Treatment of familial hypercholesterolaemia. United Kingdom lipid clinics study of pravastatin and cholestyramine


Abstract

**Objective**—To compare the efficacy and safety of cholestyramine, an anion exchange resin, and pravastatin, a new hydrophilic specific inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, in the treatment of heterozygous familial hypercholesterolaemia.

**Design**—Double blind, double dummy, placebo controlled study with three parallel groups.

**Setting**—Six specialist lipid clinics in the United Kingdom.

**Patients**—128 patients aged 18-70 with heterozygous familial hypercholesterolaemia diagnosed on strict biochemical and clinical findings.

**Main outcome measures**—Total plasma cholesterol, triglyceride, and lipoprotein subfractions and biochemical and haematological safety parameters.

**Results**—Pravastatin (40 mg/day) led to a 25% reduction in total plasma cholesterol concentration and a reduction in low density lipoprotein cholesterol concentration of 30%. Cholestyramine (24 g/day) led to similar reductions in concentrations of total cholesterol (23%) and low density lipoprotein cholesterol (31%). No consistent changes occurred in high density lipoprotein cholesterol values with either compound. Plasma triglyceride concentrations showed a small rise (18%) on resin therapy. No serious adverse drug reactions occurred during the study.

**Conclusions**—Pravastatin seems to be a highly effective, well tolerated drug for severe hypercholesterolaemia. Patients chosen for this study were recruited on the basis that they could tolerate a full dose of cholestyramine, and in this situation cholestyramine was also highly effective in lowering plasma low density lipoprotein cholesterol concentrations.

Introduction

Increasing evidence points to a causal role for low density lipoprotein in atherosclerosis related disease, particularly coronary heart disease. Primary prevention trials of cholesterol lowering drugs in high risk, middle aged men have provided strong evidence of benefit in terms of reduced incidence of coronary heart disease. In addition, recent coronary angiographic studies have shown that lipid lowering therapy has a significant impact on atheroma plaque development, progression, and regression.

People with familial hypercholesterolaemia have a particularly high risk of coronary heart disease. This autosomal dominant disorder is characterised clinically by hypercholesterolaemia, tendon xanthomas, and the development of premature coronary heart disease; over half of male heterozygotes and 15% of women die before the age of 60. The genetic abnormality has been well described by Brown and Goldstein and colleagues and consists of decreased low density lipoprotein cholesterol catabolism due to absent or defective cell membrane low density lipoprotein receptors. As a consequence the plasma residence time of the lipoprotein is prolonged and the plasma concentration of low density lipoprotein cholesterol is doubled in heterozygotes and quadrupled in homozygotes with this condition.

Heterozygous familial hypercholesterolaemia affects roughly one in 500 of the United Kingdom population. Plasma cholesterol concentrations show little response to dietary measures, and hypolipidaemic drug therapy is almost invariably indicated in these patients. Often more than one drug is required for satisfactory reduction of plasma cholesterol concentrations.

The introduction of specific competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase into clinical practice represents a major advance in therapy for reducing plasma low density lipoprotein cholesterol concentrations. We have compared the safety and efficacy of pravastatin and cholestyramine in 128 patients heterozygous for familial hypercholesterolaemia. Pravastatin is a hydrophilic, specific inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the main rate determining enzyme in cholesterol biosynthesis. Cholestyramine is an anion exchange resin which binds bile salts and is widely used as a first line treatment for hypercholesterolaemia.

Subjects and methods

One hundred and twenty eight patients with heterozygous familial hypercholesterolaemia were entered into the study. Patients were recruited from six specialist lipid clinics in London, Oxford, Manchester, Birmingham, Leicester, and Bath. The study was performed during 1988 to 1991.

Familial hypercholesterolaemia was defined as a total plasma cholesterol concentration >7.5 mmol/l, low density lipoprotein cholesterol concentration >5.0 mmol/l, and tendon xanthomas present in the patient or a first degree relative. Patients were also entered into the study if, in addition to raised total plasma and low density lipoprotein cholesterol concentrations, they had a parent who had died prematurely of myocardial infarction—that is, a father who had died below the age of 50 or a mother who had died below the age of 60.

All patients were known to be tolerant of a minimum of four and preferably six sachets of cholestyramine daily before entry. Participants were men and postmenopausal or surgically sterile women aged 18-70 who had no other primary or secondary causes of hyperlipidaemia and no significant renal, hepatic, or
endocrine (except stable thyroid replacement) disease.

Patients with hypertension (blood pressure 
\(>160\) mm Hg systolic or \(>100\) mm Hg diastolic), 
poorly controlled cardiac failure, obesity (\(>130\%\) of 
ideal body weight), recent myocardial infarction 
(within three months), unstable angina, and excess 
alcohol intake (\(>5\) units/day) were excluded, as were 
patients with medical conditions (other than coronary 
heart disease) likely to limit life span to less than five 
years.

Patients receiving corticosteroids, oestrogens, 
androgens, lipid lowering agents, anticoagulants, 
theophylline, barbiturates, or regular aluminium con-
taining antacids were excluded unless these agents 
could be withdrawn at least eight weeks before ran-
domisation.

TRIAL DESIGN

Before entry to the study patients had any lipid 
lowering agents withdrawn for four weeks (bile seques-
trant resins), 12 weeks (probufol), or eight weeks (all 
other agents). All patients were of stable weight and 
had been taking an established low fat, low cholesterol 
lipid lowering diet for at least three months before 
randomisation. Patients were instructed in the prin-
ciples of diet in accordance with recommendations of 
the European Atherosclerosis Society and American 
Heart Association.10

Checks on dietary compliance by professional dieti-
tians with four day food record were undertaken before 
entry to the study and at 12 and 24 weeks. All patients 
had a dietary lead in period of six weeks before 
randomisation. Randomisation was stratified by centre 
and treatment units assigned consecutively to obtain 
equal numbers of patients in the three treatment 
groups.

The study was double blind, double dummy, and 
placebo controlled with the following three parallel 
groups: (1) pravastatin 20 mg twice daily and choles-
tryramine placebo, (2) cholestyramine 16-24 g daily 
in divided doses and pravastatin placebo, and (3) prava-
statin placebo and cholestyramine placebo.

The primary focus of the study was comparison of 
the two treatment groups with the placebo group at 12 
weeks. However, to obtain more long term data groups 
1 and 2 were continued on treatment for 24 weeks. In 
addition, group 3 receiving double placebo were re-
randomised to receive active treatment with pravas-
tatin or cholestyramine with appropriate placebo for 
a further 12 weeks.

Cholestyramine (16-24 g) was taken well diluted 
with fluid meals in two or three divided doses 
and built up to full dose over two weeks from week 
zero. Pravastatin or its placebo was taken before 
morning and evening meals, at least one hour before 
cholestyramine. Morning drug dosages were delayed 
on visit days until after blood sampling.

MEASUREMENTS AND ETHICS

A full clinical history and physical examination were 
performed before entry and at 12 and 24 weeks. 
Intercurrent illnesses, possible use of non-study drugs, 
and any adverse effects were monitored at 2, 4, 8, 14, 
16, 20, and 24 weeks. Full ophthalmological assessment 
with slit lamp examination and slit lamp camera 
photography using a detailed standard protocol was 
conducted before initial randomisation and at 24 
weeks. A chest x ray picture and an electrocardiogram 
were obtained before randomisation and electrocardio-
graphy repeated at 12 and 24 weeks.

Plasma total cholesterol, plasma total triglyceride, 
and high density lipoprotein cholesterol concentrations 
were measured and low density lipoprotein cholesterol 
value calculated before dietary lead in (minus six 
weeks), two weeks before randomisation, and at 2, 4, 8, 
12, 14, 16, 20, and 24 weeks in venous samples taken 
from recumbent patients after a 14 hour fast. Lipid 
values were measured by standard enzymatic color-
metric techniques using the cholesterol oxidase/
peroxidase-amidopropine method for cholesterol 
and glycerolphosphatase oxidase-amidopropine 
method for triglycerides (Boehringer Mannheim, 
Lewes, Sussex). High density lipoprotein cholesterol 
was measured after precipitation of apoprotein B 
containing lipoproteins with heparin and manganese.

Low density lipoprotein cholesterol values were 
calculated using the Friedewald formula.11

Haematological and biochemical safety parameters 
were assessed before dietary lead in, two weeks before 
randomisation, and at 2, 4, 8, 12, 14, 16, 20, and 24 
weeks. Haematological measurements included full 
blood count, platelet count, activated partial thrombo-
plasin time, and prothrombin time. Biochemical 
measurements included plasma creatinine, urea, 
creatinine, glucose, urate, calcium, bilirubin, albumin, 
globulin, alkaline phosphatase, alanine aminotrans-
ferase, aspartate aminotransferase, \(\gamma\)-glutamyltrans-
ferase, and creatine kinase values.

The protocol was approved by the ethics committee 
at each participating institution. The nature and 
purpose of the study were explained in detail to each 
patient, each patient was given an information sheet, 
and written informed consent was obtained. The 
patients' general practitioners were informed before 
study commencement.

STATISTICS

Lipid and lipoprotein values are presented as means 
and standard error. Analysis of covariance was used to 
compare the treatment groups with respect to changes 
in lipid and lipoprotein concentrations from baseline 
values. Log transformation of raw data was performed 
before analysis. Data on patients withdrawn from the 
study (\(n=10\)) are included in the analysis up to the 
point of withdrawal. Statistical analysis was confined 
to the 12 week placebo controlled study period.

Results

Baseline characteristics of the hypercholes-
terolaemic subjects studied are shown in table I. Lipid 
and lipoprotein concentrations were similar in the 
three groups.

The 12 week comparison of the pravastatin, chole-
syramine, and placebo treated groups are shown in 
table II. Similar reductions were observed in total 
cholesterol concentration, low density lipoprotein

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TABLE I—Baseline mean (SEM) lipid and lipoprotein concentrations in three study groups

<table>
<thead>
<tr>
<th>Group</th>
<th>No of men</th>
<th>No of women</th>
<th>Total cholesterol (mmol/l)</th>
<th>Total triglyceride (mmol/l)</th>
<th>Low density lipoprotein cholesterol (mmol/l)</th>
<th>High density lipoprotein cholesterol (mmol/l)</th>
<th>Low density lipoprotein cholesterol: high density lipoprotein cholesterol ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>31/12</td>
<td></td>
<td>9.48 (1.26)</td>
<td>1.55 (0.12)</td>
<td>7.47 (0.26)</td>
<td>1.13 (0.04)</td>
<td>6.59 (0.37)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td></td>
<td>9.87 (1.26)</td>
<td>1.52 (0.10)</td>
<td>7.82 (0.29)</td>
<td>1.17 (0.05)</td>
<td>6.63 (0.40)</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>30/12</td>
<td></td>
<td>9.51 (1.23)</td>
<td>1.42 (0.12)</td>
<td>7.63 (0.23)</td>
<td>1.08 (0.04)</td>
<td>7.07 (0.36)</td>
</tr>
</tbody>
</table>

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TABLE II—Lipid and lipoprotein concentrations in subjects with familial hypercholesterolaemia treated with placebo, pravastatin, or cholestyramine for 12 weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pooled mean at baseline</th>
<th>Percentage change from baseline (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>9.62 mmol/l</td>
<td>-2.7 to -4.1 (25 to 21)</td>
</tr>
<tr>
<td>Total triglyceride</td>
<td>1.50 mmol/l</td>
<td>-2.1 to -3.5 (15)</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol</td>
<td>7.64 mmol/l</td>
<td>-2.9 to -4.3 (35)</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol</td>
<td>1.13 mmol/l</td>
<td>-0.9 to -1.9 (10)</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol: high density lipoprotein cholesterol ratio</td>
<td>6.76</td>
<td>4.9 to 18 (38 to 20)</td>
</tr>
</tbody>
</table>
cholesterol concentration, and ratio of low density lipoprotein cholesterol to high density lipoprotein cholesterol in the two active treatment groups compared with the placebo group (p<0.001). Pravastatin was associated with a 25% fall in plasma cholesterol concentration at 12 weeks. A significant fall in plasma cholesterol value was seen at 2 weeks and was maximal at 4 weeks. The reduction in total plasma cholesterol concentration was explained by a reduction in low density lipoprotein cholesterol of 30%. There was no change in the concentration of high density lipoprotein cholesterol, but a highly significant reduction in the ratio of low density lipoprotein cholesterol to high density lipoprotein cholesterol was observed (p<0.001). Plasma triglyceride concentration fell by 14%; this reduction was not significantly different from that in the placebo group, although it was significantly different from baseline (p<0.05).

Cholestyramine produced similar reductions in total plasma cholesterol concentration (23%), low density lipoprotein cholesterol concentration (31%), and ratio of low density lipoprotein cholesterol to high density lipoprotein cholesterol (34%) to those observed with pravastatin. However, plasma triglyceride concentrations rose (18%) on treatment with the resin (p<0.01). The results observed at 12 weeks for lipid and lipoprotein parameters were maintained at 24 weeks. In the pravastatin treated group the mean reductions in total and low density lipoprotein cholesterol concentrations were 24% and 30% respectively. Plasma triglyceride concentration was reduced by 17%. In the cholestyramine treated group the mean reductions in total and low density lipoprotein cholesterol values were 20% and 26% respectively. Plasma triglyceride concentration was increased by 6%. The placebo groups assimilated at 12 weeks were not distinguishable at 24 weeks from the active treatment groups.

WITHDRAWALS AND ADVERSE EVENTS
No serious adverse drug reactions occurred during the study. Six patients were withdrawn because of symptoms, four on cholestyramine and one on placebo because of gastrointestinal symptoms and one from the pravastatin group for a rash which resolved after the drug was stopped. These patients were withdrawn within the 12 week placebo controlled treatment period.

No patient withdrew because of ocular problems or myositis-like symptoms. Three patients (one taking cholestyramine, one pravastatin, and one placebo) withdrew within the first 12 weeks for personal reasons (two due to job commitments, one unwilling to enter long term treatment). One further patient was withdrawn from the cholestyramine group because baseline lipid values were below the inclusion eligibility level.

LABORATORY EVALUATIONS
No patient was withdrawn from the study because of changes in liver function values. Transient increases in γ-glutamyltransferase activities (>1.5 × baseline) were seen in three patients taking pravastatin and five on cholestyramine. However, activities of this enzyme rose above the upper limit of the normal range in only two patients, one on cholestyramine and one on pravastatin. This abnormality was observed at two time points in the cholestyramine treated patient and one time point in the pravastatin treated patient. Nine patients receiving pravastatin showed transient disturbances of other hepatic enzyme values, which were not associated with clinical symptoms and did not lead to withdrawal of the patients. In addition, similar changes in hepatic enzyme values were observed in three patients receiving cholestyramine and one receiving placebo. There were no significant alterations in haematological parameters. No patient showed persistently raised creatine kinase activities during the study. Transient increases (>4 × baseline) were observed in eight subjects—four on placebo, two on cholestyramine, and two on pravastatin.

Discussion
The cellular cholesterol pool regulates the expression of cell membrane low density lipoprotein receptors which play a major part in controlling plasma low density lipoprotein cholesterol concentrations. When the cellular cholesterol pool is reduced low density lipoprotein receptor numbers increase which bind and take up low density lipoprotein cholesterol to maintain near normal plasma cholesterol concentrations. The major regulatory step in cellular cholesterol synthesis is the conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonic acid, which is catalysed by the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase. The discovery of naturally occurring inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase provided the opportunity for a physiological means of modifying cholesterol biosynthesis and the cellular cholesterol pool. The introduction of these inhibitors into clinical practice represents a major advance in the pharmacological modification of low density lipoprotein cholesterol concentrations.

In this study we have compared the safety and efficacy of pravastatin, a new hydrophilic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, with cholestyramine. Pravastatin increases the expression of low density lipoprotein receptors in human liver. Cholestyramine is a basic anion exchange resin which remains unabsorbed after oral administration and binds to bile acids in the intestine, preventing their reabsorption. In response, more bile acid is produced in the liver from cholesterol, leading to increased expression of low density lipoprotein receptors. Hepatic cholesterol synthesis is also increased, which partially offsets the cholesterol lowering effect.

PATIENT SELECTION
The patients chosen for this study were heterozygous for familial hypercholesterolaemia and at high risk of premature coronary heart disease. These patients almost invariably require drug therapy in addition to nutritional counselling to reduce plasma low density lipoprotein cholesterol concentrations to near normal. At present there is no straightforward biochemical measure of low density lipoprotein receptor activity which will fully discriminate between heterozygotes for familial hypercholesterolaemia and normal people. Therefore, the familial hypercholesterolaemic subjects were identified on strict biochemical and clinical criteria, including the presence of tendon xanthomas to ensure as homogeneous a population as possible for study. This inevitably leads to bias in the selection of subjects, in that subjects without xanthomas (or without xanthomas in a first degree relative) were excluded. However, there is no evidence to suggest a differential response to treatment between xanthomatosus and non-xanthomatosus disease.

DRUG EFFECTS
In this study pravastatin and cholestyramine produced similar, substantial reductions in plasma cholesterol concentrations through the reduction of plasma low density lipoprotein cholesterol. The reduction of low density lipoprotein cholesterol of 30% with pravastatin was in line with results in a dose-response study in primary hypercholesterolaemia. The response to cholestyramine in this study was greater than some other studies would predict. However, patients chosen for study were recruited on the basis that they were able to tolerate a full or near full dose of the resin.
Nevertheless, cholestyramine was highly effective in lowering low density lipoprotein cholesterol concentrations in this study in resin tolerant patients. No consistent changes in values of high density lipoprotein cholesterol were observed with either pravastatin or cholestyramine. Plasma triglyceride concentrations showed the expected small increase with cholestyramine.28

Pravastatin was generally well tolerated and side effects were few. The principal problems with other available reductase inhibitors have been rises in hepato-
cellular enzyme activities (greater than threefold increase) in 1-0-1-5% of patients and a rare myositis-like syndrome with raised plasma activities of creatine kinase (>10-fold increase) in 0-5% of subjects.29 These effects are generally reversible on cessation of treatment although rhabdomyolysis has rarely been described in patients receiving lovastatin combined with cyclo-
sporin, nicotinic acid, and gemfibrozil.30,31 In this study no patient was withdrawn because of a myositis-
like syndrome or excessive rises in creatine kinase activities. No patients were withdrawn because of disturbances in hepatic enzymes.

Careful ophthalmological examination revealed no changes in ophthalmic status in any patient on either treatment. This is of importance as the compound triparanol, which was in trial in the 1960s as an inhibitor of cholesterol synthesis, led to cataract formation. However, this compound inhibits chole-
sterol synthesis at a late stage in the synthetic pathway, leading to a build up of toxic intermediates.4 Cataract development has not been observed in animals given long term high dose pravastatin. Furthermore, the other available reductase inhibitors which can produce cataract formation in some high dose toxicity studies in animals have not resulted in ophthalmological problems in humans.32-36

CONCLUSION

In conclusion, pravastatin seems to be an effective, well tolerated compound for treating severe hyper-
cholesterolaemia. Cholestyramine when tolerated at high dose is also highly effective. Evidence from other studies indicates that the combination of pravastatin with cholestyramine has a greater effect in reducing low density lipoprotein cholesterol values than either compound used alone.44 Moreover, with regard to compliance, particularly when the drug needs to be taken with cholestyramine, it is now recognised that once daily dosing in the evening is as effective as twice daily dosing at the same total daily dosage.45

3 Oliver NF, Heads JA, Morris JN, Cooper J, Gascova H, Gerasin L, et al. Atorvastatin: A cooperative trial in the primary prevention of ischemic heart disease using clofibrate: a report from the Committee of Principal Investiga-
6 Bläckenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Axen SP, Cashin-
8 Kane JP, Mallory MJ, Pors T, Phillips NR, Dahl JH, Havel RJ. Regression of coronary atherosclerosis during treatment of familial hypercholes-
13 Grundy SN. HMG-CoA reductase inhibitors for treatment of hypercholes-
14 La Rosa JC, ed. Advances in the control of lipid metabolism. focus on pravastatin. London: Royal Society of Medicine, 1989. (International congress and symposium series No 162.)
22 Meier VMG, Thompson GR. HMG-CoA reductase inhibitors as lipid-
24 Rudling MJ, Richter E, Karnosch K, Ewerst S, Angelii B. Low density lipoprotein receptor-binding activity in human tissue: quantitative impor-
27 Curtin LD, Dickson AC, Lung KLE, Betteridge JJ. Combination treatment with cholestyramine and bezafibrate for heterogeneous familial hypercholes-
28 Brown MS, Goldstein JL. Drugs used in the treatment of hyperlipopro-