Sustained reduction of serum cholesterol in low-dose 6-year simvastatin treatment with minimum side effects in 51,321 Japanese hypercholesterolemic patients - Implication of the J-LIT study, a large scale nationwide cohort study

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Sustained Reduction of Serum Cholesterol in Low-Dose 6-Year Simvastatin Treatment With Minimum Side Effects in 51,321 Japanese Hypercholesterolemic Patients

— Implication of the J-LIT Study, a Large Scale Nationwide Cohort Study —

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The Japan Lipid Intervention Trial (J-LIT) study, a nationwide cohort study utilizing the clinical practice of general physicians, was designed to clarify the relationship between the incidence of coronary heart disease and serum lipid concentrations during simvastatin therapy, as well as the safety of the therapy, in a large number of Japanese hypercholesterolemic patients. All the enrolled patients were treated with simvastatin. The current study analyzed the lipid lowering effect and safety of the low-dose simvastatin therapy used in the J-LIT study. Open-labeled simvastatin was given to 51,321 patients at an initial dose of mostly 5 mg/day. After 6 months of the treatment, the average serum total cholesterol (TC) and low density lipoprotein-cholesterol concentrations in all the patients followed up were reduced by 18.3% and 26.0%, respectively, and that of high density lipoprotein-cholesterol increased 2.3% on average. These concentrations were well maintained throughout the 6-year treatment period. A minority of patients (1.4%) unexpectedly had a remarkable reduction in TC concentration by more than 40%. Hyper-responders, even to low-dose statin, were found for the first time in this large-scale and long-term investigation. Overall adverse drug reactions occurred in 3.3% of subjects during the 6-year treatment, the major events being hepatic and musculoskeletal disorders, of which the incidence was less than 1%. Low-dose simvastatin therapy of 5 mg/day effectively controlled the serum TC concentration by reducing it by approximately 20% on average in hypercholesterolemic Japanese patients, a reduction that corresponds to the effect of simvastatin 20 mg/day in Western studies. In addition, the low incidence of drug-related adverse events in this study may be also related to the low dosage of simvastatin. (*Circ J* 2003; **67**: 287–294)

Key Words: Cholesterol-lowering medication; Cohort study; Drug tolerance; Safety; Simvastatin

The Japan Lipid Intervention Trial (J-LIT) study was the first nationwide cohort study conducted to elucidate the relationship between serum lipid concentrations and the incidence of coronary heart disease (CHD), and was designed to reflect ordinary clinical practice for lipid lowering therapy in Japan! In order to maintain patient compliance under these conditions, it was essential for simvastatin to be administered to all patients, and we believed that by analyzing a large amount of clinical data for the correlation between the serum lipid concentrations and prevalence of coronary events under simvastatin treatment, the possible benefit of lipid lowering therapy in prevention of coronary events would be elucidated even without the use of placebo. Our study design was compatible with the ethical standards of the Declaration of Helsinki, which was revised on October 2000 to include the conditions for the use of a placebo control group. Therefore, the present protocol may be a practical method for the confirmation of the effectiveness and safety of other widely used drugs.

There have been a number of epidemiological studies in Western countries that have demonstrated a close relationship between the concentration of serum cholesterol and the incidence of CHD, the most well known being the Framingham study conducted in the USA[2] In those studies, patients with lower serum cholesterol concentrations had a reduced risk of CHD. In the past, cholesterol-lowering treatments using resins[3] and fibrates[4,5] were reported to reduce the risk of CHD. Recently, statins, including simvastatin, were found to selectively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway, and reduce the serum total cholesterol (TC) and low density lipoprotein-cholesterol (LDL-C) concentrations[6] In

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Table 1 Demographics and Clinical Characteristics of Japanese Hypercholesterolemic Patients Receiving Long-Term, Low-Dose Simvastatin

Total (N = 52,421)	
Age (years)	*57.9±7.9*
Male, no. (%)	*17,424 (33.2)*
BMI	*24.0±3.2*
Blood pressure (mmHg)	
Systolic	*139±19*
Diastolic	*82±11*
Hospitalization (%)	*0.8*
Hypertension (%)	*45.2*
Diabetes mellitus (%)	*15.4*
Obesity (%)	
BMI ≥25	*32.0*
BMI ≥30	*3.7*
ECG abnormality (%)	*18.4*
Family history of CHD (%)	*5.2*
Current smoker (%)	*16.6*
Male (%)	*41.9*
Ex-smoker (%)	*4.5*
Renal disorder (%)	*2.2*
Hepatic disorder (%)	*8.0*
Coronary heart disease (%)	*9.8*
Cerebrovascular disease (%)	*3.0*
Alcohol consumption (%)	*29.1*
Male (%)	*70.7*
FH (%)	*2.6*
Serum cholesterol level (mg/dl)	
TC	*269±34*
HDL-C	*52.6±15.1*
LDL-C	*182±34*
Triglyceride (mg/dl)	*196±169*
Atherogenic index (TC/HDL-C)	*5.6±1.9*

BMI, body mass index; CHD, coronary heart disease; FH, familial hypercholesterolemia; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Data are presented as the mean±SD.

the Scandinavian Simvastatin Survival Study (4S), simvastatin significantly reduced the mortality of patients with hypercholesterolemia[7] and other statins have also been reported to reduce the incidence of CHD[8–11]

The dose of statins prescribed in Japan is lower than that in Western countries; for example, the daily dose of simvastatin approved in Japan is 5–10 mg in contrast to 20–40 mg in Western countries![12] The present study examined the safety and drug tolerance, as well as the efficacy of long-term treatment, of relatively low dose simvastatin in Japanese hypercholesterolemic patients.

Methods

Patient Selection

In the J-LIT study, 54,203 Japanese hypercholesterolemic (TC ≥220 mg/dl) patients were screened from November 1992 through June 1993 by 6,511 investigators, almost all of whom were general practitioners, at 5,289 institutions from all 47 prefectures in Japan. Of those patients, 52,421 study subjects (17,424 men aged 35–70 years and 34,997 postmenopausal women) under 70 years of age were recruited and of them, 47,294 were eligible as the primary prevention cohort, and the remaining 5,127 patients with a history of CHD were enrolled as the secondary prevention cohort. Patients who had previously been treated with lipid-lowering agents were screened for eligibility after a washout period of at least 4 weeks, and the washout period was at least 12 weeks for those previously treated with probucol. Exclusion criteria included a recent (≤1 month) history of myocardial infarction (MI) or stroke, a history of severe MI or stroke, uncontrolled diabetes mellitus, serious concurrent hepatic or renal disease, secondary hypercholesterolemia, malignant disease, or other illness with a poor prognosis.

Study Design

The design of the J-LIT study has been reported previously in detail! During the screening period at the local recruiting site, body weight and blood pressure were determined, and fasting serum lipid profiles were measured twice consecutively. Every 6 months after enrollment, body weight, blood pressure, and serum lipid concentrations were measured and drug compliance, number of cigarettes smoked (none, 1–10, 11–19 or ≥20 per day), alcohol consumption (none, <25, 25–49 or ≥50 g/day) and amount of exercise (none, occasional, frequent or every day) were recorded. Hepatic and renal functions were assessed and an electrocardiogram was obtained every 12 months. Every patient started treatment with open-labeled simvastatin 5–10 mg/day, and lipid concentrations, adverse events and CHD events were monitored for 6 years. Diet and exercise therapies for hyperlipidemia were recommended by the investigators. Other lipid-lowering agents were added only when the investigator considered that the patient's serum TC concentration had not responded adequately to simvas-

Table 2 Sequential Changes of Treatment Profiles in Cholesterol-Lowering Therapy During 6 Years Follow-up

	Year						
	0	*1*	*2*	*3*	*4*	*5*	*6*
Simvastatin							
5 mg monotherapy	*n=48,428*	*39,519*	*32,900*	*28,981*	*25,461*	*22,823*	*20,518*
10 mg monotherapy	*1,729*	*2,081*	*2,069*	*2,025*	*1,966*	*1,812*	*1,668*
Other monotherapy	*1*	*168*	*249*	*293*	*295*	*261*	*229*
Simvastatin monotherapy total	*50,158*	*41,768*	*35,218*	*31,299*	*27,722*	*24,896*	*22,415*
Simvastatin + other lipid-lowering agent	*1,163*	*1,688*	*1,968*	*2,133*	*1,993*	*1,813*	*1,845*
Other lipid-lowering agent	*0*	*56*	*235*	*463*	*509*	*525*	*814*
No or Unknown medication	*0*	*6,576*	*10,419*	*11,655*	*12,074*	*12,190*	*11,821*
Total	*51,321*	*50,088*	*47,840*	*45,550*	*42,298*	*39,424*	*36,895*
Simvastatin total	*51,321*	*43,456*	*37,186*	*33,432*	*29,715*	*26,709*	*24,260*
5 mg (%)	*49,495 (96.4)*	*40,946 (94.2)*	*34,561 (92.9)*	*30,694 (91.8)*	*27,065 (91.1)*	*24,246 (90.8)*	*21,994 (90.7)*
10 mg (%)	*1,825 (3.6)*	*2,332 (5.4)*	*2,365 (6.4)*	*2,422 (7.2)*	*2,334 (7.9)*	*2,183 (8.2)*	*2,018 (8.3)*
Other (%)	*1 (0.0)*	*178 (0.4)*	*260 (0.7)*	*316 (0.9)*	*316 (1.1)*	*280 (1.0)*	*248 (1.0)*

tatin monotherapy. No restrictions were placed on treatments for other medical conditions. The LDL-C concentration in patients with serum triglyceride (TG) concentrations under 400 mg/dl was calculated using the Friedewald formula[13] At the beginning of this study, each patient was informed of the study purpose and was given information on drug efficacy and the need for long-term treatment.

Examination of Adverse Events

All adverse events were graded by the collaborating investigators according to the direct relation to simvastatin as definite, possible, unclear or not, as judged from the available information. All simvastatin-related adverse events were pooled and described as adverse drug reactions (ADRs). Cases of patient death were evaluated by the Endpoint Classification Committee, and all adverse events were reviewed by the Adverse Event Subcommittee, which consisted of 3 specialists who were not part of the J-LIT study group. The adverse events, such as hepatic dysfunction (aspartate aminotransferase (AST) ≥80 IU/L, alanine aminotransferase (ALT) ≥80 IU/L, γ-glutamyl transpeptidase (γ-GTP) ≥100 IU/L, or a diagnosis of hepatobiliary disorder), thrombocytopenia (platelets <100,000/mm^3, presence of purpura or pancytopenia), musculoskeletal disorder (rhabdomyolysis, elevated creatine kinase (CK) concentration (≥1,000 IU/L) and elevated creatine kinase concentration (≥600 IU/L) with muscle symptoms), and other serious adverse events, were reviewed in detail. Hepatitis was diagnosed as AST or ALT ≥120 IU/L, or γ-GTP ≥150 IU/L with abnormal AST or ALT (≥80) as judged by an investigator, rhabdomyolysis as CK ≥10,000 IU/L with muscular symptoms, and myopathy as muscle symptoms (malaise, muscular pain or cramp) with CK ≥1,900 IU/L in men or ≥1,500 IU/L in women.

Statistical Analysis

Differences between groups in baseline characteristics were compared using the unpaired t-test or the chi-square test. Results are expressed as mean±SD, and differences were considered statistically significant at $p<0.05$. Continuous variables within and between subgroups were assessed using the paired or unpaired t-test, or trend test. Analysis of covariance was used for this purpose when a significance in between-group incompatibility existed at baseline. Differences in categorical data between groups were compared using the chi-square test. Patients who received at least one dose of simvastatin during the trial was included in the analysis of adverse events. All statistical calculations were performed using SAS software (version 6.12, SAS Institute, Inc, Cary, NC, USA).

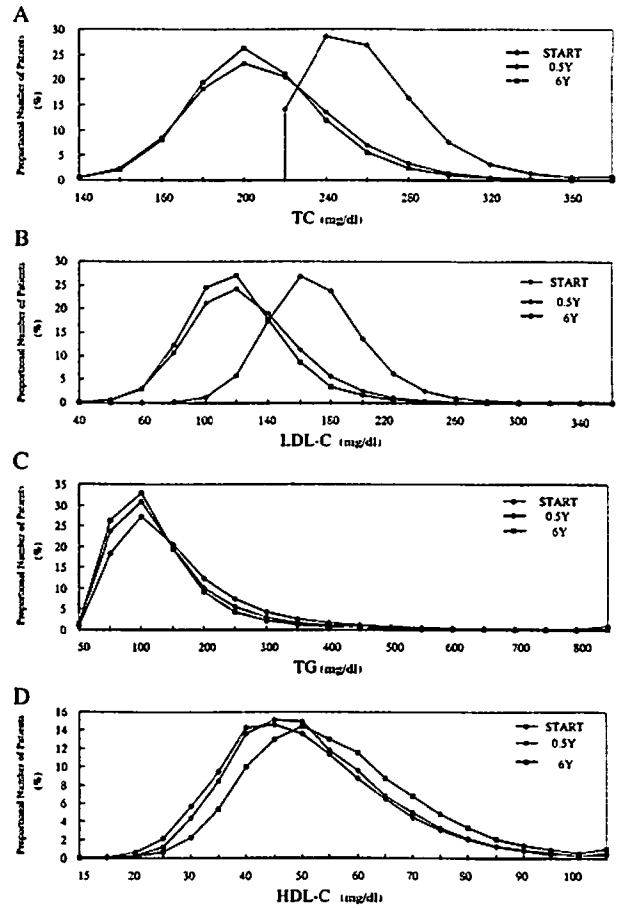

Fig 1. Distribution of proportional number of patients by serum lipid concentration at baseline, after 6 months and 6 years of low-dose simvastatin therapy. (A) Total cholesterol, (B) LDL-C, (C) triglyceride and (D) HDL-C.

Results

Patient Follow-up

The patients' clinical characteristics have been described before[1] and the baseline characteristics of the current 52,421 cohort members are summarized in Table 1. The average age was 57.9 years and 33% were male. After enrollment, 1,100 patients were excluded for the following reasons: violation of initial dosage (68 patients), missing follow-up data (1,025 patients) and unwillingness to participate (7 patients). Sequential changes in the treatment profile of the different cholesterol-lowering therapies during the 6 years of follow-up is summarized in Table 2. Of 51,321 patients, the majority (96.4%) received the most common starting dose of simvastatin 5 mg/day, and only

Table 3 Sequential Changes in Lipid Concentrations During Simvastain Treatment

	Baseline (mg/dl)	*6 months*		*6 years*	
		(mg/dl)	*(%)*	*(mg/dl)*	*(%)*
TC	*269±34*	*220±37**	*(−18.3)*	*217±34**	*(−19.3)*
LDL-C	*182±33*	*135±35**	*(−26.0)*	*129±32**	*(−28.9)*
TG	*196±169*	*167±126**	*(−14.7)*	*155±103**	*(−21.0)*
HDL-C	*52.6±15.1*	*53.8±14.8**	*(2.3)*	*58.1±15.7**	*(10.5)*

Data are presented as the mean±SD.
**p<0.0001 vs Baseline.*

Table 4 Percent Change in TC and Number of Patients With Adverse Drug Reactions in the Hypercholesterolemic Patients Receiving Long-Term, Low-Dose Simvastatin Therapy

	Reduction in TC (%)						
	>40	31–40	21–30	11–20	≤10	Lipid data missing	Total
All ADRs*	24 (3.29)	146 (3.16)	427 (2.70)	458 (2.73)	282 (3.04)	333	1,670
Hepatic*	8 (1.10)	57 (1.23)	148 (0.94)	147 (0.88)	81 (0.87)	59	500
Musculoskeletal*	10 (1.37)	50 (1.08)	126 (0.80)	138 (0.82)	70 (0.75)	45	439
Digestive*	4 (0.55)	8 (0.17)	47 (0.30)	65 (0.39)	66 (0.71)	101	291
Skin*	0 (0.00)	12 (0.26)	40 (0.25)	44 (0.26)	30 (0.32)	59	185
Total no. of patients (%)	729 (1.4)	4,618 (9.0)	15,827 (30.8)	16,780 (32.7)	9,279 (18.1)	4,088 (8.0)	51,321 (100)

*No. of incodence (%), described in Tables 6–8.

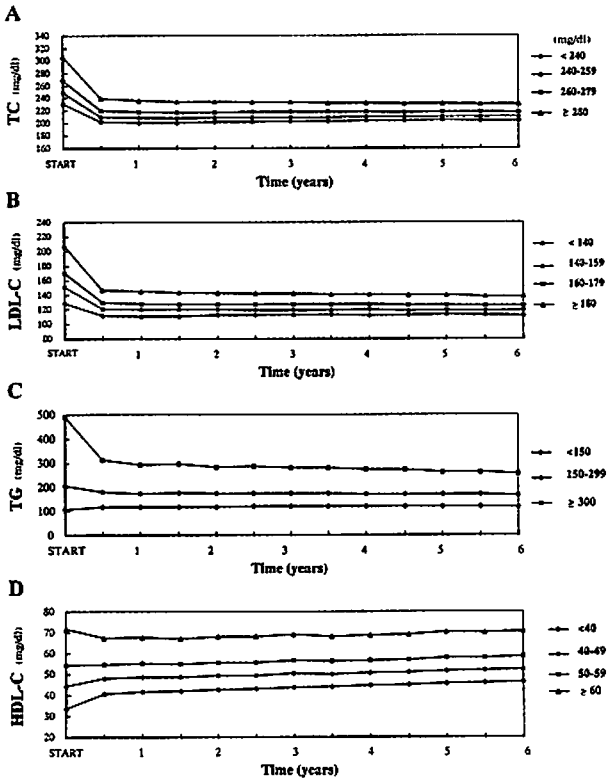

Fig 2. Sequential changes in the serum lipid concentrations as a function of the duration of simvastatin treatment for groups of patients categorized by their baseline lipid concentrations. (A) Total cholesterol, (B) LDL-C, (C) triglyceride, (D) HDL-C.

3.6% (1,825 patients) started at 10 mg/day, with 1 patient starting at 7.5 mg/day. At the 6th year, 36,895 patients remained in the study. The average follow-up period was 5.3±1.4 years (0.5–6.0 years). At the 6th year, 20,518 patients had received simvastatin 5 mg/day alone, 1,668 patients had received simvastatin 10 mg/day alone, 1,845 patients had received other lipid-lowering drugs in addition to simvastatin and 814 patients had received other lipid-lowering drugs. The ratio of patients treated with simvastatin 10 mg/day to those on 5 mg/day slightly increased during the course of treatment, nonetheless, more than 90% of patients remained on 5 mg/day for 6 years. The cumulative treatment term was 174,769 patient-years and the average term of drug treatment was 3.41 years per patient.

Changes in Serum Lipid Concentrations

After 6 months of treatment, the distribution curve of patient number by serum TC and LDL-C concentrations shifted lower in comparison with the baseline in all the patients followed up (Fig 1). The average reduction in serum TC and LDL-C was 18.3% and 26%, respectively, after 6 months, and these concentrations were maintained during the 6-year treatment period (Table 3). After 6 years of treatment, TC and LDL-C concentrations were reduced by 19.3 and 28.9%, respectively, although a minority (1.4%) had an unexpectedly remarkable reduction by more than 40% in serum TC concentration (Table 4). That group had 1.7-fold more men and 4.4-fold higher incidence of complications of renal disease, 2.2-fold of hepatic disease and 1.8-fold of diabetes mellitus when compared with the group of patients with a 10-20% reduction in TC concentration. In the contrast, the serum high density lipoprotein-cholesterol (HDL-C) concentration increased on average by 2.3% after 6 months of treatment, and kept gradually increasing throughout the treatment period up to 10.5% by the 6th year. Although no change in the serum TG distribution pattern was observed, the average value decreased by 14.7% at the 6th month and by 21 % during the 6-year treatment period in comparison with baseline.

The time course of the effect of treatment on lipid concentrations can be seen when the patient groups are stratified by their baseline lipid concentrations (Fig 2). The serum TC and LDL-C concentrations decreased with the treatment in all groups, but the reduction was greater in the patients with a higher baseline TC or LDL-C concentration (Table 5). The mean concentration of serum HDL-C increased after 6 months of the treatment and continued to increase during the treatment period. The serum HDL-C concentration after 6 years of treatment did not change in patients whose baseline HDL-C was 60 mg/dl or more, but in those with a baseline concentration less than 60 mg/dl the increase in serum HDL-C after the treatment was greater as the baseline concentration decreased. The serum TG concentrations decreased markedly in patients with a higher baseline TG concentration, particularly in patients with the highest range of concentrations (TG ≥300 mg/dl) for whom the reduction was 41.4% of the baseline. On the other hand, the TG concentration increased slightly in the group with a low baseline TG concentration.

Clinical Adverse Effects

Overall, treatment with simvastatin was well tolerated. ADRs were reported in 1,670 patients (2,470 events), and the overall frequency of ADRs during the treatment for 6 years was 3.3% of subjects (Table 4). The incidence of ADRs is demonstrated with the patient groups stratified by the reduction in serum TC concentration during the treatment (Fig 3, Table 4). There was no significant difference in the incidence of ADRs in these groups, except in the patients with less than 10 % decrease in TC concentration

Table 5 Baseline Serum Lipid Concentration and Percent Changes at 6 Years With Low-Dose Simvastatin Therapy in Japanese Hypercholesterolemic Patients

Baseline serum lipid concentration (mg/dl)	*n*	*% changes*	*p value for trend test*
TC			
<240	*2,836*	*−12.0±12.8*	
240–259	*6,059*	*−16.5±11.7*	
260–279	*5,771*	*−19.4±11.2*	
≥280	*6,404*	*−24.4±11.7*	
			<0.001
LDL-C			
<140	*1,193*	*−13.5±22.2*	
140–159	*3,134*	*−21.9±17.9*	
160–179	*4,918*	*−26.8±16.1*	
≥180	*9,129*	*−33.3±14.6*	
			<0.001
TG			
<150	*9,960*	*17.3±55.7*	
150–299	*8,352*	*−17.6±40.1*	
≥300	*2,500*	*−41.4±35.9*	
			<0.001
HDL-C			
<40	*3,322*	*40.7±61.8*	
40–49	*5,684*	*18.0±24.6*	
50–59	*5,055*	*8.3±21.4*	
≥60	*5,692*	*−0.4±20.9*	
			<0.001

% changes are presented as the mean±SD.

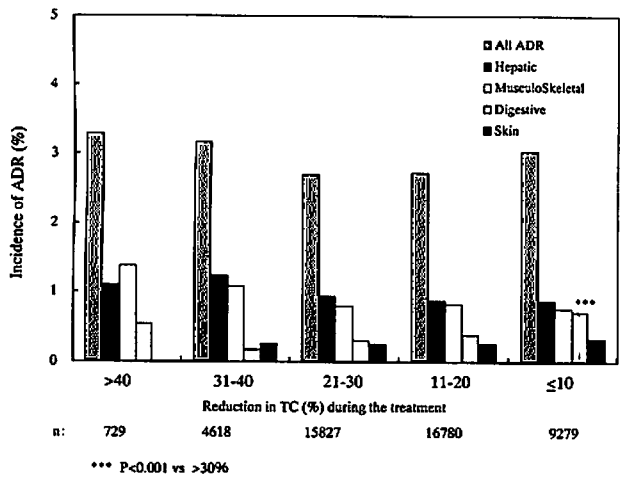

Fig3. Incidence of adverse drug reactions in long-term, low-dose simvastatin therapy as a function of the change in the total cholesterol concentration during the treatment.

who showed an increase in the incidence of digestive ADRs. The incidence of musculoskeletal ADRs had a tendency to increase slightly in proportion to the reduction of TC concentration, and the added incidence in the group of patients with a greater than 30% decrease in serum TC concentration was significantly higher when compared to the group with a 20–30% decrease.

The ADRs summarized by different organ system are shown in Table 6. The most frequently observed ADRs were hepatic disorders in 500 cases (838 events) with an incidence of 0.97%. Of these, 411 cases (82%) represented abnormal laboratory values without clinical significance (Table7). Hepatitis occurred in 80 patients with an incidence of 0.16%. There were 3 cases of elevated AST and/or ALT greater than 500IU/L. The severity of hepatic disorders was mild in 421 cases, and moderate in 79 cases. None

Table 6 Summary of Adverse Drug Reactions (ADRs) in Hypercholesterolemic Japanese Patients on Long-Term, Low-Dose Simvastatin Therapy

ADR	*n (no. of patients)*
Hepatic (described in Table 7)	*838 (500)*
Musculoskeletal (described in Table8)	*492 (439)*
Digestive	*352 (291)*
Abdominal symptoms	*187*
Diarrhea	*45*
Nausea	*31*
Anorexia	*27*
Miscellaneous	*62*
Generalized	*220 (200)*
Malaise	*49*
Headache	*39*
Dizziness	*38*
Weakness	*29*
Miscellaneous	*65*
Skin	*190 (185)*
Rash	*131*
Pruritus	*47*
Miscellaneous	*12*
Kidney	*108 (96)*
BUN increased	*39*
Hematuria	*20*
Miscellaneous	*49*
Neurological	*101 (93)*
Sleep disorder	*25*
Numbness	*23*
Miscellaneous	*53*
Blood	*71 (62)*
Anemia	*27*
Miscellaneous	*44*
Laboratory test abnormality	*71 (67)*
Uric acid increased	*26*
Miscellaneous	*45*
Miscellaneous	*27 (26)*

of the cases was considered serious by the Adverse Event Subcommittee. The second most common ADRs were musculoskeletal disorders (439 cases, 492 events), which

Table 7 Hepatic Disorders as Adverse Drug Reaction (ADR) in Hypercholesterolemic Japanese Patients on Long-Term, Low-Dose Simvastatin Therapy

ADR	Mild	Moderate	Serious	Total
Hepatitis	9	71	0	80
Fatty Liver	20	7	0	27
Cholelithiasis	1	0	0	1
Liver function test abnormality	408	3	0	411
AST increased	206	2	0	208
ALT increased	232	1	0	233
γ-GTP increased	115	2	0	117
ALP increased	48	0	0	48
LDH increased	83	0	0	83
Bilirubin increased	16	0	0	16
Miscellaneous	25	0	0	25
Total	755	83	0	838
No. of patients	421	79	0	500

AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyltranspeptidase, ALP, alkaline phosphatase; LDH, lactate dehydrogenase.
Serious = life-threatening condition, Moderate = requiring medical treatment or discontinuation of simvastatin treatment, Mild = others.

Table 8 Musculoskeletal Disorders as Adverse Drug Reaction (ADR) in Hypercholesterolemic Japanese Patients on Long-Term, Low-Dose Simvastatin Therapy

ADR	Total (with elevated CK)
Rhabdomyolysis	0
Myopathy	4 (4)
Myalgia	97 (32)
Muscle cramp	36 (9)
Muscle atrophy	1 (0)
Arthralgia	8 (1)
Myoglobin increased	2 (1)
Elevated CK (IU/L)	
≥1,900 (Men), ≥1,500 (Women)	2
≥1,000	21
≥600 with symptoms	18
Other	303
Total	492
No. of patients	439

CK, creatine phosphokinase.

occurred with incidence of 0.86% (Table 8). Among them, 344 events had an elevated CK concentration; 6 patients showed a 10-fold increase of the normal values and 4 patients were considered to have myopathy because of the occurrence of pathognomonic symptoms. There was no case of rhabdomyolysis as defined by the ADR assessment subcommittee as CK greater than 10,000 IU/L with muscular symptoms. The significant increase of musculoskeletal ADRs that accompanies treatment with fibrate agents was not observed. Among the digestive adverse reactions, abdominal symptoms were reported in 187 cases (0.36%) and for skin reactions, a rash developed in 131 cases (0.26%) (Table 6). Twenty five patients had a sleep disorder (0.05%).

Information for 10 patients who died or were hospitalized because of simvastatin-related adverse events is summarized in Table 9. One death was caused by thrombocytopenia in the 3rd month of the treatment. That patient received 9 drugs concomitant to the simvastatin, and the platelet count had not been determined prior to or at the start of simvastatin therapy. The platelet count was less than 10,000/μL after 3 months of the therapy, and the patient died 5 days after the finding of thrombocytopenia, which the reporting physician did not considered to be related to the simvastatin. However, the relationship of thrombocytopenia to simvastatin could not be denied. Of 9 patients requiring hospitalization from possible serious ADRs, 3 had thrombocytopenia.

The frequency of overall ADRs was 9.6 cases per 1,000 patients-year and that of death and hospitalization was 57 cases per 1,000,000 patients-year.

Discussion

The J-LIT study is the first prospective cohort study to successfully establish a correlation between serum lipid concentrations and the incidence of CHD in Japanese hypercholesterolemic patients. In this study, low-dose simvastatin (mostly 5 mg/day) administered for 6 years effectively reduced serum TC and LDL-C concentrations, and increased the HDL-C concentration, in Japanese subjects with hypercholesterolemia and the treatment was safe and well tolerated. The number of participating subjects was approximately 50,000 and the total study period of 6 years simulated long-term simvastatin treatment for patients with hypercholesterolemia. A study without placebo control was required to obtain information of the safety and efficacy of simvastatin in Japanese patients for following reasons. First, this long-term and large-scale study was only possible through ordinary standard clinical practices in Japan. Under those conditions, administering simvastatin to every subject was critical to ensure the compliance of patients, because the availability of the well established health insurance to every Japanese patient without exception meant that this study provided no additional financial incentive to the participants. Second, statins are already a proven effective treatment for hypercholesterolemia and it was difficult to convince physicians and patients to participate if the lives of the hypercholesterolemic patients in the placebo group would be compromised because of the possible consequences of coronary events. In this regard, the study plan is in agreement with the October 2000 revised Declaration of Helsinki and could be a practical method for assessing the effectiveness and safety of other widely used drugs with life saving effects.

Hypercholesterolemia has been identified as a major risk factor for CHD[1-14] and previous studies have demonstrated that cholesterol-lowering medication can reduce the risk of CHD[2-10] or death[9] Of those medications, simvastatin, which

Table 9 Summary of Death and Hospitalization in Hypercholesterolemic Japanese Patients Receiving Long-Term, Low-Dose Simvastatin Therapy

ADR	*Sex*	*Age (years)*	*Month of treatment*	*Details*
Thrombocytopemia	*M*	*56*	*3*	**Platelet <1.0×10⁴/μL Death 5 days after emergency hospitalization.*
Thrombocytopenia	*F*	*59*	*30*	**Platelet <2.0×10⁴/μL Simvastatin discontinued, recovery after hospitalization.*
Thrombocytopenia	*F*	*51*	*31*	**Platelet <7.5×10⁴/μL, Not recovered with discontinuation of simvastatin, hospitalization.*
Aplastic anemia	*F*	*62*	*52*	*Subcutaneous hemorrhage continued after cassation of simvastatin. Hospitalization. Simvastatin resumed.*
Myalgia	*F*	*56*	*31*	*CK 1,402 IU/L. Hospitalization because of continued thigh muscle pain.*
Renal failure	*M*	*61*	*2*	*CK 865 IU/L. Dialysis.*
Vertigo, nausea	*F*	*51*	*2*	*Hospitalization because of severe vertigo and nausea. CT normal. Symptoms improved in 1 week after sodium bicarbonate infusion.*
Dizziness	*F*	*66*	*40*	*Hospitalization because of difficulty walking with dizziness. Recovered in 1 month.*
Pancreatitis	*M*	*56*	*53*	*Hospitalization because of vomiting and epigastric pain. Diagnosis stage 4 pancreatitis. Pancreatitis improved after treatment with camostat mesilate.*
Fever, vomiting, diarrhea, Creatinine · BUN ↑	*F*	*66*	*49*	*Hospitalization with fever, vomiting, diarrhea and creatinine · BUN increase. Details unknown.*

**No data for baseline platelet count.*

is a powerful drug for normalizing serum lipid concentrations, is one of the most widely prescribed statins in the world[5] A comparable long-term large-scale study of simvastatin conducted in a Western country was the 4S study in which the effect of 20–40 mg/day of simvastatin in hypercholesterolemic subjects was examined for 5.4 years on average[7] In Japan, the recommended starting dose is 5 mg/day, which is 1/4 of the dose used in Western countries,[12] and during the initial 6-month simvastatin treatment period, the serum concentrations of TC and LDL-C decreased 18.3% and 26.0% of their baseline values, respectively. The magnitude of the reductions was similar to those observed in higher dose simvastatin studies performed in Western countries, such as the 4S study. However, the reasons why Japanese patients responded differently from those in Western countries are not clear. We speculate that differences in patient susceptibility to simvastatin because of differences in intrinsic metabolism and/or the nature of dietary intake or genetic factors in both populations could account for the dose difference. In particular, the difference may be related to dietary differences, because there seems to be basically no difference in the pharmacokinetics of the drug and the effect of simvastatin on the reduction of LDL-C has been enhanced by lower fat diet![15,16] Treatment with low-dose statin in combination with a low-fat diet might benefit patients in Western countries. With the recent progress in understanding the genetic factors associated with hyperlipidemia, the genetic characteristics of both populations that contribute to the difference in dosage may be clarified in the near future.

A minority(1.4%) of the present patient population had an exceptional reduction of serum TC (>40%) with the low dose of simvastatin, and this is the first time such a phenomenon has been documented. That group of patients had more male subjects and a higher incidence of complications of renal disease, hepatic disease and diabetes mellitus when compared with the group of patients whose TC concentration was reduced by 10–20%. In the past, cancer was suggested as a possible cause of hypocholesterolemia![17] but the reduction reported here may have included other causes. Hyper-responders have an increased risk of death![19] so patients who show a remarkable decrease in TC or LDL-C concentration with low-dose statin therapy should be monitored closely. We will report on these hyper-responders in detail in another paper.

Patients with hypercholesterolemia require long-term treatment to normalize and maintain their cholesterol concentration, but because these patients frequently have concomitant medical conditions, such as hypertension, diabetes mellitus, and cardiac disease, they are usually treated with multiple medications. Hence, in the selection of cholesterol-lowering drug, safety is an important consideration for daily clinical care.

The well-known ADRs of statins are rhabdomyolysis and hepatitis. Serious cases of rhabdomyolysis have been reported in Western countries, especially with concomitant treatment with substrates or inhibitors of cytochrome P450 3A4 enzyme, such as cyclosporin A and itraconazole. Generally, close monitoring of the patient for rhabdomyolysis is recommended strongly when statins are prescribed. Although there were 4 cases of myopathy with CK elevation in this study, the ADR assessment subcommittee judged that there were no cases of rhabdomyolysis (CK ≥10,000 IU/L with muscular symptoms), which may have been because there was early detection of symptoms and abnormal CK values of patients receiving simvastatin and countermeasures were taken by the physicians who were aware of the risk of musculoskeletal ADRs. In the 4S study, there was a case of rhabdomyolysis that was relieved by discontinuation of simvastatin. The incidence of musculoskeletal ADRs increased in proportion with the magnitude of the increased TC lowering effect, which suggests that the pathophysiology of this ADR is related to the biochemical mechanism of the cholesterol-lowering effect of the drug.

Hepatitis occurred only in 0.16% of the patients in the present study, and none of the cases was serious, which may also be a result of the careful patient monitoring by the physicians. Following the safety information on the drug is critical for the prevention of ADRs.

Thrombocytopenia is an uncommon but serious and sometimes fatal ADR that is associated with a variety of

drugs. One patient in this study died from thrombocytopenia. This patient received 10 different drugs, 5 of which were continued until the death occurred, and so the causal relationship between this complication and simvastatin therapy is unclear. Medication should have been discontinued when the thrombocytopenia was detected and withheld until the platelet count normalized. There is a possibility that simvastatin impairs heamatopoiesis. One case of aplastic anemia occurred and the incidence of aplastic anemia is higher in Japanese patients than in Western countries[18] for reasons that are still unclear.

The rate of serious drug-related adverse events was only 57 cases per 1,000,000 patients-year, and the overall frequency of ADRs over the 6 years was 3.3% of subjects.

We have also reported[19,20] that the concentration of serum cholesterol correlated with the incidence of CHD in Japanese hypercholesterolemic patients with or without a history of CHD in the J-LIT study, which strongly suggests that cholesterol-lowering medication prevents CHD in Japanese hypercholesterolemic patients.

In conclusion, cholesterol-lowering therapy using low-dose simvastatin is highly effective in controlling serum lipid concentration and is safe, and well tolerated by Japanese hypercholesterolemic patients. Additionally, a low fat diet may be beneficial to patients, by decreasing the incidence of drug-related adverse events.

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