease from baseline as early as 4 weeks of treatment. A statistically significant difference ($p<0.001$) between the atorvastatin and placebo groups in lowering LDL-C levels was observed. Similar significant reductions were obtained for the secondary variables, including total cholesterol and triglycerides which were up 31% and 23%, respectively, after 4 to 8 weeks of treatment. The HDL-C levels also demonstrated a significant increase by 11% at week 8 ($p=0.043$) (Figure 2, Table II). The results also showed that atorvastatin-treated patients were able to achieve LDL-C target goals in the different risk factor categories after 8 weeks of treatment, 100% in category A, 93% in category B, and 40% in category C (Table III).

Table III. Number of Patients who met LDL-C Target Goals Based on CHD risk factors

CHD risk factor category	Atorvastatin <i>n</i> =26			Placebo <i>n</i> =28		
	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
A (<2)						
≥160 mg/dl	1	0	0	3	3	3
<160 mg/dl	0	1	1	0	0	0
B (≥2)						
≥130 mg/dl	15	3	1	6	6	6
<160 mg/dl	0	12	14	0	0	0
C (Established CHD)						
>100 mg/dl	10	8	6	19	19	19
<100 mg/dl	0	2	4	0	0	0

CHD=coronary heart disease.

Table IV. Number of Patients at Different Levels of Safety-related Laboratory Tests

Laboratory data	Atorvastatin (<i>n</i> =26)		Placebo (<i>n</i> =28)	
	Baseline	Week 8	Baseline	Week 8
SGOT				
<2 × UNL	26	26	28	28
2-3 × UNL	0	0	0	0
>3 × UNL	0	0	0	0
SGPT				
<2 × UNL	26	25	28	27
2-3 × UNL	0	1	0	1
>3 × UNL	0	0	0	0
CPK				
<5 × UNL	26	25	28	28
5-10 × UNL	0	0	0	0
>10 × UNL	0	1	0	0

Safety results: There were no clinically important elevations in ALT, AST and CPK during treatment. There were no clinically significant changes in vital signs, laboratory examination or physical examination (Table IV). A transient increase in CPK levels (10 times) without myalgia was identified in one patient who withdrew from the study. The CPK level eventually recovered 2 weeks later. The most common adverse events were insomnia and rhinitis (Tables V and VI)

Table V. Adverse Events in Atorvastatin and Placebo Groups

Event	Atorvastatin <i>n</i> =26	Placebo <i>n</i> =28
Hypertension	1 (4%)	0 (0%)
CPK ↑	1 (4%)	0 (0%)
Edema	1 (4%)	0 (0%)
Dizziness	1 (4%)	0 (0%)
Insomnia	1 (4%)	1 (4%)
Vertigo	1 (4%)	0 (0%)
URI like S×	1 (4%)	3 (12%)
Eczema	0 (0%)	1 (4%)

Sx=symptom; URI=upper respiratory tract infection.

Table VI. Number of Adverse Events by Body System and COSTART

Adverse event	Atorvastatin <i>n</i> =26				Placebo <i>n</i> =28			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Body as a whole				1				0
Pain, neck	1	0	0	1	0	0	0	0
Cardiovascular				1				0
Hypertension	1	0	0	1	0	0	0	0
Metabolic				2				0
CPK increase	0	1	0	1	0	0	0	0
Edema, peripheral	1	0	0	1	0	0	0	0
Central nervous				4				1
Dizziness	1	0	0	1	0	0	0	0
Ischemia	1	0	0	1	1	0	0	1
Ischemia, cerebral	0	1*	0	1	0	0	0	0
Vertigo	1	0	0	1	0	0	0	0
Respiratory								
Laryngitis	0	0	0	0	1	0	0	1
Pharyngitis	0	0	0	0	1	0	0	1
Rhinitis	1	0	0	1	1	0	0	1
Skin				0				1
Eczema	0	0	0	0	1	0	0	1
Urogenital				0				1
Breast, fibrocyst	0	0	0	0	1	0	0	1

DISCUSSION

Dyslipidemia, including elevated serum concentrations of LDL-C, TC and reduced serum concentrations of HDL-C, is a major risk factor in the premature development of atherosclerosis and CHD. Clinical trials have demonstrated that lowering elevated serum cholesterol concentrations decreases cardiovascular morbidity and mortality in patients with or without established CHD (secondary and primary prevention). The goal of therapy in patients with hyperlipidemia is to normalize lipoprotein cholesterol levels. Dietary modification and exercise are the initial steps in the non-pharmacologic treatment of patients with hyperlipidemia. If patients fail to respond to these primary measures, then pharmacological intervention should be considered. The primary endpoint of this study was the percent change from baseline in LDL-C levels after treatment with either atorvastatin or placebo. It showed that the LDL-C was significantly reduced by 42% compared with baseline after 8 weeks of treatment in atorvastatin treated patients. This significant lowering effect of atorvastatin was demonstrated by a 40% decrease from baseline at as early as 4 weeks of treatment.

It has been shown that aggressive lipid lowering could reduce angina and coronary events,¹⁹⁻²⁰⁾ part of the benefit may relate to the rate and speed of the lowering effect of diet and/or drugs, such as HMG-CoA reductase inhibitors. The hypothesis of "the lower the better" in the lipid lowering effect of statins has not been well established in large randomized trials. However, early observation studies in rural China have showed that in the 1970s and 1980s, average non-HDL levels were as low as 1 mmol/l (40 mg/dl) in many communities and that less than 1% of all deaths were due to CHD. These studies support the hypothesis that a more aggressive lipid-lowering treatment may significantly reduce cardiovascular morbidity and mortality.¹⁷⁾ A published trial has demonstrated that post-CABG patients with lower post-treatment serum LDL-C levels (<80/95-109/125-139/>155 mg/dl), had less graft lesion progression (27.9/40.9/44.7/64.2%) and a lower occlusion rate (5.4/15.0/18.3/25.9%).¹⁹⁾ A meta-analysis of angiographic data has suggested that LDL-C reductions of at least 45% are necessary to prevent and even reverse the progression of atherosclerosis.¹⁷⁾ The AVERT study also showed that aggressive lipid-lowering therapy is at least as effective as angioplasty in reducing the incidence of ischemic events in low-risk patients with stable coronary heart disease.²⁰⁾ The rapid lowering of LDL-C levels may produce an early benefit for the coronary endothelium in patients with coronary heart disease. A recently published report has demonstrated the effect of atorvastatin on blood lipid levels in the first 2 weeks of treatment. By day 5, there were significant reductions in TC and LDL-C levels. The TC level fell by 25% and LDL-C fell 35% by day 14. Triglyceride levels declined by 24%. There was no signifi-

cant difference in HDL-C. However, the total/HDL-C levels dropped from 4.54 to 3.32 and LDL-C/HDL-C levels dropped from 2.92 to 1.88; both results were highly significant.²¹⁾ In our study, atorvastatin showed similar lipid-lowering effects by week 4.

High concentrations of HDL-C play a protective role in CHD. This study has shown that atorvastatin treated patients achieved a statistically significant change by increasing HDL-C levels up to 11% from baseline to week 8.

Meta-analysis of population-based prospective studies has demonstrated that increased plasma TG is associated with a 32% increase in the risk of cardiovascular disease in men and a 76% increase in women. Even after adjustment for HDL-C, TC and other risk factors, these risks had increased 14% in men and 37% in women, and both were still statistically significant.²²⁾ Recent prospective studies have also shown that serum TG and LDL particle size, two highly interrelated risk factors, can predict subsequent coronary artery disease.²³⁾ These results demonstrate growing evidence of the importance of TG as an independent risk factor for cardiovascular disease. Both our study and the published trials have demonstrated that statins could be effective in lowering TG according to the baseline value. Statins have been recommended as first line therapy in hyperlipidemic patients with moderate hypertriglyceridemia (200-400 mg/dl).²⁴⁾

In the NCEP guideline, the intensity of treatment and goals of therapy depend on the patient's CHD risk status. For primary prevention, in patients without a history of CHD but with elevated LDL-C and with less than 2 risk factors (Category A), the recommended goal of therapy is to lower the LDL-C level to 160 mg/dl, or LDL-C <130 mg/dl in patients with >2 risk factors (Category B). For secondary prevention, in patients with established CHD, the goal should be more aggressive, to lower LDL-C to <100 mg/dl. The present study shows that atorvastatin-treated patients were able to achieve these goals in the different risk categories after 8 weeks of treatment-100% in category A, 93% in category B, and 40% in category C. Our results were even better than those achieved in a large clinical study on 10 mg atorvastatin for 16 weeks.

The prevalence of coronary artery disease is 3-7% in Chinese, which is roughly one-quarter that in Caucasian.²⁵⁾ In addition, an epidemiological study has also showed that the mean cholesterol levels were lower in a Japanese cohort than in the United States and Northern European populations (160-170 mg/dl vs 240-260 mg/dl).²⁶⁾ A racial difference in lipid metabolism has been documented in genetic-based studies.^{27,28)} However, ethnic differences in the lipid-lowering effects of statins between Western and Oriental countries have not been established. Compared with the CURVE study, the LDL-C and TC lowering effects by atorvastatin 10 mg/day did not show significant superiority in our population compared to Caucasians (Table VII).¹²⁾ Averaged national cholesterol levels, diet

Table VII. Mean Percent (%) Change in Lipoprotein Concentrations

Study	TC	TG	HDL-C	LDL-C
CURVES (<i>n</i> =73)				
8 weeks	-28	-13	+5.5	-38
VGH-TC (<i>n</i> =26)				
4 weeks	-31	-25	+6.0	-40
8 weeks	-32	-23	-11	-42

CURVES: reference 12; VGH-TC=Veterans General Hospital-Taichung.

habits, and body mass index might be important influencing factors.

In addition, no clinically important differences between treatment groups were noted for vital signs, laboratory examination, urinalysis, or physical examination.

Hepatic dysfunction (raised serum aspartate or alanine aminotransferase levels) and myopathy (myalgia and abnormal creatinine phosphokinase levels >10 times the normal limit) are the most serious concerns associated with HMG-CoA reductase inhibitors. To date, myopathy has not yet been reported with atorvastatin. In this study, one patient experienced high levels of CPK, but they did not persist and were not associated with myalgia.

Conclusion: Atorvastatin at a dose of 10 mg/day produced significant reductions in LDL-C, TC, and TG as well as an elevation in HDL-C levels when used as an adjunct to diet therapy in Asian patients with hyperlipidemia in all risk categories. The majority of the clinical effects could be attained within 4 weeks after starting treatment. The overall safety profile of atorvastatin was similar to that of placebo. Atorvastatin was considered to be well tolerated in these patient cohorts.

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