ORIGINAL ARTICLE

Efficacy and Safety of Slow-release Fluvastatin 80 mg Daily in Chinese Patients with Hypercholesterolemia

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Background: Before this study, the efficacy and safety of doubling the dosage of fluvastatin from 40 mg/day to 80 mg/day in Chinese patients with primary hypercholesterolemia remained to be determined.

Methods: In this open-label, active-controlled randomized 2-center study, patients with primary hypercholesterolemia were randomized to treatment with immediate-release fluvastatin 40 mg/day ($n = 30$) or slow-release fluvastatin 80 mg/day ($n = 31$) for 12 weeks. The primary efficacy variable was percent change in low-density lipoprotein (LDL) cholesterol level from baseline. Secondary efficacy variables were percent changes in total cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol levels, and the percent of patients achieving LDL cholesterol goals of the US National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) II.

Results: Both fluvastatin dosages (40 mg/day vs 80 mg/day) effectively reduced LDL cholesterol (–22.5% vs –29.9%; $p = 0.087$), total cholesterol (–17.3% vs –22.5%; $p = 0.140$), and triglyceride levels (–14.0% vs –12.3%; $p = 0.813$) (all $p < 0.0001$ for comparison with baseline), and slightly increased HDL cholesterol levels (+5.2% vs +5.6%; $p = 0.917$), after 12 weeks of treatment. The percent of patients achieving LDL cholesterol goals of the NCEP ATP II was 37% versus 65% ($p < 0.05$). The adverse event profiles for the 2 fluvastatin dosages were similar.

Conclusion: In Chinese patients with primary hypercholesterolemia, doubling the dosage of fluvastatin from 40 to 80 mg once daily was effective and safe regarding reduction of LDL cholesterol level, and allowed more patients to achieve LDL cholesterol goals of the NCEP ATP II. [*J Chin Med Assoc* 2005;68(8):353–359]

Key Words: fluvastatin, HMG-CoA reductase inhibitors, hypercholesterolemia

Introduction

Hypercholesterolemia is one of the major risk factors for cardiovascular disease.[1,2] Recent clinical outcome studies with statins demonstrated significant reductions in mortality and cardiovascular-related events for a mean 25–35% reduction in low-density lipoprotein (LDL) cholesterol.[3,4] Accordingly, there is a trend towards setting the therapeutic goal of LDL cholesterol reduction to at least this magnitude in most patients. However, in a recent survey (Lipid Treatment Assessment Project, L-TAP),[5] only 32–46% of patients reached the target LDL cholesterol levels determined by the US National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) II.[6] Further, although most patients in the Scandinavian Simvastatin Survival Study (4S) reached the study goal of total cholesterol less than 200 mg/dL, some patients might have benefited from additional cholesterol-lowering.[3]

Fluvastatin is a wholly synthetic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor that has been shown to reduce LDL

cholesterol levels by 20–26% at a dosage of 20–40 mg/day in clinical studies completed in more than 2,500 patients with hypercholesterolemia in Europe and North America.[7,8] The dose-response curves for LDL cholesterol reduction with most HMG-CoA reductase inhibitors are log-linear and, with dosage doubling, an additional reduction in LDL cholesterol level of approximately 6% is observed.[9–11] A slow-release formulation of fluvastatin 80 mg was introduced worldwide as a new once-a-day dose offering enhanced LDL cholesterol lowering while retaining an excellent safety profile.[4] The current study was designed to compare the efficacy and safety of slow-release fluvastatin 80 mg/day with immediate-release fluvastatin 40 mg/day regarding LDL cholesterol reduction when both regimens were administered at bedtime in Chinese patients with primary hypercholesterolemia.

Methods

Study population
Men and women (who were not pregnant or lactating) who were aged ≥ 18 years with primary hyper-cholesterolemia (LDL cholesterol ≥ 160 mg/dL, triglycerides ≤ 400 mg/dL) were eligible for inclusion in this study. Patients were excluded if they had severe uncontrolled hypertension, congestive heart failure, severe or unstable angina pectoris, diabetes mellitus, uncontrolled hypothyroidism, renal impairment (serum creatinine > 1.5 times the upper limit of normal [ULN]), chronic liver disease, or elevated serum transaminase levels (alanine transaminase [ALT] or aspartate transaminase [AST] > 1.5 times the ULN), muscle disease of any type, or elevated serum creatine kinase level (creatine kinase > twice the ULN). Other exclusion criteria included any acute illness or severe trauma within the 3 months before study, and myocardial infarction, major surgery, or percutaneous transluminal coronary angioplasty within the 6 months before study. Concomitant treatment with oral contraceptives, any systemic steroid hormones, oral anticoagulants, or other lipid-lowering agents, was not permitted during the study.

Study design
This was an open-label, active-controlled randomized study involving 2 parallel groups. Patients were screened for eligibility 4 weeks before study entry (week –4) and at baseline (week 0). During this 4-week placebo/dietary run-in period, 1 placebo capsule was administered daily at bedtime. Patients were instructed about, and encouraged to maintain, an NCEP step I or

II diet throughout the study. At the first screening visit, written informed consent approved by our institutional review board was obtained from each patient and medical histories were reviewed. Eligible patients who completed the run-in period entered a 12-week treatment phase with either a slow-release fluvastatin 80-mg tablet, or an immediate-release fluvastatin 40-mg capsule, each administered once daily at bedtime. Patients were asked to attend the center on 7 occasions during the trial (screening, week –2, baseline, and weeks 2, 4, 8 and 12). At each of these visits, adverse events, concomitant medication usage, and treatment compliance, were recorded. The total study duration for each patient, including the placebo/dietary run-in period, was 16 weeks.

Efficacy criteria
The primary efficacy endpoint was the mean percent change in LDL cholesterol level from baseline to study end. Secondary efficacy variables were percent changes from baseline to study end in total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, apolipoprotein A1 and apolipoprotein B levels, and the percent of patients attaining NCEP ATP II target LDL cholesterol levels: for patients with coronary heart disease (CHD), < 100 mg/dL; for patients without CHD but with ≥ 2 risk factors for CHD, < 130 mg/dL; and for patients without CHD and < 2 risk factors for CHD, < 160 mg/dL.

Safety criteria
Safety and tolerability were evaluated by adverse event reporting, laboratory studies and recording of vital signs. Patients were questioned at every visit about the occurrence of adverse events using non-leading questions. A physical examination and electrocardiogram were performed on day 1 and at study end. Fasting blood chemistry, complete blood count, urinalysis parameters, and thyroid stimulating hormone levels were measured during the study. Patients with elevated ALT or AST levels to ≥ 3 times the ULN were retested within 1 week; persistence of such elevation led to patient discontinuation. Patients with unexplained elevation of creatine kinase to ≥ 10 times the ULN were also discontinued from the study.

Statistical analysis
The primary efficacy endpoint, the percent decrease from baseline in LDL cholesterol, was calculated from the mean of the final 3 measurements in the run-in phase and the measurement after 12 weeks of treatment. The results were analyzed on an intention-to-treat basis. A series of secondary endpoints were also

evaluated, including percent and mean absolute changes in total cholesterol, HDL cholesterol, and triglyceride levels, and the percent of patients attaining NCEP ATP II target levels for LDL cholesterol. Continuous variables were expressed as mean ± standard deviation (SD). To assess the efficacy of treatment, paired comparisons before and after treatment were performed using the paired t test. Comparisons between the 80 mg/day and 40 mg/day groups were performed using the 2-sample t test. Categoric variables were analyzed using the Chi-squared test. Statistical significance was set at $p < 0.05$. Safety results were reported for all randomized patients who had received at least 1 dose of active medication.

Results

Demographic and clinical characteristics

Of the 109 patients screened, 61 met entry criteria and were randomized to treatment with slow-release fluvastatin 80 mg/day ($n = 31$) or immediate-release fluvastatin 40 mg/day ($n = 30$). Six patients in the 80 mg group and 10 in the 40 mg group had a history of CHD. One patient in the 80 mg group and 3 in the 40 mg group had a history of other atherosclerotic diseases; all of these patients also had CHD. Otherwise, there were no significant differences between treatment groups regarding baseline demographic characteristics. Of the 61 patients randomized, 52 completed the study. In the 80 mg group, 3 patients discontinued the study because of adverse events (back pain, abdominal pain) or laboratory abnormalities. In the 40 mg group, 6 patients discontinued the study because of adverse events (impaired urination, abnormal liver function tests), prohibited medication used, concomitant illness, loss to follow-up, or withdrawal of consent (Table 1).

Effects on lipids and lipoproteins

Lipid and lipoprotein levels were compatible between the 2 treatment groups at baseline. Figure 1 and Table 2 summarize the effects of treatment on lipid and lipoprotein levels at baseline and after treatment. After 12 weeks of fluvastatin therapy plus an NCEP step I or II diet, the mean percent decrease from baseline in LDL cholesterol level was 29.9% for the 80 mg/day group (from 186 ± 33 to 130 ± 41 mg/dL, $p < 0.0001$) and 22.5% for the 40 mg/day group (from 191 ± 33 to 148 ± 42 mg/dL, $p < 0.0001$).
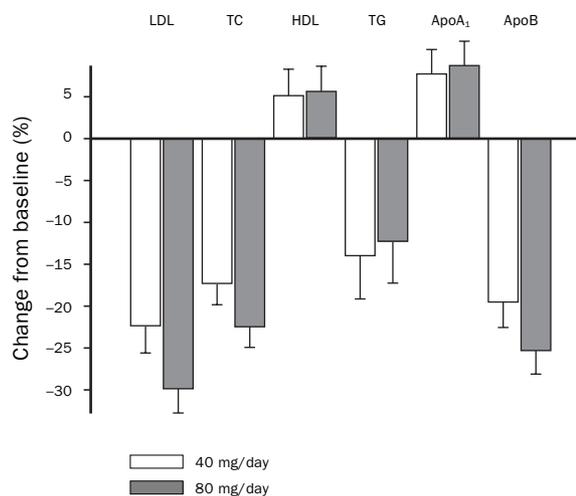

Figure 1. Effects of 12 weeks of treatment with fluvastatin 40 mg/day versus 80 mg/day on plasma lipid and lipoprotein profiles in 61 Chinese patients with primary hypercholesterolemia. There were no significant differences between the 2 groups regarding changes in levels of low-density lipoprotein (LDL) cholesterol, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, triglycerides (TG), apolipoprotein A1 (ApoA$_1$) and apolipoprotein B (ApoB).

Table 1. Demographic data of study patients

	Fluvastatin		p
	80 mg/day ($n = 31$)	40 mg/day ($n = 30$)	
Age (yr)	64 ± 12	64 ± 12	0.968
Gender (M/F)	16/15	13/17	0.528
Weight (kg)	64 ± 10	61 ± 10	0.139
Height (cm)	159 ± 7	158 ± 9	0.671
Body mass index (kg/m^2)	25.3 ± 3.0	24.1 ± 2.9	0.112
Systolic blood pressure (mmHg)	125 ± 16	125 ± 16	0.828
Diastolic blood pressure (mmHg)	77 ± 9	76 ± 9	0.943
Heart rate (beats/min)	68 ± 8	70 ± 8	0.297
Previous statin therapy, n (%)	13 (41.9)	15 (50.0)	0.483

Values shown are mean ± standard deviation unless indicated otherwise.

Table 2. Effects of fluvastatin 40 mg/day and 80 mg/day on fasting lipid and lipoprotein profiles

	Baseline (mg/dL)	Week 12 (mg/dL)	% change	95% confidence interval	*p**
Total cholesterol					
40 mg/day	269 ± 40	222 ± 45	–17.3	–17.5, –27.5	0.140
80 mg/day	266 ± 37	204 ± 45	–22.5	–12.1, –22.5	
LDL cholesterol					
40 mg/day	191 ± 33	148 ± 42	–22.5	–16.1, –28.8	0.087
80 mg/day	186 ± 33	130 ± 41	–29.9	–23.7, –36.0	
HDL cholesterol					
40 mg/day	48 ± 12	50 ± 13	5.2	–1.3, 11.6	0.917
80 mg/day	47 ± 11	50 ± 13	5.6	–0.6, 11.9	
Triglycerides					
40 mg/day	151 ± 68	123 ± 50	–14.0	–3.7, –24.3	0.813
80 mg/day	158 ± 66	124 ± 49	–12.3	–2.4, –22.3	
Apolipoprotein A1					
40 mg/day	135 ± 22	143 ± 29	7.8	–0.3, 15.9	0.855
80 mg/day	131 ± 27	143 ± 26	8.7	–1.4, 16.0	
Apolipoprotein B					
40 mg/day	155 ± 30	121 ± 30	–19.5	–15.8, –27.1	0.079
80 mg/day	150 ± 29	113 ± 28	–25.4	–22.7, –33.2	

*p values between groups. Values for all parameters are mean ± standard deviation.

Table 3. Patients reaching low-density lipoprotein cholesterol (LDL-C) goals (responders) of the US National Cholesterol Education Program at study end

Risk category	LDL-C goal	Fluvastatin 80 mg/day		Fluvastatin 40 mg/day	
		Patients, *n*	Responders, *n* (%)	Patients, *n*	Responders, *n* (%)
CHD	< 100 mg/dL	6	1 (17)	10	0 (0)
≥ 2 risk factors	< 130 mg/dL	20	16 (80)	18	9 (50)
< 2 risk factors	< 160 mg/dL	5	3 (60)	2	2 (100)
All categories	–	31	20 (65)	30	11 (37)

CHD = coronary heart disease.

The percent changes in LDL cholesterol were not significantly different between the 2 groups (p = 0.087). The proportion of patients with a more than 15% reduction from baseline in LDL cholesterol level was 77% in the 80 mg/day group and 70% in the 40 mg/day group. Overall, more patients in the 80 versus 40 mg/day group reached LDL cholesterol goals of the NCEP ATP II (65% vs 37% of patients, $p < 0.05$; Table 3).

The reductions in total cholesterol levels were 22.5% (from 266 ± 37 to 204 ± 45 mg/dL) in the fluvastatin 80 mg/day group and 17.3% (from 269 ± 40 to 222 ± 45 mg/dL) in the 40 mg/day group. HDL cholesterol levels increased slightly by 5.6% in the 80 mg/day group (47 ± 11 to 50 ± 13 mg/dL), and by 5.2% in the 40 mg/day group (from 48 ± 12 to 50 ± 13 mg/dL). The reduction in triglyceride levels was 14% (from 151 ± 68 to 123 ± 50 mg/dL) in the 40 mg/day group and 12.3% (from 158 ± 66 to 124 ± 49 mg/dL) in the 80 mg/day group. Apolipoprotein A1 levels increased by 8.7% in the 80 mg/day group (from 131 ± 27 to 143 ± 26 mg/dL), and by 7.8% (from 135 ± 22 to 143 ± 29 mg/dL) in the 40 mg/day group. Apolipoprotein B levels decreased by 25.4% (from 150 ± 29 to 113 ± 28 mg/dL) in the 80 mg/day group, and by 19.5% (from 155 ± 30 to 121 ± 30 mg/dL) in the 40 mg/day group. Percent changes in total cholesterol, triglyceride, HDL cholesterol,

apolipoprotein A1, and apolipoprotein B levels were not statistically significantly different between the 2 treatment groups.

Safety

No statistically significant differences were found in the incidence of adverse events between the 2 treatment groups. Overall, 9 patients (29%) in the fluvastatin 80 mg/day group and 3 (10%) in the 40 mg/day group reported adverse events during treatment, but the difference was not significant ($p = 0.105$). Drug-related myalgia occurred in 4 patients (12.9%) in the 80 mg/day group, but in none in the 40 mg/day group. No cases of myalgia were critical or notable as defined by the study protocol (i.e. accompanied by elevations of creatine kinase to ≥ 5 times the ULN).

The incidence of serum transaminase elevations to more than 3 times the ULN on non-consecutive (not notable) or 2 consecutive (notable) occasions was similar between the 2 treatment groups (3.2% in the 80 mg/day group, and 3.5% in the 40 mg/day group). No critical (≥ 5 times the ULN) or notable (≥ 10 times the ULN) creatine kinase elevations were observed in either treatment group.

Two patients in the fluvastatin 80 mg/day group had non-fatal, serious adverse events during treatment (abdominal pain and coronary artery disorder), yet neither of these events was considered by the investigators to be related to the study medication. No clinically significant differences in vital signs, body weight, or abnormalities on physical examination, were noted between the 2 treatment groups.

Discussion

This study showed that, in Chinese patients with primary hypercholesterolemia, doubling the dosage of fluvastatin from 40 to 80 mg once daily at bedtime resulted in an additional 7.5% decrease in LDL cholesterol level. Further, the 80 mg/day schedule was well tolerated, with an adverse effect profile similar to that of the 40 mg/day regimen.

Trends exist towards greater LDL cholesterol reductions in some patients during treatment with higher rather than lower dosages of statins, even though dose-response curves for statins are curvilinear and not proportional. In general, doubling statin dosages above minimal effective levels will decrease LDL cholesterol by an additional 6%.[9,10] However, ethnic differences exist in dose-response relationships for statins, as demonstrated in the Expanded Clinical

Evaluation of Lovastatin (EXCEL) study.[12] Thus, it was necessary to determine the efficacy and safety of doubling the dosage of fluvastatin from 40 to 80 mg/day in the Chinese population.

In the present study, such doubling of the fluvastatin dosage caused an additional 7.5% decrease in LDL cholesterol from baseline, which is greater than the 6% decrease reported in earlier studies.[9,10] The mean LDL cholesterol decrease in the current study was 22.5% in the fluvastatin 40 mg/day group; this is consistent with previous studies in Europe and North America that demonstrated a 24% decrease in LDL cholesterol with this dosage.[7] Although the additional LDL cholesterol reduction with the fluvastatin 80 mg/day versus 40 mg/day schedule in the current study was not statistically significant, it still allowed almost twice as many patients to attain goals for LDL cholesterol suggested by NCEP ATP II, which emphasize more intensive LDL cholesterol lowering in patients with established CHD. Soon after the completion of our study, updated NCEP ATP III guidelines were released, and the importance of intensive LDL cholesterol lowering was extended to certain patients with high CHD risk, even in cases of primary prevention.[13]

Fluvastatin increased HDL cholesterol by 5.2% in the 40 mg/day group, and by 5.6% in the 80 mg/day group. These elevations in HDL cholesterol were smaller than in a previous study in Europe and North America, which demonstrated a mean increase of 7.8%.[7] The determinants of HDL cholesterol response to statins are not well defined. In a study in Israel of fluvastatin 40 mg/day in patients with heterozygous familial hypercholesterolemia, changes in HDL cholesterol were related to a specific LDL-receptor mutation, to several constitutional factors, and to baseline lipid profiles.[14] Whether differences exist between Chinese and Caucasian populations regarding HDL cholesterol responses to statins requires further investigation in larger numbers of patients.[15]

In the present study, triglyceride levels were reduced by 12.3% in the fluvastatin 80 mg/day group, and by 14% in the 40 mg/day group. This was similar to results from another study in Chinese patients in Hong Kong, which showed that fluvastatin 20–40 mg/day reduced serum triglyceride levels by 12%.[16] Data from previous studies in Europe and North America showed that fluvastatin 40 mg/day reduced triglyceride levels by 10.6%.[7] Although the triglyceride-lowering effects of statins are usually dose-dependent,[12] in our study, the 80 mg/day group did not have a markedly greater reduction in triglycerides than the 40 mg/day group, despite

similar baseline triglyceride and HDL cholesterol levels. The effects of statins on HDL cholesterol and triglyceride levels depend not only on dosage, but also on baseline lipid levels, i.e. the higher the baseline triglyceride level, the greater the subsequent change.[17] It remains to be determined whether the lack of difference in triglyceride-lowering is related to the ceiling effect or the small sample size.

No significant difference in the incidence of adverse events was noted between the 2 fluvastatin groups in our study. The most important adverse events associated with statins are myopathy and asymptomatic increases in serum transaminase levels.[18] However, no patients developed myopathy (muscle pain accompanied by an increase in creatine kinase to ≥ 10 times the ULN); further, none of the 4 patients in the 80 mg/day group who developed myalgia had critical or notable creatine kinase elevations as defined by the study protocol. Although dose-dependent increases in transaminase levels have been observed during statin therapy,[5] there were no such increases in, and no differences between, the 2 fluvastatin groups in our study. These results indicate that fluvastatin 80 mg/day is equally as safe and well tolerated as a 40 mg/day regimen in Chinese patients.

Although the sample size in the present study was relatively small, the lipid-lowering effects of fluvastatin were consistent with published data.[7,8] Nevertheless, we acknowledge that, because of our small sample size, there may have been insufficient statistical power to demonstrate a difference between the 2 fluvastatin schedules.

In conclusion, in Chinese patients with primary hypercholesterolemia, doubling the dosage of fluvastatin from 40 mg to 80 mg once daily is effective and safe in terms of reducing LDL cholesterol; such dosage doubling might also permit more treated patients to achieve NCEP ATP II goals for LDL cholesterol.

Acknowledgments

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