Extended-release fluvastatin 80 mg shows greater efficacy, with comparable tolerability, versus immediate-release fluvastatin 40 mg for once daily treatment of primary hypercholesterolaemia

DONALD B HUNNINGHAKE, MICHAEL DAVIDSON, HOWARD R KNAPP, HELMUT G SCHROTT, SHERYL MANFREDA, AND THE FLUVASTATIN STUDY GROUP

Abstract

A new extended-release (XL) formulation of fluvastatin has been developed for once daily treatment of primary hypercholesterolaemia. This study was designed to determine the safety and effect of fluvastatin XL 80 mg on a range of lipid parameters compared with the immediate-release (IR) formulation of fluvastatin 40 mg.

In a multicentre, double-blind study, 555 patients with primary hypercholesterolaemia (Fredrickson types IIa or IIb) were randomised to 24 weeks treatment with fluvastatin XL 80 mg or IR 40 mg, each given once daily at bedtime. The study found the least square mean reduction in LDL-C after 24 weeks treatment was 32.6% in the fluvastatin XL 80 mg group (n=312) and 23.9% in the fluvastatin IR 40 mg group (n=165), an 8.7% between-treatment difference (95% confidence interval: 6.5%, 10.9%) in favour of the XL formulation (p<0.001). A higher proportion of patients in the fluvastatin XL 80 mg group achieved ≥ 35% reductions in low-density lipoprotein cholesterol (42.3% *vs.* 13.3%). High-density lipoprotein cholesterol levels were increased by 9.1% and 7.0%, respectively in the XL and IR groups; median triglyceride levels fell by 19% and 13%, respectively. Tolerability was comparable in the two groups, and there were no laboratory safety concerns.

The study concluded that fluvastatin XL 80 mg once daily is safe as a starting dose and effectively lowers low-density lipoprotein cholesterol and triglyceride levels in patients with primary hypercholesterolaemia.

Key words: fluvastatin, extended-release formulation, hypercholesterolaemia, low-density lipoprotein (LDL) cholesterol.

Departments of Medicine and Pharmacology, University of Minnesota, Minneapolis, USA.
Donald B Hunninghake, Director, Heart Disease Prevention Clinic

Chicago Center for Clinical Research, Chicago, Illinois, USA.
Michael Davidson, President and CEO

Deaconess Billings Clinic, Billings, Montana, USA.
Howard R Knapp, Executive Director, Research Division

University of Iowa, Iowa City, Iowa, USA.
Helmut G Schrott, Director, Lipid Research Clinic

Novartis, East Hanover, New Jersey, USA.
Sheryl Manfreda, Division of Clinical Development and Regulatory Affairs

Correspondence to: Dr DB Hunninghake, Departments of Medicine and Pharmacology, Box 192 UMHC, 151 VCRC, Minneapolis, MN 55455, USA.
(email: hunni001@maroon.tc.umn.edu)

Introduction

The place of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ('statins') as first-line therapy in the treatment of elevated cholesterol levels is well established.[1] This conclusion is based on the results of numerous, large-scale outcome studies with these agents, in which reductions in low-density lipoprotein cholesterol (LDL-C) levels of 25–35% were associated with considerable reductions in cardiovascular morbidity and mortality.[2-6]

Fluvastatin (Novartis Pharma, Basel, Switzerland), the first totally synthetic competitive inhibitor of HMG-CoA reductase, effectively lowers LDL-C, total cholesterol, triglyceride and apolipoprotein-B levels, raises high-density lipoprotein cholesterol (HDL-C), and is well tolerated in the treatment of primary hypercholesterolaemia and mixed dyslipidaemias.[7-9] At once daily doses of 20–40 mg, for example, the immediate-release (IR) formulation of fluvastatin achieves mean reductions in LDL-C of 22–25% with long-term treatment.[8] Some patients may require titration to a dosage of 80 mg/day (i.e. 40 mg twice daily) to achieve 25–35% reductions in LDL-C and their respective therapeutic targets. In order to do so, twice daily administration of a 40 mg IR dose is presently required. However, fluvastatin IR

exhibits non-linear pharmacokinetics at high doses, and saturable hepatic uptake.[10,11] This limitation may be overcome or minimised by providing slower delivery of the drug to the liver. Such an approach, i.e. by altering the pharmacokinetics of fluvastatin absorption, might also be expected to increase hepatic availability and, hence, its pharmacodynamic effect on LDL-C, without raising systemic drug levels. Once daily bedtime administration of an extended-release (XL) formulation of fluvastatin would maximise patient convenience and optimise its effects on lipoprotein levels throughout the period when cholesterol biosynthesis is maximal.[12]

A comprehensive evaluation of delivery systems providing sustained drug release has led to the development of a fluvastatin 80 mg matrix tablet XL formulation. This delivery system provides sustained release of the drug over an eight-hour period, resulting in markedly lower systemic drug levels than an identical dosage of the marketed IR formulation.[13] The primary objective of the present study was, therefore, to determine the long-term safety and efficacy of fluvastatin XL 80 mg once daily, compared with fluvastatin IR 40 mg once daily, in lowering LDL-C levels in patients with primary hypercholesterolaemia. The secondary objectives of the study included an assessment of effects on other lipoprotein parameters.

Methods

This was a prospective, randomised, double-blind, parallel-group study in male and female patients aged ≥18 years with primary hypercholesterolaemia (Fredrickson types IIa or IIb) conducted at 30 centres in the USA. The total study duration was 28 weeks, comprising a four-week placebo/dietary run-in period followed by 24 weeks active treatment.

Ethics

The study protocol was approved for each participating centre by an ethics committee, and all patients gave informed, written consent prior to enrollment. Conduct of the study complied with the revised Declaration of Helsinki directives.

Patients

Patients discontinued all hypolipidaemic drugs and received dietary counselling for at least four weeks prior to the placebo/dietary run-in period. Each patient was required to follow a low-fat, cholesterol-restricted diet (European Atherosclerosis Society [EAS] or National Cholesterol Education Program [NCEP] Step I or II diet) during this period and for the remainder of the 28-week study. Only those patients who adhered to the diet were eligible to commence the four-week placebo run-in phase. Patients meeting the lipid inclusion criteria (LDL-C ≥ 4.1 mmol/L, triglycerides ≤ 4.5 mmol/L) on two occasions during the run-in phase were eligible for entry into the 24-week, double-blind phase of the study. Week 0 values were not used to determine eligibility. Eligible patients were randomised (2:1 ratio) to receive oral therapy with either fluvastatin XL 80 mg tablets or fluvastatin IR 40 mg capsules, each administered once daily at bedtime. Patients attended the clinic at 2–4 week intervals for safety and compliance assessments (counting of returned, unused medication) and lipid determinations. Concomitant treatment with other hypolipidaemic drugs, antiplatelet drugs (other than stable dosages of aspirin and ticlopidine), oral contraceptives/systemic steroidal hormones (except stable dosages of non-cyclic oestrogen/progestogen hormone replacement therapy), insulin or oral hypoglycaemic agents, cyclosporin or continuous systemic erythromycin was not permitted during the study.

Patients were excluded from the study if they had homozygous familial hypercholesterolaemia, type I, III, IV or V hyperlipoproteinaemia (WHO classification), hyperlipidaemia secondary to other causes, or abnormal laboratory evaluations. Other exclusion criteria included: pregnancy, lactation or inadequate mechanical contraception in women of child-bearing potential; any current condition that might significantly alter drug pharmacokinetics; any acute illness or trauma during the previous three months; uncontrolled hyperthyroidism; myocardial infarction, major cardiac surgery or angioplasty during the prior six months; severe or unstable angina pectoris; inadequately controlled congestive heart failure or hypertension; prior or current musculoskeletal disease; or, history of drug abuse. Use of probucol within the previous year was also a reason for exclusion, as was any history of resistance/hypersensitivity to lipid-lowering therapy.

Evaluations

Measurement of lipids

At each visit, 12-hour fasting blood samples were obtained for determination of total cholesterol (TC), LDL-C, HDL-C, triglycerides (TG) and LDL:HDL ratio. LDL-C was calculated using the Friedewald formula;[14] direct measurement of LDL-C was required if TG levels were > 4.5 mmol/L during the active treatment phase. Levels of apolipoproteins A1 and B (apo A1, apo B) were measured at weeks 0, 12 and 24. Investigators and patients were blind to lipid results throughout the study.

Safety and tolerability

Safety was assessed at every visit by evaluating newly occurring or worsening adverse events, vital signs, laboratory parameters and electrocardiogram (ECG) recordings. The main laboratory evaluation comprised measurement of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and the muscle enzyme creatine kinase (CK). All adverse events (volunteered spontaneously by the patient, or identified by the investigator through questioning or test findings) were recorded, irrespective of likely causality.

A central laboratory (Medical Research Laboratory, Highland Heights, KY, USA) performed all laboratory tests for this study, including lipid and laboratory safety assays.

Statistics

The sample size was considered adequate not only to detect a clinically meaningful 6% between-treatment difference for change in LDL-C from baseline (primary efficacy variable) when the daily dose is doubled, but also adequate to provide sufficient

Table 1. Summary of patient demographic and clinical characteristics at baseline for all randomised patients

Parameter	Fluvastatin XL 80 mg (n=370)	Fluvastatin IR 40 mg (n=185)
Male:female	193:177	88:97
Mean age ± SD (range), years	58 ± 12 (21–87)	57 ± 12 (18–85)
Mean body mass index ± SD, kg/m^2	27 ± 3	28 ± 4
Previous use of HMG-CoA reductase inhibitors[a]	42%	41%
History of coronary heart disease	30%	27%
Mean lipid values ± SD (mmol/L)[b]	n=369	n=183
TC	7.19 ± 0.85	7.21 ± 1.01
LDL-C	4.94 ± 0.80	5.02 ± 0.96
HDL-C	1.29 ± 0.31	1.27 ± 0.31
LDL:HDL ratio	4.0 ± 1.1	4.2 ± 1.3
TG	2.07 ± 0.81	2.11 ± 0.81
Apo A1[c]	3.88 ± 0.65	3.83 ± 0.70
Apo B[c]	4.63 ± 0.62	4.68 ± 0.78

Key: [a]n= 369 and n=183 for fluvastatin XL 80 mg and IR 40 mg, respectively; [b]Categories include only patients in the intention-to-treat analysis (n=369 and n=183 for fluvastatin XL 80 mg and IR 40 mg, respectively); [c]n=354 and n=178 for fluvastatin XL 80 mg and IR 40 mg, respectively; XL = extended release; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; IR = immediate release; n = number of patients; SD = standard deviation; TC = total cholesterol; TG = triglycerides.

Table 2. The least squares mean (SE) per cent change from baseline to week 24 in lipid parameters for all randomised patients

Parameter	Treatment group	
	Fluvastatin XL 80 mg (n=312)	Fluvastatin IR 40 mg (n=165)
TC	-23.1% (0.59)[a]	-16.9% (0.77)
LDL-C	-32.6% (0.75)[a]	-23.9% (0.97)
HDL-C	9.1% (0.81)	7.0% (1.05)
LDL:HDL ratio	-37.5% (0.85)[a]	-28.2% (1.10)
TG	-15.1% (1.86)	-10.1% (2.41)
Apo A1[b]	8.1% (0.73)	6.9% (0.95)
Apo B[b]	-24.7% (0.70)[a]	-17.5% (0.91)

Least squares means are adjusted for centre.

Key: [a]p<0.001 compared with fluvastatin IR 40 mg (two-way ANOVA with treatment and centre as factors); [b]Data missing for two patients in each treatment group; Apo A1 = apolipoprotein A1; apo B = apolipoprotein B; XL = extended release; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; IR = immediate release; n = number of patients; SE = standard error of the least squares mean; TC = total cholesterol; TG = triglycerides.

patient numbers for safety evaluation. Efficacy analyses were based on the intention-to-treat principle; namely, all randomised patients with a baseline and at least one post-baseline efficacy measurement for a given variable were included. Comparison of least squares mean per cent change from baseline in lipid variables between treatment groups was performed by two-way analysis of variance (ANOVA) with treatment and centre as factors. The primary efficacy variable (LDL-C) was analysed at last assessment by a standard two-sided test to demonstrate superiority of fluvastatin XL 80 mg over fluvastatin IR 40 mg. An overall two-sided significance level of 5% was preserved by using Hochberg's multiple-testing step-up procedure.[15] For week 24 analyses of all lipid variables, a two-sided test for the difference between treatment groups was used. Two-sided 95% confidence intervals were calculated for between-treatment differences for all efficacy variables.

Key baseline and demographic variables were evaluated by standard descriptive summaries and between-group tests at the two-sided 5% significance level (Cochran–Mantel–Haenszel chi-square test or F-test from a two-way ANOVA with treatment and centre as factors). Baseline was defined as the mean of each patient's lipid levels at week 0 and the last previous value (either week two or week one), while for apo A1 and apo B, baseline was defined as the week 0 value. All patients who had received at least one dose of study medication, and who subsequently had at least one safety evaluation, were included in the safety analysis.

Results

A total of 1,187 patients were screened for enrollment; 555 (47%) of these patients were randomised at the end of the placebo/dietary run-in period: 370 in the fluvastatin XL 80 mg group and 185 in the fluvastatin IR 40 mg group. The most common reasons for discontinuation prior to randomisation were protocol violations (87%, mainly lipid ineligibility), withdrawal of consent (5%) and abnormal laboratory values (4%).

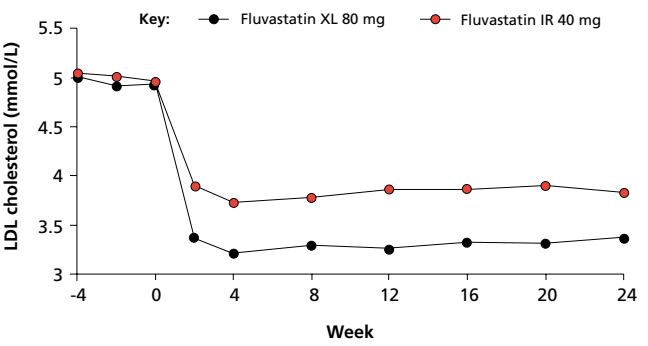
The two randomised treatment groups were similar with respect to most baseline demographic and background characteristics, although there was a small (but statistically significant, p<0.05) difference in LDL:HDL ratio (table 1). This difference was found to have no bearing on the outcome of the primary efficacy analysis involving LDL-C reductions.

A total of 477 patients (86%) completed the study: 313 in the fluvastatin XL 80 mg group and 164 in the fluvastatin IR 40 mg group. The most common reasons for premature discontinuation were withdrawal of consent, adverse events and abnormal laboratory values. Withdrawals due to adverse events showed higher frequency in the fluvastatin XL 80 mg group (18 patients [5%]) compared with the fluvastatin IR 40 mg group (three patients [2%]). A satisfactory level of compliance and adherence to diet was achieved in both treatment groups during the study.

Efficacy

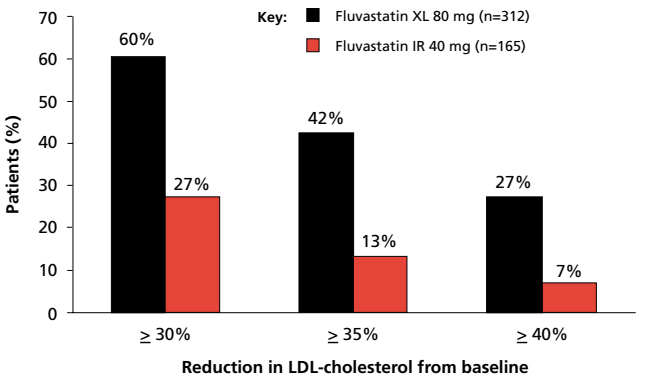
A significantly greater decrease in LDL-C levels at last assessment was evident in patients treated with fluvastatin XL 80 mg com-

Figure 1. Mean LDL-cholesterol levels in all evaluable randomised patients over the 28-week study period; randomisation took place at week 0



Key: XL = extended release; IR = immediate release; LDL = low-density lipoprotein

Figure 2. Categorical analysis of per cent reduction in LDL-cholesterol from baseline to 24 weeks



Key: XL = extended release; IR = immediate release; LDL = low-density lipoprotein

Table 3. Mean (SD) and median per cent change from baseline to last assessment in lipid parameters, analysed according to phenotype: Fredrickson type IIa (TG level < 2.3 mmol/L) or IIb (TG level ≥ 2.3 mmol/L)

Parameter	Fluvastatin XL 80 mg		Fluvastatin IR 40 mg	
	IIa (n=230)	IIb (n=139)	IIa (n=114)	IIb (n=69)
LDL-C	-30.3 (13.9), -32	-30.5 (15.3), -31	-23.3 (10.7), -23	-21.0 (15.2), -25
HDL-C	5.8 (12.8), 5	12.3 (14.3), 11	5.9 (11.0), 5	8.3 (12.4), 7
TG	-8.8 (28.8), -13	-22.5 (26.6), -23	-4.4 (31.4), -8	-16.7 (24.3), -16

Key: XL = extended release; IR = immediate release; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; SD = standard deviation; TG = triglycerides

pared with the fluvastatin IR 40 mg group: 31.0% versus 23.0%, respectively, a difference of 8.0% points in favour of the fluvastatin XL 80 mg group (95% CI: 5.6 to 10.4; p<0.001). At week 24, a similar pattern was seen, with an 8.7% difference (95% CI: 6.5 to 10.9; p<0.001) between the two treatment groups (table 2).

Most of the reduction in LDL-C occurred during the first two weeks of treatment in both groups (figure 1), with maximal reduction observed by week four – a mean 36% reduction with fluvastatin XL 80 mg and 26% with fluvastatin IR 40 mg was achieved by week four. LDL-C reductions were maintained for the remaining 20 weeks of the treatment period. Categorical analysis showed that 42% of patients in the fluvastatin XL 80 mg group achieved ≥ 35% reductions in LDL-C, and the proportion of patients with LDL-C reductions of ≥ 40% was approximately four-fold more compared with the fluvastatin IR 40 mg group (27% versus 7%, respectively; figure 2).

Reductions in TC, TG, LDL:HDL ratio and apo B were also greater in patients treated with fluvastatin XL 80 mg, and between-treatment comparisons were statistically significant for TC, LDL:HDL ratio and apo B (table 2).The mean increase in HDL-C was greater in the group treated with fluvastatin XL 80 mg (9.1% versus 7.0%) but did not achieve statistical significance.

A greater TG-lowering effect was seen in patients with mixed dyslipidaemia (type IIb, baseline TG ≥ 2.3 mmol/L) compared with patients with primary hypercholesterolaemia (type IIa; baseline TG < 2.3 mmol/L) (table 3) for both treatment groups. Median decreases in TG levels for the type IIb patients were 23% in the fluvastatin XL 80 mg group and 16% in the fluvastatin IR 40 mg once daily group. Increases in HDL-C were also more marked in these patients, with a mean increase of 12.3% in the fluvastatin XL 80 mg group compared with a mean increase of 8.3% in the fluvastatin IR 40 mg group (table 3).

Safety and tolerability

A total of 552 patients were included in the safety analysis (three randomised patients were excluded because no safety data were available post-randomisation): 369 in the fluvastatin XL 80 mg group and 183 in the fluvastatin IR 40 mg group. There were no major differences between the two treatment groups in terms of

Table 4. Summary of the most commonly reported adverse events

	Fluvastatin XL 80 mg (n=369)		Fluvastatin IR 40 mg (n=183)		
Adverse event	**Total**	**Drug-related**	**Total**	**Drug-related**	**p-value***
Number of patients experiencing adverse events	275 (74.5%)	58 (15.7%)	129 (70.5%)	28 (15.3%)	ns
Body as a whole general disorders	79 (21.4%)	6 (1.6%)	45 (24.6%)	2 (1.1%)	ns
Central and peripheral nervous system	39 (10.6%)	9 (2.4%)	18 (9.8%)	2 (1.1%)	ns
Gastrointestinal system	95 (25.7%)	34 (9.2%)	46 (25.1%)	17 (9.3%)	ns
Musculoskeletal system	86 (23.3%)	9 (2.4%)	45 (24.6%)	6 (3.3%)	ns
Respiratory system	114 (30.9%)	0	52 (28.4%)	0	ns
Vision disorders	9 (2.4%)	0	10 (5.5%)	0	ns

Key: XL = extended release; IR = immediate release; ns = p<0.05; *fluvastatin XL 80 mg *vs.* fluvastatin IR 40 mg

Table 5. Summary of number and proportions of patients with newly occurring or worsening serious adverse events during active treatment period

Serious adverse event	Fluvastatin XL 80 mg (n=369)	Fluvastatin IR 40 mg (n=183)
Chest pain	5 (1.4%)	0
Hypertension	1 (0.3%)	0
Syncope	1 (0.3%)	0
Headache	1 (0.3%)	0
Meningitis	1 (0.3%)	0
Migraine	1 (0.3%)	0
Ear disorder	1 (0.3%)	0
Bradycardia	0	1 (0.5%)
Cholelithiasis	1 (0.3%)	0
Osteomyelitis	1 (0.3%)	0
Angina pectoris	3 (0.8%)	0
Coronary artery disorder	2 (0.5%)	0
Aortic insufficiency	1 (0.3%)	0
Mitral insufficiency	1 (0.3%)	0
Myocardial infarction	1 (0.3%)	0
Chest pain	0	1 (0.5%)
Basal cell carcinoma	1 (0.3%)	0
Malignant neoplasm	1 (0.3%)	0
Pulmonary carcinoma	1 (0.3%)	0
Dyspnoea	1 (0.3%)	0
Pulmonary disorder	1 (0.3%)	0
Cerebrovascular disorder	1 (0.3%)	0
Embolism (blood clot)	1 (0.3%)	0
Blindness	1 (0.3%)	0

frequency or type of adverse events, which were generally mild to moderate in nature. Overall, there was no statistically significant difference in adverse events between the two treatment groups (table 4). The most frequent adverse events involved the respiratory, gastrointestinal and musculoskeletal systems. None of the respiratory adverse events were suspected as being drug-related. Gastrointestinal adverse events were suspected to be drug-related in 51 patients (fluvastatin XL 80 mg, n=34 [9%]; fluvastatin IR 40 mg, n=17 [9%]) and musculoskeletal adverse events in 15 patients (fluvastatin XL 80 mg, n=9 [2%]; fluvastatin IR 40 mg, n=6 [3%]). Although 17 adverse events were considered to be serious (fluvastatin XL 80 mg, n=15; fluvastatin IR 40 mg, n=2) (table 5), none of these were classified as drug-related. A total of 13 patients (fluvastatin XL 80 mg, n=10 [3%]; fluvastatin IR 40 mg, n=3 [2%]) discontinued the study due to adverse events suspected to be related to study medication. These were predominantly gastrointestinal events (nine patients). One case of abnormal ALT level and elevated alkaline phosphatase and bilirubin was reported in the fluvastatin XL 80 mg group and resulted in discontinuation from the study. Following discontinuation, the patient recovered without sequelae within three weeks. There were no deaths reported during the active treatment phase of the study.

Persistent elevations of transaminase levels (> 3x ULN [upper limit of normal] on two consecutive occasions) were reported in nine patients (2%) in the fluvastatin XL 80 mg group and five patients (3%) in the fluvastatin IR 40 mg group. Only one patient in the latter treatment group had a confirmed CK increase ($\geq$ 10 x ULN). Overall, 22 patients (4%) discontinued treatment due to abnormalities of primary laboratory safety parameters, with a similar percentage of discontinuations in each treatment group: 16 patients (4%) in the fluvastatin XL 80 mg group (including the patient with abnormal ALT, alkaline phosphatase and bilirubin) and six patients (3%) in the fluvastatin IR 40 mg group (including the patient with confirmed CK elevation). Time from randomisation at which the abnormalities resulting in discontinuation were observed to occur ranged from 17 to 133 days, with 80% occurring between days 28 and 56 of treatment. There were no clinically relevant trends for other laboratory safety parameters or changes in vital signs and body weight in either treatment group.

Discussion

The results of this study demonstrate that a starting and maintenance dose of fluvastatin XL 80 mg reduced mean LDL-C levels at week 24 by 8.7% more than the reduction in LDL-C that was associated with fluvastatin IR 40 mg. This exceeded the 7% between-treatment difference usually cited for a doubling of statin dose (see reference 16). The greater efficacy of fluvastatin XL 80 mg was seen at all time points throughout the study. Onset of LDL-C-lowering was rapid; maximal effect was observed after four weeks of active treatment and was maintained over the remaining 20 weeks of the study. The results of this study are, therefore, in concordance with previous short-term investigations,[17] and support the hypothesis that altering the pharmacokinetic properties of the fluvastatin formulation by changing the mode of drug delivery can be of benefit in treating hypercholesterolaemia.

In the present study, baseline LDL-C levels were approximately 4.9 mmol/L. Many patients had multiple concomitant risk factors for coronary heart disease. According to the US National Cholesterol Education Program (NCEP) guidelines,[18] such patients should achieve target LDL-C levels of < 3.4 mmol/L (European guidelines have a target of < 3.0 mmol/L).[19] A reduction of LDL-C of at least 35% was needed to achieve the < 3.4 mmol/L target. The results of this study show that over 40% of patients treated with fluvastatin XL 80 mg achieved this target level of LDL-C reduction.

Thus, for patients in whom aggressive lipid-lowering is advocated, a starting and maintenance dosage of fluvastatin XL 80 mg once daily provides a favourable means of achieving NCEP goals. Once daily administration of fluvastatin XL 80 mg has the added benefit of maximal patient convenience, potentially facilitating good compliance during long-term therapy.

Alterations in other lipid variables were also more marked among patients treated with fluvastatin XL 80 mg once daily, significantly so for TC, LDL:HDL ratio and apo B. Differences in TG and HDL-C levels in both treatment groups were most evident in patients with mixed dyslipidaemia, who tend to present with lower HDL-C and higher triglyceride levels. Alterations in HDL-C and TG levels without clinically relevant changes in LDL-C levels have been shown to confer clinical benefit.[20]

In addition to the favourable effects on the lipoprotein profiles, the present study provides a meaningful evaluation of the safety and tolerability of fluvastatin XL 80 mg administered over a period of 24 weeks. Overall, fluvastatin XL 80 mg was shown to be well tolerated. The type and incidence of adverse events experienced with fluvastatin XL 80 mg were similar to those observed with fluvastatin IR 40 mg. The fact that no increased frequency of musculoskeletal adverse events/CK abnormalities was apparent for the XL 80 mg dosage, is an important observation and is probably due to the decreased systemic exposure. The lack of CK abnormalities in fluvastatin recipients contrasts with the effect of cerivastatin in patients with primary hypercholesterolaemia. In a double-blind, parallel-group study, cerivastatin increased CK levels to > 10 x ULN in 5/90 (i.e. > 5%) of women aged over 65 years, with seven (i.e. > 7%) of these women experiencing associated symptoms.[21]

Key messages

- In patients with primary hypercholesterolaemia, a starting and maintenance dose of a new extended-release (XL) formulation of fluvastatin XL 80 mg once daily reduced mean LDL-C levels at week 24 by 32.6% *vs.* 23.9% in the fluvastatin IR 40 mg group
- Tolerability was good in both the fluvastatin IR and XL groups
- Fluvastatin XL 80 mg once daily is safe as a starting dose

Although more patients in the 80 mg XL group reported serious adverse events, there is no evidence of a safety risk as most events were reported only by one patient. Only events expected in this population were reported by more than one patient. Furthermore, other studies of similar duration have shown no higher incidences of serious adverse events or adverse event-related withdrawals with fluvastatin XL 80 mg compared with fluvastatin IR 40 mg.[22,23]

Transient elevation of transaminases is a well-known, albeit infrequent, complication of treatment with HMG-CoA reductase inhibitors. Such enzyme elevations are typically dose-dependent.[24] The rates of transaminase and other abnormalities with the 80 mg XL formulation were consistent with previous clinical experience with the IR formulation of fluvastatin, and no different than the lower dose of 40 mg IR in this study. These findings support the conclusion that the XL formulation achieves an increased efficacy without increasing the incidence of adverse laboratory abnormalities.

Conclusions

Fluvastatin XL 80 mg once daily effectively reduces LDL-C levels, produces favourable effects on other key lipoprotein parameters, and is well tolerated in the treatment of primary hypercholesterolaemia and mixed dyslipidaemia, achieving an 8.7% greater decrease in LDL-C levels than fluvastatin IR 40 mg and with similar tolerability. Thus, for patients in whom aggressive lipid-lowering is advocated, a starting and maintenance dosage of fluvastatin XL 80 mg once daily represents an adequate therapeutic option.

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