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One year experience in the treatment of familial hypercholesterolaemia with simvastatin

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Summary: Patients with heterozygous familial hypercholesterolaemia (FH) have a substantially increased risk of atherosclerosis due to very high plasma levels of cholesterol. Recent evidence has shown that coronary heart disease in these patients may regress with lipid-lowering therapy. In this study the efficacy and safety of simvastatin, an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A, was investigated in 30 patients with FH over a period of one year. Substantial reductions in the plasma concentrations of total cholesterol (– 28%), low-density lipoprotein (LDL) cholesterol (– 32%), intermediate-density lipoprotein (IDL) cholesterol and apolipoprotein (apo) B (– 33%) were achieved with 20 mg/day of simvastatin; there were no significant changes in triglycerides high-density lipoprotein cholesterol or apo A. In contast to previous studies, 40 mg/day of simvastatin did not result in a further statistically significant fall in LDL cholesterol, IDL cholesterol or apo B in the group as a whole. The drug was well tolerated and no adverse clinical or laboratory events were recorded. In particular, no ophthalmological, hepatic or renal disorders were observed and there were no sleep disturbances. We conclude that simvastatin is an efficacious and safe drug to treat patients with heterozygous FH and that rarely will the dose need to be increased above 20 mg/day.

Introduction

Patients with heterozygous familial hypercholesterolaemia are at substantial risk of premature coronary atherosclerosis due to elevated plasma concentrations of low-density lipoprotein (LDL) cholesterol. A study by Stone[1] showed that in men the cumulative probability of non-fatal or fatal coronary artery disease by age 40 was 16% (1 in 6) and 52% (1 in 2) by age 60. The response to diet is seldom adequate, LDL cholesterol considerably exceeding the levels at which pharmacological intervention is considered appropriate.[2,3] The results of both the Lipid Research Clinics trial[4] and the Helsinki Heart Study[5] showed that cholesterol reduction by drug therapy reduces the incidence of coronary heart disease in hypercholesterolaemic subjects. Vigorous lipid-lowering therapy has also been shown to retard and in some cases reverse the course of coronary atheroma,[6] even in patients with familial hypercholesterolaemia.[7]

In clinical practice, the side effects of some of the available lipid-lowering drugs have led to poor patient compliance, and better tolerated drugs have been awaited. Simvastatin belongs to a unique group of cholesterol-lowering agents that act by inhibition of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase in the liver.[8] Since it was only recently licensed for the treatment of hypercholesterolaemia in the UK, long-term clinical experience concerning efficacy and safety is limited.

In this study the long-term effects of simvastatin on plasma lipids, lipoproteins and apolipoproteins and the incidence of untoward effects were investigated over a 12-month period in 30 patients with heterozygous familial hypercholesterolaemia. We were also interested in ascertaining the most efficacious dose to lower plasma cholesterol in these patients.

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Materials and methods

Patients and design

Thirty patients with heterozygous familial hypercholesterolaemia who were attending the Lipid Clinic at St Thomas' Hospital were invited to take part in the study. Selection criteria included a plasma cholesterol greater than 7.8 mmol/l due to elevation of LDL while on a fat-modified diet alone

and the presence of tendon xanthomas in the index patient or a first degree relative, and/or hypercholesterolamia in two or more first degree relatives.

Grounds for exclusion were: pregnancy and lactation; risk of pregnancy during the study; age under 20 years; history of drug or alcohol abuse; current use of other lipid-lowering drugs; abnormal liver function tests; documented myocardial infarction or coronary artery bypass grafts, or other major surgery, within the last 3 months; multiple or severe allergies; treatment with cyclosporin or any investigational drug; presence of secondary hyperlipidaemia. A minimum of three fasting blood samples were obtained during a 2 month period before treatment was initiated. The patients followed a lipid-lowering diet[2] throughout the baseline and treatment periods.

The initial dose of simvastatin used was 20 mg/day, taken with the evening meal. This was increased to 40 mg/day after 12 weeks in patients in whom the fall in plasma cholesterol was less than 30% relative to the mean level at baseline.

Blood samples were taken before treatment and then at 6, 12, 24, 36 and 52 weeks. Compliance was assessed by unused tablet count at each visit. Safety data were also obtained at each visit and a full ophthalmic examination was performed at the start and end of the study. The study design was approved by the Research (Ethics) Committee of St Thomas' Hospital.

Laboratory methods

Venous blood samples were drawn without venous stasis, with the patient in the semi-recumbent position and after a 12 hour overnight fast. Blood was placed in 10 ml glass tubes containing EDTA (1 mg/ml), plasma being separated within 30 minutes of venepuncture. All samples were analysed within 72 hours of collection.

Very low-density (VLDL) lipoproteins and intermediate density (IDL) lipoproteins were isolated by stepwise preparative ultracentrifugation at background density 1.006 kg/l and 1.017 kg/l. Low-density lipoprotein (LDL) was estimated by difference: LDL chol. = total chol. – (VLDL chol. + IDL chol. + HDL chol.). Cholesterol and triglyceride were measured in plasma and the lipoprotein fractions by enzymatic methods (Boehringer Mannheim CHOD-PAP for cholesterol; Wako GPO-PAP for triglyceride) on a Cobas-Bio (Roche) centrifugal analyser; inter-batch imprecision for cholesterol was 1.8% and for triglyceride 3.8%. HDL cholesterol was estimated by precipitation of apolipoprotein (apo) B lipoproteins with dextran sulphate and magnesium; inter-batch imprecision ranged from 1.3% to 2.5%. Apolipoprotein A-1 and B were analysed by an immunoturbidimetric assay:[9] inter-batch imprecision for both assays ranged from 2.4% to 3.5%.

Safety evaluation

Laboratory measurements performed at baseline and at each visit were: haemoglobin, haematocrit, white cell count, platelet count, glucose, electrolytes, urea, creatinine, calcium, phosphate, creatine kinase (CK), bilirubin, total protein, albumin, alkaline phosphatase, aspartate (AST) and alanine transaminase (ALT). Urine was tested for protein and glucose at each visit using N-multistix reagent strips (Ames Division, Miles Laboratories Ltd).

At baseline, at 24 weeks and at 52 weeks a detailed clinical interview and examination were carried out. At other visits pulse rate, blood pressure and weight were measured and the patient questioned about symptoms. Because drug-induced lens opacities had been reported in dogs receiving HMGCoA reductase inhibitors at very high dosage,[10] full ophthalmological examination was performed before and after one year of treatment. Visual acuity, colour vision, visual fields, motility and pupillary reaction were examined. Ophthalmoscopy and slit-lamp examination of the cornea, anterior chamber and lens were performed after full dilatation. These examinations were made by the same ophthalmologist.

Statistical methods

Patients spent differing periods on the two dose levels because of the dose titration design. They had several lipoprotein measurements at each dose and there was little evidence of trends within patients while their doses were constant. Consequently, the means of these lipoprotein levels within a constant dose period were used to represent each patient's level for that dose. Subsequent analyses using these means were weighted appropriately to take account of the differing numbers of observations averaged. Using this approach the within-subject changes in lipoprotein levels for given changes of dose were obtained; analysis of pooled data then provided estimates of the dose/response effects with appropriate standard errors. Tests of differences were performed by comparing the relevant weighted means on the original scales of measurement using the appropriate t distribution. For simplicity the differences are given as percentages in the text.

Results

The clinical and demographic characteristics of the patients studied are given in Table I. Fifteen

Table I Clinical and demographic characteristics of the patients studied

Number (male/female)	30 (23/7)
Mean age in years (range)	48 (24–65)
Previous myocardial infarction	4
Symptomatic angina	6
Coronary artery surgery	5
Hypertension	1
Mean body mass index (± 2S.D.)	24.6 (± 6.2)
Tendon xanthomata	25 (83%)
Mean systolic blood pressure (mmHg) (± 2S.D.)	127 (± 46)
Mean diastolic blood pressure (mmHg) (± 2S.D.)	75 (± 24)

patients had clinical evidence of coronary artery disease. Three patients were receiving beta-blockers and one a diuretic, treatments remaining constant during the study. Neither body weight nor blood pressure altered significantly during the study.

Plasma lipids, lipoproteins and apolipoproteins (Tables II and III, Figure 1)

Plasma cholesterol, LDL cholesterol and apo B showed substantial reductions on both 20 and 40 mg/day of simvastatin. Cholesterol, LDL cholesterol and apo B fell by 26%, 32% and 33%, respectively, on 20 mg/day, with no further statistically significant response on the higher dose. Four patients (13%), however, showed further reduction in LDL cholesterol of greater than 1.5 mmol/l when the dose of simvastatin was increased from 20 to 40 mg/day of simvastatin. IDL cholesterol showed a 48% reduction on both 20 and 40 mg/day of simvastatin, with no statistically significant difference between the doses.

There were also significant reductions in plasma triglyceride, VLDL cholesterol and VLDL triglycerides, responses being comparable on both doses of the drug. HDL cholesterol and apo A did not alter during the study.

Adverse events

Simvastatin was well tolerated and compliance was good. Two patients who had had long-term insomnia reported sleep problems during the study. When the timing of the medication was changed from the evening to the morning, symptoms imp-

Table II Plasma cholesterol (chol), LDL cholesterol, IDL cholesterol, VLDL cholesterol, VLDL triglyceride (Tg) and high-density lipoprotein (HDL) cholesterol. Mean values (mmol/l) with 95% confidence intervals

		Dose of simvastatin	
	Baseline	*20 mg*	*40 mg*
Plasma chol	11.32 (10.36–12.28)	8.37 (7.13–9.61)*	8.15 (6.65–9.65)*
Plasma Tg	2.45 (1.61–3.29)	1.81 (1.27–2.35)*	2.04 (0.88–3.2)*
LDL chol	9.03 (8.07–9.99)	6.30 (5.14–7.46)*	6.34 (4.96–7.72)*
IDL chol	0.35 (0.15–0.55)	0.18 (0.14–0.22)†	0.19 (0.11–0.27)†
VLDL chol	0.68 (0.30–1.06)	0.40 (0.22–0.58)§	0.48 (0.08–0.88)‡
VLDL Tg	1.24 (0.66–1.82)	0.91 (0.55–1.27)§	1.17 (0.19–2.15)
HDL chol	1.15 (0.89–1.41)	1.22 (1.06–1.38)	1.16 (0.90–1.42)

*$P<0.0001$; †$P<0.001$; ‡$P<0.01$; §$P<0.05$; compared to baseline.

Table III Apoproteins AI and B concentrations before and during treatment with simvastatin. Mean values with 95% confidence intervals

		Dose of simvastatin	
	Baseline	*20 mg*	*40 mg*
Apo AI (g/l)	1.37 (1.21–1.53)	1.43 (1.27–1.59)	1.37 (1.19–1.55)
Apo B (g/l)	2.10 (1.86–2.34)	1.41 (1.19–1.63)*	1.57 (1.31–1.83)*

*$P<0.0001$ compared to baseline.

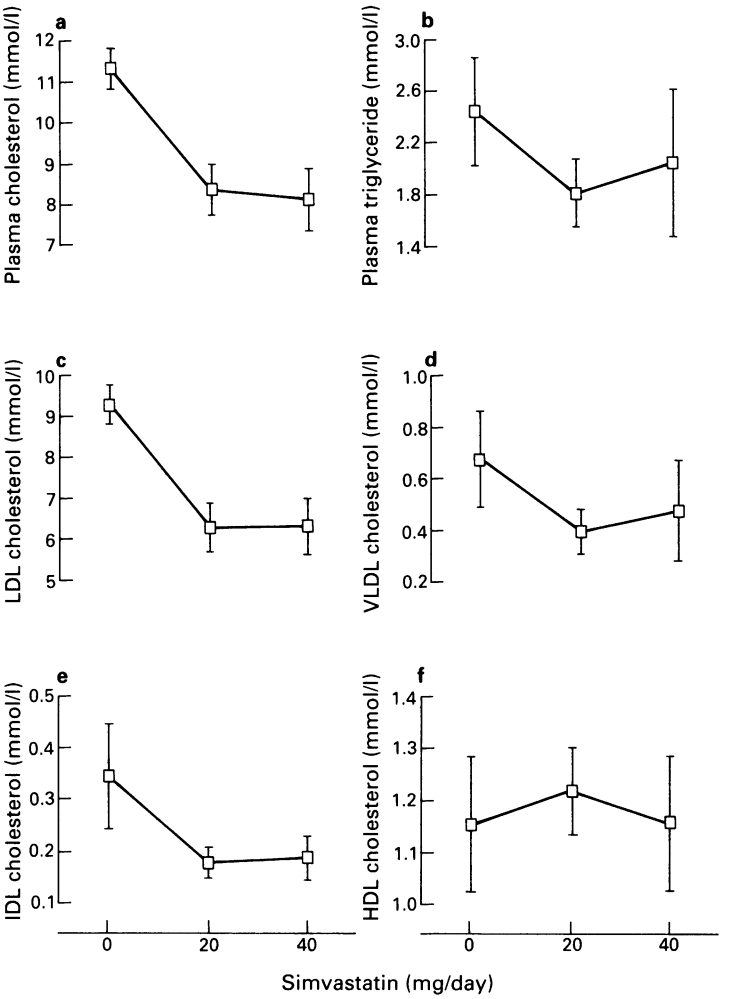

Figure 1 Effect of simvastatin on (a) plasma cholesterol, (b) plasma triglyceride, (c) LDL cholesterol, (d) VLDL cholesterol, (e) IDL cholesterol and (f) HDL cholesterol (mean ± s.e.m.; $n = 30$).

roved. One patient complained of transient diarrhoea on one occasion, attributed to gastroenteritis alone.

Renal biochemistry, plasma calcium, plasma glucose and haematological indices remained normal through the study. Urinalysis was negative for protein and glucose in all patients except one, who had been known to have orthostatic proteinuria.

The changes in plasma enzymes alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (AP) and creatine kinase (CK) are shown in Table IV. All enzymes were normal at baseline. The mean ALT did not change significantly during treatment. Eight patients, however, had transient rises in ALT to less than twice the upper limit of normal. Two patients had ALT levels between three and five times the upper limit of normal at 6 weeks on 20 mg of simvastatin: in both cases the ALT returned to normal after the drug was withdrawn for one month. After rechallenging with 10 mg/day of simvastatin, the ALT increased in only one of the patients. Mean AST showed a small non-significant rise during treatment with 20 mg/day and a significant ($P < 0.01$) rise with 40 mg/day (Table IV), but no patient showed an elevation to more than twice the upper limit of normal. No significant changes were recorded in plasma CK and AP phosphatase (Table IV). Transient elevations in ALT and CK to less than twice the upper limit of normal were seen in patients.

No changes were recorded at ophthalmological examination. In particular no new lens opacities were seen after one year of treatment.

Table IV Plasma enzyme activities before and during treatment with simvastatin. Mean values with 95% confidence intervals

	Baseline	*Dose of simvastatin* 20 mg	40 mg
ALT (IU/l)	36 (12–60)	35 (19.51)	33 (17–49)
AST (IU/l)	25 (21–29)	27 (23–31)	29 (21–37)*
CK (IU/l)	136 (86–186)	122 (82–162)	119 (79–159)†
AP (IU/l)	76 (64–88)	71 (61–81)	74 (60–88)

*$P < 0.01$; †$P < 0.05$; compared to baseline.

Discussion

Hepatic synthesis of cholesterol has long been a target for pharmacological intervention. Early research focused on the late steps in the cholesterol biosynthetic pathway and led to the development of triparanol. However, this drug caused dermal icthyosis, alopecia and cataracts in man[11,12] probably due to the accumulation of precursor steroids. Hydroxymethylglutaryl coenzyme A (HMGCoA) reductase is a major rate limiting enzyme of the early steps of cholesterol synthesis and inhibition of this enzyme does not lead to the accumulation of precursors that cannot be metabolized by other routes.

This one-year study of the effects of simvastatin in familial hypercholesterolaemia confirms the reductions in cholesterol, LDL cholesterol and apoprotein B concentrations found in earlier studies.[13,14] These reductions are predominantly mediated by increased hepatic clearance of LDL cholesterol[15,16] due to enhanced activity of LDL receptors. The mechanism of increased LDL receptor activity is consequent on the inhibition of intracellular cholesterol synthesis by simvastatin.

An important finding which disagrees with other clinical reports[13,14] is that an increase in the dose of simvastatin from 20 mg to 40 mg/day did not result in a statistically significant reduction in LDL cholesterol in the present study. Discrepancies may be due to metabolic differences in the sample population, although on clinical grounds we are confident that all our patients had the heterozygous form of familial hypercholesterolaemia. Kempen *et al.*[17] reported that in heterozygous FH patients increasing the dose of simvastatin from 20 to 40 mg/day did not decrease the plasma lathosterol:cholesterol ratio (this ratio is an index of HMGCoA reductase inhibition), consistent with the results of the present study. Moreover, we did not find that variation in response to simvastatin was dependent on age, sex, weight, apolipoprotein E genotype (data not given) or initial response to the 20 mg/day dose. We suggest that the frequency of 'responders' to 40 mg/day of simvastatin is likely to be low (10–15%) among heterozygous FH patients and that to identify them the dose of the drug should be titrated in all patients.

Elevated levels of IDL are associated with high frequency of CHD and atherosclerosis. This is particularly evident in remnant hyperlipidaemia (familial dysbetalipoproteinaemia) in man and in animals fed high cholesterol diets. Recent studies in man,[18] studying the *in vivo* transfer of IDL between plasma and arterial intima suggests that IDL shares with LDL the potential for causing lipid accumulation in the intima. The reduction of IDL cholesterol in the present study is a novel finding and is consistent with the upregulation of LDL receptors (hepatic B-E receptors) by simvastatin.[15] It is also possible, however, that simvastatin reduces the hepatic production of VLDL apo B, the precursor of IDL and LDL.[19] A reduction in IDL cholesterol has also been reported with another statin, pravastatin.[20]

Simvastatin was well tolerated. Mean serum enzyme levels were not significantly changed, except for a small fall in CK and a small rise in AST. Although a transient increase in the levels of these enzymes was seen in several patients only one was withdrawn; in this patient the ALT exceeded a predetermined cut-off point, though without any clinical manifestation. Although sleep disturbances have been reported with lovastatin,[21] Black *et al.* did not confirm this with simvastatin.[22] In this study the two patients who reported sleep problems had insomnia before drug treatment was begun.

One report[23] of long-term use of simvastatin in patients with plasma cholesterol concentrations above 8 mmol/l reported an incidence of proteinuria in 8% of patients. In our study each patient had a random urine sample examined for protein on every visit. Apart from a patient with established orthostatic proteinuria, on no occasion was proteinuria seen during treatment. Although the dipstick method used in our study is not as sensitive as the TCA-Biuret method used in the aforementioned study, it is sensitive enough to detect urine protein at a concentration of 0.49 g/l reported as the mean concentration found by Deslypere *et al.*[23]

We conclude that simvastatin is an effective and well-tolerated drug with few subjective side effects.

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