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MASAKO KITATANI, JUNJI KOIZUMI, AKIHIRO INAZU, KOUJI KAJINAMI, AND HIROSHI MABUCHI

Second Department of Internal Medicine, School of Medicine, Kanazawa University, Kanazawa, Japan

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ABSTRACT

A study was conducted to determine the clinical efficacy and tolerability of simvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase in seven patients with heterozygous familial hypercholesterolemia (FH) (defined as primary hypercholesterolemia with tendon xanthoma or primary hypercholesterolemia without tendon xanthomas and at least one first-degree relative with familial hypercholesterolemia). These patients were administrated 10 mg/d of simvastatin for up to 4 years. Simvastatin significantly reduced levels of both total cholesterol and low-density lipoprotein cholesterol during treatment; respective reduction rates were 28% and 34% after 1 month and 32% and 40% after 4 years. Serum high-density lipoprotein cholesterol levels slightly and insignificantly increased. Serum triglyseride levels fell significantly by 24% at month 6. After this study, all xanthomas had reduced in size. No adverse events related to simvastatin were observed. We conclude that long-term simvastatin therapy is clinically useful and well tolerated in patients with FH.

INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant disorder caused by low-density lipoprotein (LDL) receptor abnormalities resulting from a gene mutation.[1,2] The level of serum cholesterol in heterozygotes with FH is twice that of normal adults, and patients with FH frequently develop coronary artery disease (CAD) at a relatively young age.[3] It is now clear that the CAD in patients with FH stems from elevation of LDL cholesterol (LDL-C), which serves as a carrier of cholesterol in the blood. Aggressive lipid-lowering treatment of FH in its early stages may prevent the development of CAD. Thus an effective and safe medication to reduce the serum cholesterol level is essential in treating patients with FH.

Address correspondence to: Masako Kitatani, Second Department of Internal Medicine, School of Medicine, Kanazawa University, Takara-machi 13-1, Kanazawa 920, Japan.
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Specific competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (eg, lovastatin, pravastatin, simvastatin, and fluvastatin) have been widely used. Simvastatin is a lovastatin derivative obtained by chemical semisynthesis.[4] By suppressing cholesterol synthesis in the liver, these drugs enhance LDL receptor activity and eliminate LDL from the blood.[5] These drugs are effective and well tolerated in patients with heterozygous FH.[6]

Encouraging results have been published on the short-term (4 weeks)[7] and long-term (2 years) use of simvastatin.[8]

In this study, simvastatin (10 mg once a day taken after a meal) was administered to seven heterozygous patients with FH for a period of 4 years, and the clinical efficacy and tolerability of this medication were assessed.

PATIENTS AND METHODS

Seven patients with heterozygous FH (2 men and 5 women; age range, 20 to 59 years) were studied. Criteria for the diagnosis of FH were (1) primary hypercholesterolemia (total cholesterol level >230 mg/dL in any age group) with tendon xanthoma or (2) primary hypercholesterolemia without tendon xanthoma and at least one first-degree relative with familial hypercholesterolemia.[9] None of these patients had diabetes, and all had normal thyroid, renal, and hepatic functions. One patient had ischemic heart disease. All patients gave informed consent to participate in the study.

Patients had previously received dietary instruction, and all other lipid-lowering drugs were withdrawn at least 4 weeks before the start of the study. Before this study, Achilles tendon thickness, xanthoma, or any other complications were observed, and electrocardiograms were recorded. Then treatment with simvastatin at a dose of 10 mg/d was begun. At each visit patients were seen in the morning, after having fasted for at least 12 hours. During this study, patients were advised not to change their dietary habits and to keep their body weight unchanged. Fasting venous blood samples were obtained at 6-month intervals for up to 4 years. Achilles tendon thickness was measured radiographically before and after treatment.[10]

Serum total cholesterol and triglyceride levels were determined by using the enzymatic method.[11,12] High-density lipoprotein cholesterol (HDL-C) was assayed in the supernatant of the calcium chloride–heparin precipitation[13] using a commercial kit. LDL-C was calculated using the Friedewald formula.[14] Six apolipoproteins (apo) (A-I, A-II, B, C-II, C-III, and E) were determined by the method of immunoturbidmetry using the reagent kit ApoAuto (Daiichi Chemical Co. Ltd., Tokyo, Japan).[15] All serum lipids and apolipoprotein levels were measured at SRL research laboratory (Tokyo, Japan).

At each visit patients were questioned about possible side effects, and physical examinations were performed. Laboratory toxicity data, which included measurements of transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), gamma-glutamyl transpeptidase (GGTP), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK), were also obtained.

Statistical Analysis

Statistical analysis was performed using Student's *t* test. Values given are mean ± SE.

RESULTS

Serum Lipids and Apolipoproteins

Changes in serum cholesterol levels in each patient are shown in Figure 1. Serum cholesterol rapidly decreased with 10 mg/d simvastatin and continued to decrease during the treatment period in all seven patients. The mean level of total cholesterol significantly fell from 382 ± 14 mg/dL to 275 ± 5 mg/dL (28%), 252 ± 9 mg/dL (34%), 254 ± 12 mg/dL (34%), 257 ± 11 mg/dL (33%), and 258 ± 11 mg/dL (32%), at months 1, 12, 24, 36, and 48, respectively. The mean LDL-C level fell from 312 ± 17 mg/dL to 204 ± 6 mg/dL (34%), 183 ± 8 mg/dL (41%), 183 ± 16 mg/dL (41%), 186 ± 12 mg/dL (40%), and 188 ± 12 mg/dL (40%), at months 1, 12, 24, 36, and 48, respectively. Administration of simvastatin resulted in a rapid and highly significant decrease in mean total cholesterol and LDL-C levels during treatment, to a maximum decrease of 34% and 42%, respectively (Figure 2). HDL-C levels slightly and insignificantly increased. Serum triglyceride levels fell significantly ($P < 0.05$) from 121 ± 19 mg/dL to 90 ± 13 mg/dL (26%) at month 6.

Changes in the serum apolipoprotein levels are shown in Table I. Apo B showed a significant reduction ($P < 0.01$) and apo A-I showed a slight increase at month 1 ($P < 0.05$). Apo C-II and E decreased significantly from 4.0 ± 0.2 mg/dL at baseline to 3.1 ± 0.2 mg/dL (23%) at month 6 ($P < 0.05$), to 2.7 ± 0.3 mg/dL (33%) at month 18 ($P < 0.01$), to 2.7 ± 0.2 mg/dL (33%) at month 24, and to 2.9 ± 0.3 mg/dL (28%) at month 30 ($P < 0.05$). Apo E levels decreased significantly from 7.6 ± 0.5 mg/dL at baseline to 6.2 ± 0.4 mg/dL (18%) at month 1 ($P < 0.05$), to 5.8 ± 0.2 mg/dL (24%) at month 12 ($P \pm 0.05$), to 5.2 ± 0.5 mg/dL (32%) at month 18 ($P < 0.05$), to 5.5 ± 0.2 mg/dL (28%) at month 30 ($P < 0.05$), and to 6.4 ± 0.3 mg/dL (16%) at month 42 ($P < 0.05$). A-II and C-III showed no significant changes.

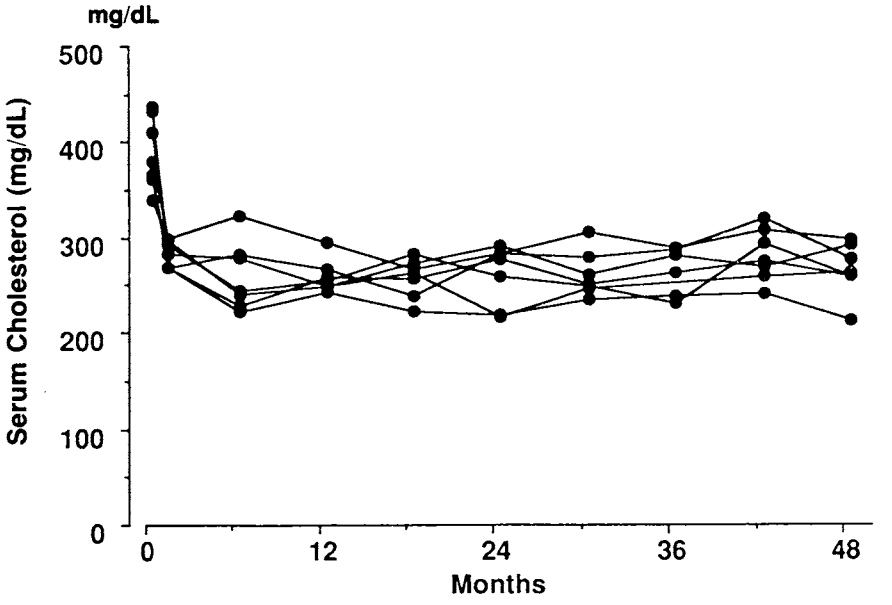

Figure 1. Changes in serum cholesterol levels in seven patients with heterozygous familial hypercholesterolemia.

Achilles Tendon Thickness and Xanthoma

Achilles tendon thickness, which was measured by the side view of Achilles tendon radiographs taken before and after the study, decreased from 12.7 ± 4.7 mm to 12.5 ± 5.1 mm on the right side, and 13.1 ± 4.1 mm to 12.7 ± 4.0 mm on the left side. Mean levels of Achilles tendon thickness showed a slight regression, but the differences did not reach statistical significance. Before the study, 3 patients had xanthelasma, 2 patients had xanthomas of the extensor tendons of the hands, and 2 patients had xanthomas of the elbows. All xanthomas were reduced in size by the end of the 4-year treatment.

Side Effect and Toxicity Data

There were no serious clinical or laboratory adverse events during the study. Laboratory side effects were limited to elevations of GGTP and LDH. One patient showed high levels of GGTP during the study. This patient's levels were higher than the 20% to 30% upper normal level and were high prior to the study. It appears that this event had no relationship to simvastatin therapy. Another patient experienced an increase in LDH levels above the 40% upper normal level for a period of 2 months. The abnormalities in these two patients were not accompanied by clinical manifestations. AST, ALT, and CPK abnormalities were not observed. No new

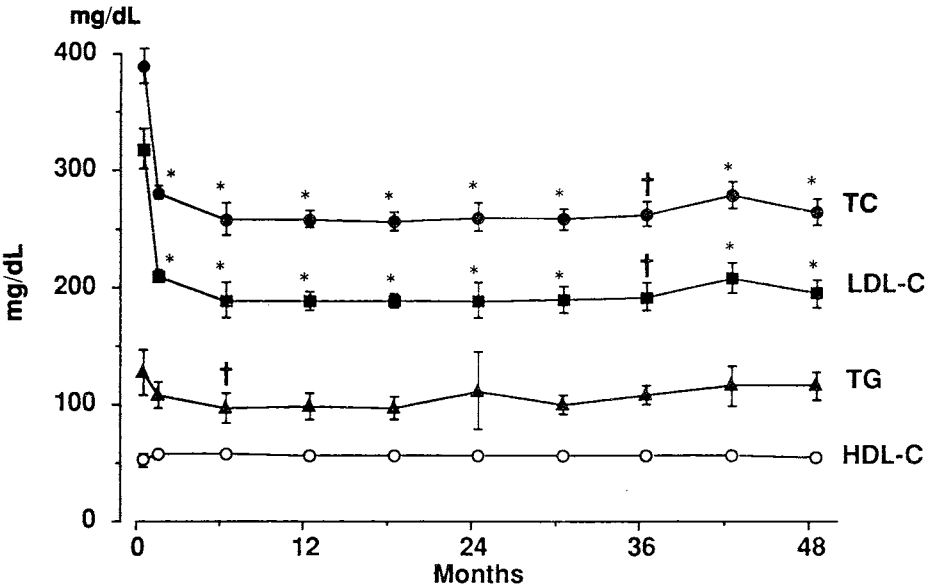

Figure 2. Changes in serum cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) levels in patients with heterozygous familial hypercholesterolemia. Values are given as mean ± SE. $^{*}P < 0.01$, $^{\dagger}P < 0.05$ versus before study.

electrocardiographic findings or heart attacks were noted. No patients reported any symptoms of myalgia or myopathy.

DISCUSSION

The long-term effect of simvastatin on serum lipids in heterozygous FH was investigated. The total cholesterol and LDL-C levels were significantly reduced at 1 month and continued to decrease during the study period. During the study, serum total cholesterol and LDL-C levels were maintained at approximately 250 mg/dL and 185 mg/dL, respectively. The LDL-C level was significantly reduced, by about 40%, over the 4 years of treatment. These changes in serum lipoproteins may be beneficial in preventing the development of atherosclerosis. No significant changes were noted in serum HDL-C and triglyceride levels during this study.

Several studies of the therapeutic efficacy of simvastatin have been reported.[16–19] In these studies the simvastatin dose ranged from 2.5 to 40 mg/d and serum total cholesterol and LDL-C levels were reduced by 23% to 41% during treatment. In contrast, serum HDL-C levels increased by 12% to 20% during the same period.

In this study, we administered 10 mg/d of simvastatin for a longer period than in previous studies. The 10-mg dose of simvastatin produced a significant reduction in LDL-C levels and this reduction continued for 48

Table I. Changes in serum apolipoprotein levels (mg/dL) produced by simvastatin in heterozygous patients with familial hypercholesterolemia. Values are given as mean ± SE.

Apolipoprotein Type	Before Study	Time of Measurement (mo)								
		1	6	12	18	24	30	36	42	48
A-I	125 ± 8	139 ± 8*	133 ± 6	124 ± 5	117 ± 9	125 ± 4	123 ± 6	124 ± 7	120 ± 6	121 ± 4
A-II	30 ± 1	33 ± 2	31 ± 1	28 ± 1	28 ± 2	29 ± 1	27 ± 1	29 ± 2	31 ± 1	30 ± 1
B	171 ± 4	129 ± 7†	126 ± 7†	121 ± 4†	116 ± 4†	137 ± 7*	131 ± 6†	133 ± 6*	133 ± 8†	127 ± 7†
C-II	4.0 ± 0.2	3.5 ± 0.2	3.1 ± 0.2*	2.9 ± 0.4	2.7 ± 0.3†	2.7 ± 0.2*	2.9 ± 0.3*	3.3 ± 0.4	3.4 ± 0.4	3.5 ± 0.4
C-III	9.3 ± 0.9	9.0 ± 0.8	8.3 ± 0.8	8.1 ± 0.7	7.4 ± 0.9	9.0 ± 1.1	8.9 ± 0.5	9.6 ± 0.4	10.2 ± 1.2	11.1 ± 0.7
E	7.6 ± 0.5	6.2 ± 0.4*	6.1 ± 0.5	5.8 ± 0.2*	5.2 ± 0.5*	6.1 ± 0.6	5.5 ± 0.2*	5.9 ± 0.4	6.4 ± 0.3*	6.8 ± 0.3

* $P < 0.05$ versus before study. † $P < 0.01$ versus baseline.

months. Studies of simvastatin used in heterozygous FH patients are summarized in Table II. In the study by Valerio et al,[22] 10 mg of simvastatin administered for 8 weeks resulted in a 35% reduction in LDL-C. Other studies showed that a 20- to 40-mg dose of simvastatin resulted in a 34% to 40% reduction in LDL-C.[26] From these results, 10 mg/d of simvastatin may be sufficient for the long-term treatment of patients with heterozygous FH.

A reduction in the serum levels of total cholesterol and LDL-C is of prime importance in the prevention of CAD, and the antiatherosclerotic effect of simvastatin has recently attracted attention. In the Multicentre Anti-Atheroma Study,[27] 20 mg of simvastatin alone was administered to 381 patients with CAD during a period of 4 years. The serum level of total cholesterol decreased by 23% and the LDL-C level by 31% as a result of simvastatin administration. In contrast, the HDL-C level increased by 9%. The antiatherosclerotic effect of simvastatin was demonstrated by using quantitative coronary arteriography. In addition, the Scandinavian Simvastatin Survival Study (4S)[28] showed that simvastatin treatment significantly reduced total mortality and coronary death.

Xanthomas were examined before and after the trial. Regression of all xanthomas was confirmed at the end of administration of simvastatin, but the measurement of Achilles tendon thickness failed to show a significant regression.

No clinical adverse events were reported during the administration of simvastatin, and transient laboratory abnormalities were reported in two cases. Elevation of transaminase levels seldom occurs with administration of simvastatin.[7,20] Elevation of CPK level and muscular symptoms have been previously reported,[7,20] but were not observed in this study, and there were no newly developed cases of CAD in this study period. No patients dropped out of the study because of clinical or laboratory side effects. Therefore, our findings demonstrated the high tolerability profile of simvastatin.

Illingworth and Bacon[29] studied the lipid-lowering effects of HMG-CoA reductase inhibitors, bile acid sequestrants, clofibrate derivatives,

Table II. Studies of low-density lipoprotein cholesterol (LDL-C) reduction by simvastatin in patients with heterozygous familial hypercholesterolemia.

Reference	No. of Subjects	Dose (mg/d)	Duration of Treatment	Reduction in LDL-C (%)
Mol et al[20]	38	20–40	24 weeks	43
Leclercq et al[7]	19	20–40	2 years	35–42
De Knijff et al[21]	120	40	12 weeks	38
Valerio et al[22]	12	10	8 weeks	35
Smit et al[23]	50	40	1 year	43
Purvis et al[24]	19	40	14 weeks	45
Quiney et al[25]	30	20	1 year	32

probucol, nicotinic acid, neomycin, and D-thyroxine in patients with heterozygous FH. They suggested that when compared with other currently available hypocholesterolemic drugs, lovastatin, simvastatin, and pravastatin are superior in their ability to lower LDL-C, but in patients with heterozygous FH, single-drug therapy with HMG-CoA reductase inhibitors frequently does not result in satisfactory control of plasma cholesterol levels, and combination drug therapy is often necessary for optimal hypocholesterolemic effects to be achieved. The National Cholesterol Education Program Expert Panel (Adult Treatment Panel II) indicated that the goal of therapy in patients with CAD was to reduce LDL-C levels to 100 mg/dL.[30] HMG-CoA reductase inhibitors combined with bile acid sequestrants strongly reduce LDL-C levels in patients with heterozygous FH.[31]

CONCLUSION

The administration of 10 mg/d of simvastatin over a period of 4 years to patients with FH produced a marked reduction in cholesterol levels without any notable side effects. Our findings show that the long-term administration of simvastatin is clinically useful and well tolerated.

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