Efficacy of a low dose-range of fluvastatin (XU 62-320) in the treatment of primary hypercholesterolaemia. A dose-response study in 431 patients

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- 1 In this randomised, double-blind, placebo-controlled study, the efficacy of four dosages of fluvastatin (2.5, 5, 10 and 20 mg day⁻¹) were assessed in 431 patients with primary hypercholesterolaemia recruited in 17 centres.
- 2 Following an 8-week dietary stabilisation phase and a 6-week placebo phase, the patients were randomised to receive placebo or fluvastatin 2.5, 5, 10 or 20 mg once daily at night for a period of 6 weeks.
- 3 Total cholesterol, β -quant LDL-C, and the β -quant LDL-C/HDL-C ratio were significantly reduced by all doses of fluvastatin, and HDL-C was significantly increased by the 10 mg and 20 mg doses. Fluvastatin 20 mg day⁻¹ also significantly decreased TG and Lp(a):B levels.
- 4 Fluvastatin was well tolerated during the study, and relatively few biochemical or haematological abnormalities occurred.
- 5 Of the dosages tested, 20 mg fluvastatin day⁻¹ is the optimal hypolipidaemic dose.

Keywords fluvastatin HMG-CoA reductase inhibitor hypercholesterolaemia
coronary artery disease lipoproteins

Introduction

A number of studies, including the Framingham Study, provide convincing evidence of the correlation between high plasma cholesterol concentrations and increased risk of coronary artery disease (CAD) [1]. Plasma concentrations of LDL (low-density lipoprotein), the major plasma lipoprotein carrier of cholesterol, are directly related to the risk of CAD; a raised level of LDL is regarded as an independent risk factor. In addition, raised levels of the LDL-like lipoprotein particle, Lp(a), are also believed to be a risk factor for atherosclerosis and CAD, either in association with, or independently

of, raised LDL levels [2,3]. By contrast, plasma levels of HDL (high-density lipoprotein) are inversely related to the risk of CAD [1,4]. In theory, therefore, a reduction in plasma LDL, Lp(a) and LDL/HDL ratio, and an increase in plasma HDL, should attenuate the risk of CAD.

Fluvastatin is a new, entirely synthetic, competitive inhibitor of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the biosynthesis of cholesterol [5]. Absorption of orally administered fluvastatin is rapid and almost complete

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(> 90%), with plasma concentrations which reach steady-state after once daily administration [5]. Fluvastatin undergoes extensive hepatic first-pass metabolism [5].

The aims of this randomised, double-blind, parallel-group, placebo-controlled study were two-fold: the primary aim was to assess the effect on plasma lipid levels (particularly LDL-C) of a range of four dosages of fluvastatin, in order to establish the optimal hypolipidaemic dose among those tested while the secondary aim was to evaluate their effects on apolipoproteins (apo) and lipoprotein particles (Lp).

Methods

Subjects

Six hundred and thirty-four primary hypercholesterolaemic men and women, between the ages of 18 and 70 years, were recruited from 12 centres in France and 5 centres in the Netherlands. Written, informed consent was given by all subjects entering the study.

An 8-week dietary stabilisation phase was followed by a 6-week placebo phase (weeks -6 to 0) and then an active treatment phase (weeks 0 to 6), in which subjects were randomised to one of five treatment regimens. All hypolipidaemic medication was discontinued 4 weeks into the dietary stabilisation phase. Subjects were considered eligible for randomisation if their plasma LDL-C and triglyceride (TG) levels at weeks -6, -4 and -2 were $\geq 4.1 \text{ mmol l}^{-1}$ and $\leq 3.4 \text{ mmol l}^{-1}$, respectively. Furthermore, only subjects who demonstrated good compliance with dietary instruction during the week preceding week -6 were eligible for randomisation. Compliance with a fat- and cholesterol-restricted diet during a 3-day dietary recording period was assessed using food record rating [FRR] scores [6,7]. Briefly, the FRR translates quantitative estimates of food intake into a single value, based on the cholesterologenic nature of foods. Thus, the higher the FRR score the greater the dietary intake of saturated fat and/or cholesterol. Only subjects with a FRR score ≤ 15 over the 3-day recording period were eligible for randomisation. The plasma levels of LDL-C and TG at week 0 were not inclusion criteria.

Pregnant or lactating women or those of childbearing potential not using an intrauterine contraceptive device were excluded from the study, as were those with homozygous familial hypercholesterolaemia or type I, III, IV or V hyperlipoproteinaemia (according to the WHO classification). The presence or any history of serious medical or surgical conditions, particularly cardiovascular, gastrointestinal, ophthalmological, hepatic or renal diseases, were also reasons for exclusion.

Of the 634 subjects recruited, 203 (32%) were considered ineligible for randomisation and were excluded during the placebo phase. The most frequent reasons for exclusion were failure to fulfil inclusion criteria for lipid parameters. Thus, 86 and 42 subjects were excluded because they had LDL-C levels $< 4.1 \text{ mmol l}^{-1}$ and TG levels $> 3.4 \text{ mmol l}^{-1}$, respectively, together represent-

ing 63.1% of all exclusions. Other major reasons for exclusion were related to previous medical history and likelihood of patient non-cooperation (15.8% each).

Protocol

The study protocol was approved by ethical committees in France and the Netherlands.

Treatment

During the 8-week dietary stabilisation phase, patients received dietary counselling and were prescribed a fat- and cholesterol-restricted diet: either the American Heart Association (AHA) phase I, the National Cholesterol Education program (NCEP) step I, or the European Atherosclerosis Society (EAS) diet. Dietary compliance was monitored using FRR scores adapted to the dietary habits of the relevant country. After 4 weeks on the diet, all hypolipidaemic medication was discontinued, and after a further 4-week period, patients entered the single-blind placebo phase (weeks -6 to 0). The diet prescribed at the start of the dietary stabilisation phase was maintained for the entire duration of the study.

At week 0, 431 patients who fulfilled the entry criteria were randomised to one of five treatment groups, receiving oral placebo or fluvastatin 2.5, 5, 10 or 20 mg, at least 2 h after the evening meal, for 6 weeks.

Investigations

Patients underwent a general physical examination during each phase of the study, at weeks -6, 0 and 6. At each (fortnightly) clinic visit, a 12 h fasting blood sample was obtained by venepuncture into Vacutainer® tubes containing 1 mg ml^{-1} ethylenediaminetetra-acetic acid (EDTA) and analysed by a central laboratory (SERLIA, Institut-Pasteur, Lille, France) to determine the plasma lipid profile, consisting of plasma total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), very-low density lipoprotein cholesterol (VLDL-C), LDL-C and TG. Plasma concentrations of apo AI, apo AII, apo CIII, apo E, Lp AI, Lp AII:AI, Lp E:B, Lp CIII:B and Lp(a):B were evaluated from blood samples obtained at weeks -6, 0, 4 and 6. All plasma samples were stored at 4°C and analysed within 48 h of venepuncture.

Concentrations of TC, HDL-C, VLDL-C and TG were determined using enzymatic methods (Boehringer Mannheim, Germany), standardised according to the methods of the National Heart, Lung and Blood Institute (NHLBI, Bethesda, MD, USA)/Centers for Disease Control (CDC, Atlanta, GA, USA) Lipid Standardization Program. Independent quality control of TC, HDL-C and TG determinations was provided by Medical Research Laboratories (Cincinnati, OH, USA), using the methods of the NHLBI/CDC part III Monitoring Program. Following the isolation of VLDL-C by ultracentrifugation, HDL-C was isolated by the modified heparin-2M MnCl_2 (manganese chloride) method, which causes the precipitation of LDL-C. LDL-C (direct

β -quant) was determined by subtraction of HDL-C and VLDL-C from TC.

Apo AI and apo B were measured using immunonephelometric assays on a laser reader (Behring, Marburg, Germany). Immunoassays were used to determine apo AII, apo CIII [8] and apo E [9]. Two-site immunoassays were used to measure Lp AI: AII [10], Lp CIII: B, Lp E: B and Lp(a): B [11]. Lp AI was quantified according to Koren *et al* [10] using differential electroimmunoassay (Sebia, Issy-les-Moulineaux, France).

Laboratory parameters were assessed at each clinic visit (every 2 weeks) throughout the study. Haematological, coagulation and secondary biochemical parameters (calcium, inorganic phosphorus, blood urea nitrogen [BUN], uric acid, glucose, total protein, total bilirubin, sodium, potassium, chloride and creatinine) were analysed by the local laboratories, while primary biochemical parameters (aspartate aminotransferase [AST/SGOT], alanine aminotransferase [ALT/SGPT], creatine phosphokinase [CK], γ -glutamyl transferase [γ -GT] and alkaline phosphatase [ALP]) were evaluated by a central laboratory (SERLIA, Institut-Pasteur, Lille, France) using colorimetric tests (Boehringer Mannheim, Germany).

An ophthalmological examination, comprising lens and non-lens examinations, was performed on each patient once during the placebo phase and within 4 weeks following the last dose of medication.

Statistical analysis

Changes from baseline (baseline for efficacy parameters was the mean of values for weeks -2 and 0) were analysed at endpoint using an intention-to-treat analysis (with no subset analyses), and at weeks 2, 4 and 6.

Endpoint was defined as the last available value after week 0 (exclusive) for a particular parameter.

Paired *t*-tests were used to detect significant within-group changes from baseline. For variables that were not normally distributed, the Wilcoxon signed-rank test was employed. Between-group differences were assessed using analysis of variance (ANOVA), or for variables that were not normally distributed, the Kruskal-Wallis test. The Cochran-Mantel-Haenszel test, adjusting for centre, was used for categorical variables. $P < 0.05$ was considered significant.

All biochemistry and haematological data were range-adjusted to provide unit-free intermediate summary statistics [12].

Results

There were no statistically significant between-group differences in terms of demographic characteristics (Table 1), coexisting diseases, concomitant medication, compliance with diet ($\geq 87\%$) or with study medication ($\geq 98\%$) between week -6 and baseline. Within the respective groups, the mean percentage change for lipid parameters between week -6 and baseline (Table 1) was statistically significant for TG in the 2.5 mg and 20 mg groups ($P > 0.05$), and for VLDL-C in the 20 mg group ($P < 0.001$). However, at baseline, no significant differences in mean percentage change for lipid parameters were evident between the treatment groups. Since no active medication was administered between week -6 and baseline, the within group changes would appear to represent expected biological variability.

Seven patients discontinued the study after randomisation: three for protocol violations, three for non-

Table 1 Patient characteristics at baseline

Characteristic	Placebo (n = 86)	Fluvastatin dosage (mg day ⁻¹)			
		2.5 (n = 87)	5 (n = 85)	10 (n = 85)	20 (n = 87)
Age, years (mean $\pm$ s.d.)	51.5 $\pm$ 11.5	51.2 $\pm$ 12.3	48.0 $\pm$ 14.2	47.8 $\pm$ 12.2	50.9 $\pm$ 10.6
Height, cm (mean $\pm$ s.d.)	169.4 $\pm$ 8.6	167.4 $\pm$ 8.4	169.0 $\pm$ 9.2	169.3 $\pm$ 8.3	167.7 $\pm$ 8.7
Weight, kg (mean $\pm$ s.d.)	69.6 $\pm$ 10.8	69.0 $\pm$ 9.4	68.6 $\pm$ 10.4	68.9 $\pm$ 10.1	68.9 $\pm$ 10.3
Body mass index, kg/m ² (mean $\pm$ s.d.)	24.3 $\pm$ 2.7	24.6 $\pm$ 2.7	24.0 $\pm$ 2.7	24.0 $\pm$ 2.6	24.4 $\pm$ 2.4
Gender (% M/F)	59/41	51/49	63/37	57/43	53/47
Race (% Caucasian)	98.8	100.0	98.8	97.6	100.0
Smoker (%)	36.0	17.2	25.0	26.7	23.0
Mean change in lipid parameters between week -6 and baseline (%):					
TG	6.0	6.5*	4.2	3.6	13.7*
VLDL-C	8.9	3.7	7.5	5.6	16.9***
HDL-C	1.8	-0.2	0.7	1.7	1.3
TC	0.5	-0.5	-0.2	-0.3	0
β -quant LDL-C	0.8	-0.3	0.4	-0.4	-1.1

Significant difference between baseline and week -6: * $P < 0.05$, *** $P < 0.001$.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

cooperation, and one patient (placebo group) suffered a myocardial infarction.

Efficacy

The mean percentage changes from baseline for the main lipid parameters within each group are summarised in Table 2.

During the 6-week active treatment phase, all doses of fluvastatin (2.5, 5, 10 and 20 mg) caused a reduction in the levels of VLDL-C, TC, β -quant LDL-C and β -quant LDL-C/HDL-C ratio at each therapy visit and at endpoint, when compared with baseline values. For each of these parameters, with the exception of VLDL-C at week 2, the change from baseline was statistically significant for all doses of fluvastatin ($P < 0.001$).

Pairwise comparisons at endpoint indicated that each dose of fluvastatin was significantly superior to placebo in reducing VLDL-C, TC and β -quant LDL-C (Table 3). At endpoint, fluvastatin 20 mg was significantly superior to 10 mg in reducing VLDL-C ($P < 0.05$), whereas mean percentage change in TC levels were significantly greater in the fluvastatin 20 mg group than in each of the other active treatment groups ($P < 0.001$). In addition, mean percentage changes in β -quant LDL-C at endpoint were significantly greater in patients treated with fluvastatin 20 mg, than those treated with 2.5 mg ($P < 0.001$), 5 or 10 mg (both $P < 0.05$). Although the effect of fluvastatin 5 and 10 mg on mean percentage

changes in β -quant LDL-C did not differ significantly, both were significantly superior to 2.5 mg ($P < 0.05$).

Furthermore, the percentage of patients at endpoint with $\geq 15\%$ reduction in β -quant LDL-C was 8.3%, 22.1%, 51.8%, 45.9% and 74.4%, for placebo and fluvastatin 2.5, 5, 10 and 20 mg, respectively. At endpoint, 22.1% of patients treated with 20 mg fluvastatin achieved normalised β -quant LDL-C levels of $< 4.0 \text{ mmol l}^{-1}$, from a mean baseline level of 6.3 mmol l^{-1} .

When compared with baseline values, the mean percentage changes in the β -quant LDL-C/HDL-C ratio at endpoint were -10.5% (2.5 mg), -12.5% (5 mg), -15.5% (10 mg) and -22.8% (20 mg) [all $P < 0.001$]. Furthermore, pairwise comparisons at endpoint indicated that each dose of fluvastatin was significantly superior to placebo in reducing the β -quant LDL-C/HDL-C ratio (all $P < 0.001$). The effect of fluvastatin on the latter ratio was dose-related, with a distinct, significant improvement from 10 to 20 mg ($P < 0.05$).

At endpoint, mean TG levels were reduced from baseline levels by all doses of fluvastatin, although only the 5 mg and 20 mg doses showed within-group statistical significance ($P < 0.05$ and $P < 0.001$, respectively). Pairwise comparisons at endpoint (Table 3) indicated that the differences between the 2.5, 5 and 10 mg doses were not significant, although the 20 mg dose was superior to each, reaching statistical significance in comparison of the 10 mg dose ($P < 0.05$).

During the 6-week active treatment phase and at end-

Table 2 Mean baseline values and percentage changes from baseline of the main lipid parameters during short-term treatment with fluvastatin 2.5–20 mg day⁻¹

Parameter	Treatment (mg)	Mean ($\pm$ s.d.) baseline value (mmol l ⁻¹)	Mean percentage change from baseline			
			Week 2	Week 4	Week 6	Endpoint
TG	Placebo	1.6 $\pm$ 0.6	2.4	8.2*	-0.3	-0.3
	2.5	1.6 $\pm$ 0.6	-1.8	-2.3	-3.6	-3.6
	5	1.4 $\pm$ 0.6	-0.1	-3.1	-5.6*	-5.6*
	10	1.6 $\pm$ 0.7	0.2	0.8	-2.4	-2.4
	20	1.6 $\pm$ 0.6	-12.4***	-11.1***	-11.8***	-11.8***
VLDL-C	Placebo	0.9 $\pm$ 0.3	2.7	3.4	-2.7	-2.7
	2.5	0.9 $\pm$ 0.4	-8.9*	-12.8***	-14.9***	-14.9***
	5	0.8 $\pm$ 0.3	-5.8	-10.5***	-15.7***	-15.7***
	10	0.9 $\pm$ 0.3	-5.7	-11.4***	-12.7***	-12.7***
	20	0.9 $\pm$ 0.4	-22.0***	-22.5***	-22.3***	-22.3***
HDL-C	Placebo	1.4 $\pm$ 0.4	0.7	1.2	1.4	1.4
	2.5	1.4 $\pm$ 0.4	3.8***	3.2**	2.3	2.3
	5	1.4 $\pm$ 0.4	2.3	4.3**	1.1	1.1
	10	1.4 $\pm$ 0.4	3.1*	2.1	3.8**	3.8**
	20	1.4 $\pm$ 0.4	4.1***	4.5**	4.7**	4.7**
TC	Placebo	8.8 $\pm$ 2.0	0.3	2.9*	1.5	1.5
	2.5	9.0 $\pm$ 2.0	-7.3***	-7.9***	-8.1***	-8.2***
	5	8.9 $\pm$ 1.9	-9.3***	-9.8***	-11.3***	-11.3***
	10	8.5 $\pm$ 1.8	-9.5***	-11.8***	-10.8***	-10.8***
	20	8.6 $\pm$ 1.7	-15.2***	-16.9***	-16.1***	-16.1***
β -quant LDL-C	Placebo	6.5 $\pm$ 1.9	0.2	3.7	2.5*	2.5*
	2.5	6.7 $\pm$ 1.9	-9.1***	-9.0***	-9.2***	-9.2***
	5	6.8 $\pm$ 1.9	-12.0***	-12.4***	-13.1***	-13.1***
	10	6.2 $\pm$ 1.8	-12.2***	-14.9***	-13.5***	-13.5***
	20	6.3 $\pm$ 1.6	-18.1***	-20.7***	-19.3***	-19.3***

Significant difference from baseline: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Abbreviations: refer Table 1.

point, HDL-C was increased by all doses of fluvastatin, but only the two highest doses caused a statistically significant increase from baseline values (3.8% [10 mg] and 4.7% [20 mg], respectively; $P < 0.01$). In comparison with placebo, mean percentage changes of HDL-C at endpoint were increased by all doses of fluvastatin, but not significantly. However, fluvastatin 20 mg was significantly superior to the 5 mg dose ($P < 0.05$).

In comparison with baseline values, significant reductions in apo B and apo E were evident at endpoint at all doses of fluvastatin ($P < 0.001$ and $P < 0.05$, respectively). However, pairwise comparisons at endpoint for each of these parameters indicated that only the mean percentage change in apo B between treatment groups was statistically significant. For example, in patients treated with fluvastatin 5 or 10 mg, the decrease in apo B levels at endpoint were significantly greater than in patients treated with fluvastatin 2.5 mg ($P < 0.01$). Moreover, fluvastatin 20 mg produced a significantly greater decrease in apo B than all other treatment groups ($P < 0.001$). Median percentage changes between baseline and endpoint for apo AI and Lp AI were not significant except in patients treated with fluvastatin 10 mg, which increased apo AI and Lp

AI by 3.4% ($P < 0.05$) and 4.3% ($P < 0.01$), respectively. However, pairwise comparisons for both of these parameters indicated that no significant differences existed between the active treatment groups. When compared with baseline levels, patients who received fluvastatin 20 mg had significantly increased Lp AII:AI levels ($P < 0.05$), and decreased Lp (a):B levels ($P < 0.05$) at endpoint (Table 4), but no significant differences were evident between treatment groups.

At endpoint, median percentage changes in apo AII, apo CIII, Lp CIII:B and Lp E:B were not significantly different from baseline at all doses of fluvastatin. Furthermore, pairwise comparisons for each of these parameters indicated that no statistically significant differences were evident between the fluvastatin treatment groups.

In general, the effects of fluvastatin were dose-related, the 20 mg dose proving consistently superior to the lower doses for all main lipid parameters tested.

Laboratory parameters

Relatively few instances of biochemical or haematological abnormalities occurred during the study. While γ -GT

Table 3 Between-groups comparison of mean percentage changes from baseline and 95% confidence intervals of the main lipid parameters during short-term treatment with fluvastatin 2.5–20 mg day⁻¹ at study endpoint

Parameter	Treatment (mg)	Mean % change from baseline	(95% CI)	n [†]
TG	Placebo	-0.3	(-6.3, 5.6)	84
	2.5	-3.6	(-13.3, 6.2)	86
	5	-5.6	(-10.7, -0.6)	83
	10	-2.4	(-8.7, 3.8)	85
	20	-11.8 ^{a,d}	(-16.3, -7.3)	86
VLDL-C	Placebo	-2.7	(-11.6, 6.0)	84
	2.5	-14.9 ^a	(-21.1, -8.6)	86
	5	-15.7 ^b	(-21.2, -10.1)	83
	10	-12.7 ^a	(-18.5, -6.9)	85
	20	-22.3 ^{c,d}	(-28.9, -15.7)	86
HDL-C	Placebo	1.4	(-0.8, 3.6)	84
	2.5	2.3	(-0.1, 4.6)	86
	5	1.1	(-1.6, 3.8)	83
	10	3.8	(1.0, 6.6)	85
	20	4.7 ^e	(1.9, 7.5)	86
TC	Placebo	1.5	(-0.4, 3.4)	84
	2.5	-8.2 ^c	(-9.8, -6.7)	86
	5	-11.3 ^{c,f}	(-14.0, -8.6)	83
	10	-10.8 ^c	(-12.9, -8.7)	85
	20	-16.1 ^{c,g,h}	(-17.8, -14.4)	96
β -quant LDL-C	Placebo	2.5	(0.0, 5.0)	84
	2.5	-9.2 ^c	(-11.3, -7.1)	86
	5	-13.1 ^{c,f}	(-16.9, -9.4)	83
	10	-13.5 ^{c,f}	(-16.0, -11.0)	85
	20	-19.3 ^{c,g,i}	(-21.4, -17.3)	86

[†]Sample size discrepancies are due to missing data.

Significant difference from placebo: ^a $P < 0.05$; ^b $P < 0.01$; ^c $P < 0.001$.

Treatment group comparisons: ^d $P < 0.05$ vs 10 mg; ^e $P < 0.05$ vs 5 mg;

^f $P < 0.05$ vs 2.5 mg; ^g $P < 0.001$ vs 2.5 mg; ^h $P < 0.001$ vs 5 mg and vs

10 mg; ⁱ $P < 0.01$ vs 5 mg and vs 10 mg.

Abbreviations: refer Table 1.

Table 4 Median percentage changes from baseline values for apolipoproteins (apo) and lipoprotein particles (Lp) at study endpoint

Parameter	Median % change from baseline [†]	
	Fluvastatin 20 mg day ⁻¹ (n = 86)	Placebo (n = 84)
apo B	-19.7 (-43.0, 5.2)***	0.8 (-26.4, 32.1)
apo E	-16.0 (-82.8, 174.3)*	-14.5 (-73.9, 213.3)
apo AI	1.7 (-27.5, 38.9)	0.9 (-28.5, 48.6)
apo AII	0.0 (-44.8, 170.1)	-1.4 (-40.5, 150.0)
Lp(a):B	-6.4 (-59.5, 100.0)*	0.3 (-78.9, 544.8)
apo CIII	-3.4 (-66.7, 215.0)	0.0 (-50.9, 283.3)
Lp CIII:B	-0.1 (-80.0, 376.9)	0.0 (-67.3, 191.7)
Lp E:B	-21.5 (-82.0, 367.5)	11.0 (-83.3, 381.5)*
Lp AI	2.0 (-49.3, 79.4)	-3.0 (-47.7, 186.7)
Lp AII:AI	10.5 (-61.9, 305.4)*	2.0 (-47.8, 118.8)

[†]Figures in brackets refer to minimum and maximum % change from baseline.

Significant difference from baseline: **P* < 0.05; ****P* < 0.001.

and CK abnormalities were the most frequent abnormal laboratory findings, only five patients (four fluvastatin, one placebo) showed notable (> 3 × upper limit of normal [ULN]) increases in γ -GT. Four of these patients were young men with elevated baseline values (> 2 × ULN). The reason for the isolated increase in γ -GT levels seen at week 6 in the other, female, patient (20 mg fluvastatin) remains unclear.

While 21 (18 fluvastatin, 3 placebo) patients developed a new or worsening elevation in CK levels, none had a clinically notable (> 10 × ULN) elevation. The 18 fluvastatin-treated patients who showed elevated CK levels were divided thus: 5 (2.5 mg), 7 (5 mg), 3 (10 mg), 3 (20 mg), which suggests that the effect was not dose-related.

A notable, worsening increase (from 41 to 52 $\mu\text{mol l}^{-1}$, ULN 23 $\mu\text{mol l}^{-1}$) in total bilirubin occurred in one patient (fluvastatin 5 mg) at week 2, which resolved spontaneously.

Tolerability

Both placebo and fluvastatin were well tolerated, and there were no withdrawals due to drug-related adverse events. The number of patients who reported at least one adverse event were comparable across the treatment groups, ranging from 20 (23.3%) in the fluvastatin 10 mg group to 27 (31.4%) in the placebo group. However, newly-occurring or worsening adverse events which could be attributed to fluvastatin with any degree of certainty were gastrointestinal and body-as-a-whole disorders. Gastrointestinal adverse events positively or possibly attributable to the study drug were reported by 3 (3.5%), 2 (2.3%), 2 (2.4%), 5 (5.8%) and 4 (4.6%) patients who received placebo, 2.5, 5, 10 and 20 mg fluvastatin, respectively. In addition, body-as-a-whole adverse events (mainly headache, *n* = 4) were reported by 1 (1.2%), 2 (2.3%), 1 (1.2%), 3 (3.5%) and 2 (2.3%) patients who received placebo, 2.5, 5, 10 and 20 mg fluvastatin, respectively.

Ten patients (nine fluvastatin, one placebo) developed

a notable reduction of visual acuity (> 40% compared with baseline) in either eye. However, in only one of these patients (a 61-year-old woman who received fluvastatin 2.5 mg), the unilateral impairment of visual acuity was accompanied by worsening lens abnormalities (subcapsular opacities and nuclear sclerosis), which was not attributable to fluvastatin.

There were three serious adverse events: myocardial infarction (1) [placebo], Papanicolaou III cervical smear (1) [fluvastatin 20 mg], and death following accidental craniocerebral trauma (1) [placebo].

Discussion

The present findings clearly demonstrate that fluvastatin 2.5 to 20 mg day⁻¹ for 6 weeks was significantly superior to placebo, and lowered TC, LDL-C, VLDL-C and the β -quant LDL-C/HDL-C ratio significantly in comparison with baseline values. Similar results have been reported by other workers [13–15]. Furthermore, an average of 48.5% (range 22.1% to 74.4%) of patients treated with fluvastatin 2.5 to 20 mg day⁻¹ achieved a clinically significant (> 15%) reduction in β -quant LDL-C at endpoint. For all main lipid parameters assessed in the present study, the 20 mg dose emerged as the optimally effective hypolipidaemic dose of those tested.

Fluvastatin was generally well tolerated. Of the few adverse events that occurred with active treatment, the majority were minor gastrointestinal effects. Due to its hepatic site of action and extensive first-pass metabolism, the effect of fluvastatin on hepatic enzyme release was investigated. In this study, notable elevations of γ -GT were usually not accompanied by concomitant elevations in plasma levels of AST/SGOT or ALT/SGPT, and most of those patients with abnormal γ -GT levels at endpoint had elevated baseline levels.

A low incidence of myopathy has been reported with cholesterol-lowering drugs, including fluvastatin [16,17]. We found no notable elevations (> 10 × ULN) in CK levels in this study, and there were no incidences of myopathy. Similarly, a low incidence of myopathy was reported in a long-term open study in 918 hypercholesterolaemic patients who received fluvastatin 20 to 40 mg daily [13]. In the latter study, only one purported case of myopathy was reported during 48 weeks' of treatment, in a patient who had a recent history of strenuous exercise.

Due to the report of lens opacities in dogs treated with fluvastatin [Sandoz, data on file], regular ophthalmological assessments were performed on all patients in this study. Of nine patients who experienced reduced visual acuity during treatment with fluvastatin, only one, a woman of 61 years treated with fluvastatin 2.5 mg, experienced worsening lens opacities and a notable ipsilateral reduction in visual acuity. However, it remains to be established whether such ophthalmological events are drug-related.

The results of this study suggest that fluvastatin in doses between 2.5 and 20 mg once daily in the evening for 6 weeks improved the plasma lipid profile of

patients with primary hypercholesterolaemia, and was well tolerated. Of the dosages investigated, fluvastatin 20 mg day⁻¹ appears to be the optimal hypolipidaemic dose.

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