Genetics and therapy of familial hypercholesterolemia

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CHAPTER 4

Two-year efficacy and safety of simvastatin 80 mg in familial hypercholesterolemia

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ABSTRACT

BACKGROUND

Patients with Familial Hypercholesterolemia (FH) have extremely elevated levels of LDL cholesterol (LDL-C) and therefore they require intensive lipid-lowering treatment. Unfortunately, conventional doses of statins rarely achieve targeted reductions of LDL-C in these patients. Consequently, this study was designed to evaluate the efficacy and safety of high-dose (80 mg) simvastatin in a large cohort of FH patients.

METHODS AND RESULTS

Patients were recruited from 37 Lipid Clinics throughout the Netherlands. A total of 508 patients were included and, after a washout period of 6 weeks, were started on monotherapy with 80 mg simvastatin for a 2-year period. At baseline, mean LDL-C (8.37 ± 2.12 mmol/L) levels were severely elevated and, after 2 years of treatment, were reduced by 48.0% to a mean of 4.29 mmol/L. Total cholesterol and triglyceride (TG) levels were reduced by 39.2% and 26.1%, respectively and HDL-C levels were increased by 12.7%. All these changes from baseline were maintained throughout 2 years. The incidence of discontinuations due to drug-related clinical adverse events (AE) was 4.3% and due to laboratory AE's 0.8%. Consecutive elevations in liver enzymes occurred only in 5 patients (1.0%) and myopathy did not occur.

CONCLUSIONS

High dose (80 mg) simvastatin is efficacious in both reducing LDL cholesterol (-48%) and triglyceride (-26%) levels and in elevating HDL cholesterol (+13%) levels in a large cohort of FH patients. No tachyphylaxis was seen during a 2-year treatment period and furthermore, therapy with simvastatin 80 mg was well tolerated.

INTRODUCTION

Familial Hypercholesterolemia (FH) is an autosomal dominant disorder of lipoprotein metabolism and affects approximately 1 in 400 people in the Netherlands.[1] Mutations in the low-density lipoprotein (LDL) receptor gene, located on the short arm of chromosome 19, underlie a reduction in the clearance of LDL in these patients, which consequently leads to a rise in LDL-cholesterol (LDL-C) levels and predisposes to the development of atherosclerosis.[2] Therefore, FH patients are at increased risk of developing premature coronary artery disease (CAD). Typically, approximately 45% of male and 20% of female patients have documented CAD by the age of 50.[3] FH patients require intensive lipid-lowering treatment to lower their elevated LDL-C down to recommended levels. Management of these patients is based on evidence from clinical trials in patients with milder dyslipidemias.[4-9] It is unknown, however, whether the efficacy of statins towards cardiovascular disease (CVD) will be similar in FH patients. Recently, true regression of the intima-media thickness (IMT) complex of the carotid artery walls of FH patients was reported after 2 year treatment with atorvastatin 80 mg.[10] In this trial, less progression but no regression was seen in FH patients randomized to simvastatin 40 mg. In another recently reported trial, simvastatin 80 mg improved endothelial function in FH patients at 12 weeks and was maintained throughout 1 year of therapy.[11] These recent results do underscore the need for intensive lipid lowering therapy in FH patients. Unfortunately, conventional doses of statins rarely achieve targeted reductions of LDL-C in FH patients. Our study was therefore designed to evaluate the efficacy and the safety of high dose (80 mg) simvastatin in a large cohort of FH patients. Furthermore, it was designed to assess the relationship between the therapeutic response and environmental and genetic factors. Here we present the 2-year efficacy and safety data of simvastatin 80 mg in more than 500 FH patients.

METHODS

Subjects

For this open label multicenter study FH patients were recruited from 37 Lipid Clinics in the Netherlands. Patients were included if they met the following criteria: all patients had to have either a molecular diagnosis for FH or were diagnosed with definite FH and had to have 6 or more points, according to an algorithm (to allow standardization

of the diagnosis of FH based on clinical findings, personal and familial clinical history and biochemical parameters)[12]; at least 18 years of age; and patients with a history of myocardial infarction, coronary artery bypass graft or percutaneous transluminal coronary angioplasty could be included if the physician thought it was medically allowed for the patient to have a washout period. Patients were excluded if they: were pregnant or nursing women, or pre-menopausal women not using adequate contraceptives; had acute liver disease, hepatic dysfunction, or persistent elevations of serum transaminases; had hypersensitivity or intolerance to simvastatin or any of its components; had hypercholesterolemia Type I, III, IV or V or homozygous FH; had a recent history of alcohol or drug abuse; had secondary hypercholesterolemia due to any cause; had inadequately controlled diabetes, unstable angina or intermediate coronary syndrome or clinically significant ventricular arrhythmia at study entry or myocardial infarction within the past 3 months; were on concurrent use of erythromycin and similar drugs affecting the cytochrome P450 enzyme or had a history of cancer. The Ethics Committees of all the 37 centers approved the protocol and written informed consent was obtained from all participants.

Study design

After a washout period of 6 weeks, patients were started on monotherapy with simvastatin 80 mg, one tablet once daily, for 2 years. No other lipid lowering medication was allowed. Medical history, physical examination and additional risk factors for cardiovascular disease as well as laboratory analysis of lipid and lipoprotein levels and routine safety parameters were obtained in all patients. The biochemical analyses of lipid levels and safety parameters were performed in the hospitals themselves at each of 8 clinic visits (at weeks: –6, 1, 6, 12, 24, years: 1, 1½ and 2) and were standardized by a virtual central laboratory. The apolipoprotein determinations were performed in the Academic Medical Center in Amsterdam.

Efficacy and safety criteria

The primary efficacy endpoint was the percent change in LDL cholesterol level relative to baseline. Secondary endpoints included percent change in total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides and the apolipoproteins A-I and B, all relative to baseline values. Safety and tolerability were evaluated with adverse event reporting, laboratory studies and vital sign recording. Patients were questioned about the occurrence of adverse events using non-leading questions. Vital signs were

measured at each visit. A physical examination was performed at baseline visit. Fasting samples for serum chemistry were taken at each visit. The proportion of patients with values of alanine-amino transferase or aspartate-amino transferase more than 3 times the upper limit of normal confirmed on repeat or sustained elevations confirmed on measurements at least 30 days apart and the proportion of patients discontinued due to these elevations at any time during the study were tabulated. Any elevations of creatine kinase of >5 times the upper limit of normal that are confirmed on repeat and accompanied by clinical signs or symptoms of myopathy, or creatine kinase elevations more than 10 times the upper limit of normal, even if asymptomatic, will be considered safety endpoints for the study. All drug-related clinical and laboratory adverse experiences as well as discontinuations due to these events were recorded. The drug relatedness was scored as definitely not, probably not, possibly, probably or definitely. Those adverse events scored as possibly, probably and definitely were considered drug-related.

Biochemical analysis

Blood samples were taken in the morning after an overnight fast. Total cholesterol, HDL cholesterol, triglycerides and safety parameters were routinely determined in the different laboratories and standardized by a virtual central laboratory. LDL cholesterol was calculated using the Friedewald formula.[13] Apolipoprotein A-I and B were determined by an immunological rate-nephelometric procedure using a polyclonal goat anti-human antibody (Array protein system, Beckman Coulter, Netherlands).[14]

Statistical analysis

Mean values in lipids and lipoproteins before and after treatment were compared using the paired sample t-test and the statistical significance of the relative change (for those patients with lipid levels at both baseline and 2 years of treatment) as compared to baseline, was tested using the one sample t-test. Triglyceride levels were compared by the non-parametric Wilcoxon test, because they had a skewed distribution. All statistical analyses were performed using the SPSS package (version 10.1, Chicago; Illinois). A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

Demographic and baseline characteristics

A total of 546 patients were considered for inclusion. Of these, 508 patients met the inclusion criteria and received simvastatin 80 mg. Of all patients, 341 had a molecular diagnosis of FH while 167 patients received the FH diagnosis based on the algorithm. All patients were on a modest lipid-lowering diet, comparable to NCEP step I, and during the study considerable attention was focused on dietary adherence. Baseline characteristics for men and women separately are given in table 1.

Table 1. Demographic and clinical baseline characteristics of 508 patients with familial hypercholesterolemia.

Characteristics	Men (n=285)	Women (n=223)
Age (year)	45.3 ± 11.5	50.0 ± 14.7
Cardiovascular Disease	38.6 %	35.4 %
Mean age of onset (year)	43.4 ± 8.1	50.9 ± 9.9
Coronary artery disease	93.6 %	87.3 %
Peripheral artery disease	15.5 %	27.8 %
Both	9.1 %	15.2 %
Smoking Current	27.4 %	24.2 %
Non smoking	72.6 %	75.8 %
Family history of premature CAD	64.2 %	66.8 %
Diabetes mellitus	1.8 %	2.2 %
Systemic hypertension	16.5 %	14.3 %
Weight (kg)	83.9 ± 11.9	70.1 ± 11.4
Height (m)	1.79 ± 0.07	1.65 ± 0.06
Body mass index (kg/m^2)	26.0 ± 3.1	25.6 ± 4.0
Xanthomas	39.6 %	49.3 %
Arcus cornealis	35.4 %	25.1 %

All values are expressed as mean ± SD or percentages. CAD, coronary artery disease.

Efficacy

Mean baseline lipid and lipoprotein levels of all patients are listed in table 2. Mean total cholesterol (10.50 mmol/L or 404 mg/dl) and LDL cholesterol (8.37 mmol/L or 322 mg/dl) levels were, as can be expected in FH patients, severely elevated. In comparison, total cholesterol and LDL cholesterol levels were 5.49 mmol/L (211 mg/dl) and 3.56 mmol/L (137 mg/dl), respectively in 3403 Dutch controls.[15]

Table 2. Treatment effects of simvastatin 80 mg on fasting lipid and lipoprotein levels.

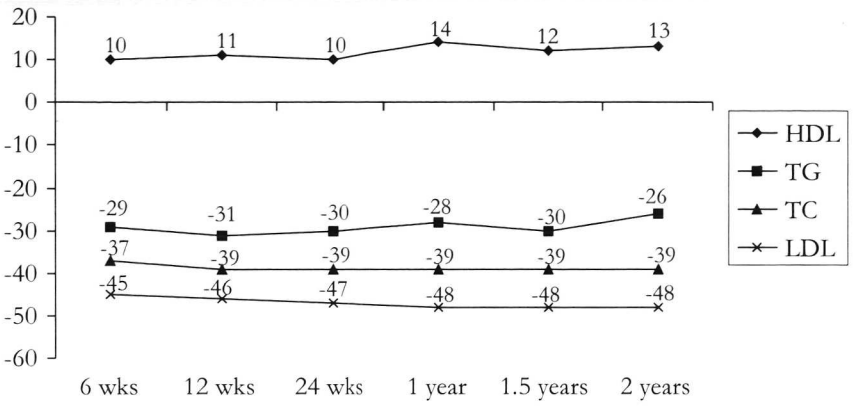
Variable	Baseline (n = 508)	Year 2 (n = 445)	% Change	95% CI	p-value
Total cholesterol					
mmol/L	10.50 ± 2.16	6.31 ± 1.42	-39.2 ± 11.8	-40.3 to -38.1	<0.0001
mg/dl	404 ± 83	243 ± 55			
LDL cholesterol					
mmol/L	8.37 ± 2.12	4.29 ± 1.32	-48.0 ± 13.5	-49.2 to -46.7	<0.0001
mg/dl	322 ± 82	165 ± 51			
HDL cholesterol					
mmol/L	1.22 ± 0.35	1.35 ± 0.36	12.7 ± 21.8	+10.7 to +14.8	<0.0001
mg/dl	47 ± 13	52 ± 14			
Triglycerides					
mmol/L	1.80 (1.20/2.40)	1.20 (0.90/1.70)	-26.1 (-46.2/-5.6)		<0.0001
mg/dl	159 (106/212)	106 (80/150)			
ApoA-I					
(g/L)	1.22 ± 0.21	1.29 ± 0.22	7.0 ± 20.9	+4.8 to +9.2	<0.0001
ApoB					
(g/L)	1.98 ± 0.44	1.20 ± 0.31	-38.2 ± 13.9	-39.7 to -36.8	<0.0001

All values are given as mean levels ± standard deviation only triglycerides are given as median with the interquartile range between brackets. CI, confidence interval, LDL-C, low-density lipoprotein cholesterol, HDL-C, high-density lipoprotein cholesterol, TG, triglycerides, ApoA-I, apolipoprotein A-I, ApoB, apolipoprotein B

After 2 years of treatment, total cholesterol levels were reduced by 39.2% to mean levels of 6.31 mmol/L (243 mg/dl) and LDL cholesterol levels by 48.0% to mean levels of 4.29 mmol/L (165 mg/dl). Triglyceride levels were reduced by 26.1% to median levels of 1.20 mmol/L (106 mg/dl). HDL cholesterol levels were raised by 12.7% to mean levels of 1.35 mmol/L (52 mg/dl). All these changes from baseline were highly statistically significant.

In figure 1 short- and long-term efficacy towards lipids and lipoproteins is presented. Mean LDL cholesterol levels were reduced by 45 to 48% at different time intervals during the 2 years of treatment. Over the same period, the 80 mg dose was also effective in reducing total cholesterol (mean changes from 37 to 39%) and triglycerides (median changes from 26 to 31%), and in raising HDL cholesterol (mean changes from 10 to 14%).

Figure 1. Short and long term efficacy of simvastatin 80 mg at different points in time.



Safety

A total of 29 patients discontinued therapy due to clinical adverse events (5.7%). Of these, 6 patients died. No deaths were considered drug-related and 4 were due to cardiovascular events. One patient experienced sudden death of unknown cause. The other patient had a history of myocardial infarction and mitral valve insufficiency and he died in the washout period. He was admitted with unstable angina and a coronary bypass procedure was performed combined with a mitral valve repair. The patient died from an aortic dissection during the procedure. From the total of 29 patients, 22 discontinuations (4.3%) were classified as drug-related. (table 3) The most common drug-related adverse events leading to discontinuation were musculoskeletal (1.8%) and gastrointestinal (1.0%) complaints, fatigue (0.6%) and headache (0.4%).

Table 3. Safety during 2 years of treatment with simvastatin 80 mg.

Variable	n	%
Discontinued due to drug-related clinical AE	22	4.3%
Discontinued due to drug-related laboratory AE	4	0.8%
Discontinued due to drug-related myalgia	7	1.4%
Myopathy	0	0.0%
Consecutive ALT or AST increases > 3x ULN	5	1.0%

AE, adverse event, ALT, alanine aminotransferase, AST, aspartate aminotransferase, ULN, upper limit of normal. Myopathy was defined as muscle pain accompanied by > 10 ULN in creatine kinase.

Only 5 patients discontinued therapy because of laboratory adverse events, 4 of which were drug-related (0.8%). Drug-related myalgia was observed in 45 patients (8.9%) and 7 of these patients discontinued therapy (1.4%). Myopathy is traditionally defined as muscle pain or weakness accompanied by creatine kinase levels >10 times above the upper limit of normal. Three patients had creatine kinase elevations above 10 times the upper limit, but only 1 patient had accompanying muscle pain. However, this was local back pain after a sporting event and creatine kinase levels returned to normal at retest within one week while treatment was continued. The other patient continued treatment and creatine kinase levels returned to normal within 7 days, but the third patient discontinued the study due to drug-related aspartate-amino transferase and creatine kinase elevations. Consecutive elevations in liver function tests of >3 times upper limit of normal are regarded as clinically significant. Only 3 patients had consecutive liver function elevations. Importantly, 1 of the 3 patients continued therapy and another patient interrupted therapy during 4 weeks after which he started again with the study medication. In both patients the levels returned to normal. The third patient withdrew from the study because of bad compliance and was lost to follow up. In 3 other patients elevated levels of liver transaminases were measured once while on therapy. Two of these patients discontinued therapy because they were considered to have a drug-related adverse event. These 2 patients are presumed to have had consecutive elevations as well, because their levels were not checked again while on the drug. In the third patient therapy was interrupted after which the levels returned to normal and remained normal after therapy was restarted. The total incidence of consecutive transaminase elevations was 1.0%.

A total of 29 patients discontinued therapy for other reasons during the 2 years of follow up.

DISCUSSION

Efficacy of simvastatin 80 mg

Mean LDL cholesterol levels were reduced by 48.0% after 2 years of therapy and more importantly, this reduction was maintained at different time points during these 2 years. Therefore, tachyphylaxis to simvastatin did not occur. Recently, a retrospective study reported that tachyphylaxis might occur with atorvastatin but not with simvastatin.[16] Not only LDL cholesterol reduction was maintained throughout the study, observations for total cholesterol and triglyceride reductions were similar. HDL

cholesterol increased by 12.9%, which was maintained during 2 years of treatment. A recent report has summarized most studies performed with simvastatin 80 mg treatment.[17] In a total of 1936 hypercholesterolemic (non FH) patients the 80 mg dose reduced LDL cholesterol by 45.7% and showed excellent safety and tolerability. However, in those studies the follow-up ranged from 36 to 48 weeks. In our study we showed that FH patients had a more pronounced LDL cholesterol reduction, which was maintained over a 2-year period.

Safety of simvastatin 80 mg

This cohort provided the opportunity to collect long-term safety and tolerability data in a large cohort of FH patients who required high dose statin therapy. No unexpected adverse events were observed. The incidence of discontinuations due to drug-related clinical (4.3%) or laboratory (0.8%) adverse events was very low. Only 3 patients had creatine kinase elevations >10 times upper limit of normal, and only 1 of these had accompanying muscle pain. The incidence of sustained elevations in hepatic liver enzymes >3 times upper limit of normal was also low (1.0%). These safety and tolerability data are in line with the results of other studies performed with simvastatin 80 mg.[17] In those 1586 patients the incidence of clinical and laboratory drug-related discontinuations was 2.5% and 1.6%, respectively, while that of consecutive elevations in liver function tests was 1.5% and of myopathy 0.6%.

In summary, high dose (80 mg) simvastatin is efficacious in both reducing LDL cholesterol (-48%) and triglyceride (-26%) levels and in elevating HDL cholesterol (+13%) levels in a large cohort of FH patients. No tachyphylaxis was seen during a 2-year treatment period and furthermore, therapy with simvastatin 80 mg was well tolerated.

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