Direct Comparison of Hypolipidemic Effects of Pitavastatin and Atorvastatin

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ABSTRACT

This study compared the effects of pitavastatin and atorvastatin in a direct switch design to evaluate differential impact of these statins on serum levels of lipids, lipoproteins and apolipoproteins. Patients ($n = 82$) who had received atorvastatin (10 mg/day) were assigned into groups who continued to receive atorvastatin (10 mg/day) ($n = 30$) or switched to receive pitavastatin (2 mg/day) ($n = 52$). After more than 3 months of treatment atorvastatin and pitavastatin similarly controlled serum levels of total cholesterol, LDL-C, triglycerides and HDL-C. Furthermore the treatment of pitavastatin did not influence serum levels of apolipoprotein A-Ⅰ, A-Ⅱ and B. Only the level of HDL cholesterol in patients with diabetes mellitus was significantly increased after the switching from atorvastatin. In conclusion, atorvastatin at 10 mg/day and pitavastatin at 2 mg/day are similar with regard to their efficacy in decreasing total cholesterol, LDL-C, triglycerides and increasing HDL-C. The change of therapy to pitavastatin from atorvastatin is well tolerated.

INTRODUCTION

Hypercholesterolemia, especially elevated low-density lipoprotein cholesterol (LDL-C) is a risk factor for coronary heart disease[1)]. Over the past decade, the inhibition of cholesterol biosynthesis by 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has emerged as one of the most effective means of reducing risk for CHD[2, 3)].

Atorvastatin is a highly efficacious statin, which has been shown to lower LDL-C levels by 41% to 61% in a dose response study in hypercholesterolemic patients[4)]. Several large clinical trials using atorvastatin have demonstrated a significant decrease in CHD morbidity and mortality in hypercholesterolemic patients in both primary and secondary prevention[5, 6)]. Pitavastatin is a recently developed and totally synthetic statin. In the clinical setting, pitavastatin has lowered total cholesterol and LDL-C levels by 28% and 40%, respectively[7)]. Moreover pharmacokinetic studies have suggested that pitavastatin is minimally metabolized by the CYP system, and its lactone form

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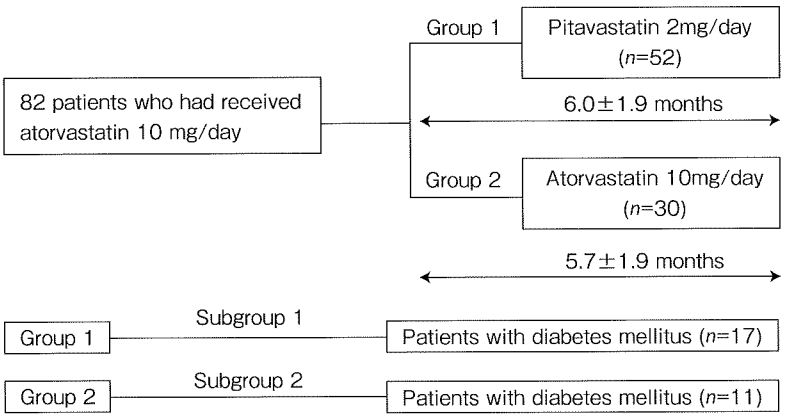

Fig. 1 Schematic representation of the study design

had no inhibitory effect on the CYP3A4-mediated metabolism of coadministrated drugs [8, 9]. It is important that we answer this question because the selection of each statin is necessary to reduce risk factors in patients with various lipid profiles. Therefore, in the present study we examined whether in hypercholesterolemic patients who were receiving atorvastatin, switching to pitavastatin results in any changes in serum levels of lipoproteins and apolipoproteins.

I METHODS

1 Subjects

The study subjects consisted of eighty-two outpatients who were diagnosed with hypercholesterolemia and received 10 mg atorvastatin at Fukui Chuoh Clinic, Takamura Hospital and Kasahara Hospital. Patients with uncontrollable diabetes mellitus, severe liver or renal dysfunction were excluded from this study. The objectives and risks of the study were explained to the patients according to the Declaration of Helsinki, and informed consent was obtained from each patient.

2 Study design

The study was designed as an open-label switch trial and only patients who were enrolled for more than three months of ongoing atorvastatin or the switch to pitavastatin were analyzed. A schematic representation of the study design is given in **Fig. 1**. Two thirds of patients were switched to pitavastatin 2mg (Group 1). The remaining patients continued to receive atorvastatin 10mg (Group 2). The group 1 consisted of fifty-two patients matched for age, gender and body mass index (BMI) with group 2 (**Table 1**). No difference was observed in the prevalence of hypertension and diabetes mellitus between two groups (**Table 1**).

3 Lipid measurements and calculation

Serum levels of total cholesterol, LDL-C and triglyceride (TG) concentration were measured by enzymatic assay. HDL-C was measured by the selective inhibitory method and apo A-I, apo A-II, and apo B by immunoprecipitation. Measurements were performed several times during statin treatments in this study.

4 Statistical analysis

All results are presented as mean ± standard deviation and a percentage. Statistical analysis was

Table 1 Baseline patient characteristics

	Group 1 ($n = 52$)	Group 2 ($n = 30$)
Gender		
Men	15	13
Women	37	17
Age (yrs)	64 ± 11	63 ± 12
Periods (months)	6.0 ± 1.9	5.7 ± 1.9
Risk factors		
Hypertension	23	12
Diabetes mellitus	17	11
Body mass index (kg/m^2)	25.2 ± 3.8	25.2 ± 3.7

Value are expressed as mean ± SD or number of patients.

Table 2 Changes in lipid values

		Group 1 ($n = 52$)	Group 2 ($n = 30$)
At baseline	Total cholesterol (mg/dL)	199.3 ± 34.6	199.6 ± 39.5
	LDL cholesterol (mg/dL)	113.7 ± 31.6	108.7 ± 28.8
	HDL cholesterol (mg/dL)	64.3 ± 17.8 *	55.0 ± 15.7
	Triglycerides (mg/dL)	170.1 ± 89.6	199.2 ± 145.6
At follow-up	Total cholesterol (mg/dL)	204.2 ± 33.0	203.8 ± 36.9
	LDL cholesterol (mg/dL)	113.7 ± 28.4	115.9 ± 30.5
	HDL cholesterol (mg/dL)	64.3 ± 16.9 *	55.4 ± 17.9
	Triglycerides (mg/dL)	151.4 ± 74.2	170.8 ± 87.3
Changes in values	% Total cholesterol	1.1 ± 22.3	2.1 ± 12.6
	% LDL cholesterol	2.1 ± 20.8	4.1 ± 18.7
	% HDL cholesterol	2.3 ± 14.7	−0.6 ± 12.5
	% Triglycerides	−0.7 ± 45.2	−3.3 ± 35.9

Values are expressed as the mean ± SD or number of patients.
* $p < 0.05$ vs. Group 2

performed with the paired t-test (the switching therapy; the group 1). In addition, levels of lipids, apolipoproteins and changes from baseline in lipoproteins and apolipoproteins were assessed using an analysis of variance (ANOVA). Differences in frequency were tested by χ^2 analysis. Analyses of changes in measures used a 0.05 two-side significance level.

Ⅱ RESULTS

1 Clinical Characteristics

Table 1 shows the patient characteristics (age, gender, BMI, periods and risk factors) in both Group 1 ($n = 52$) and Group 2 ($n = 30$). The two groups of patients did not differ significantly with regard to age, percentage of males, BMI, treatment periods and prevalence of hypertension, diabetes mellitus, or serum lipid parameters (with the exception of HDL-C) before the start of observation.

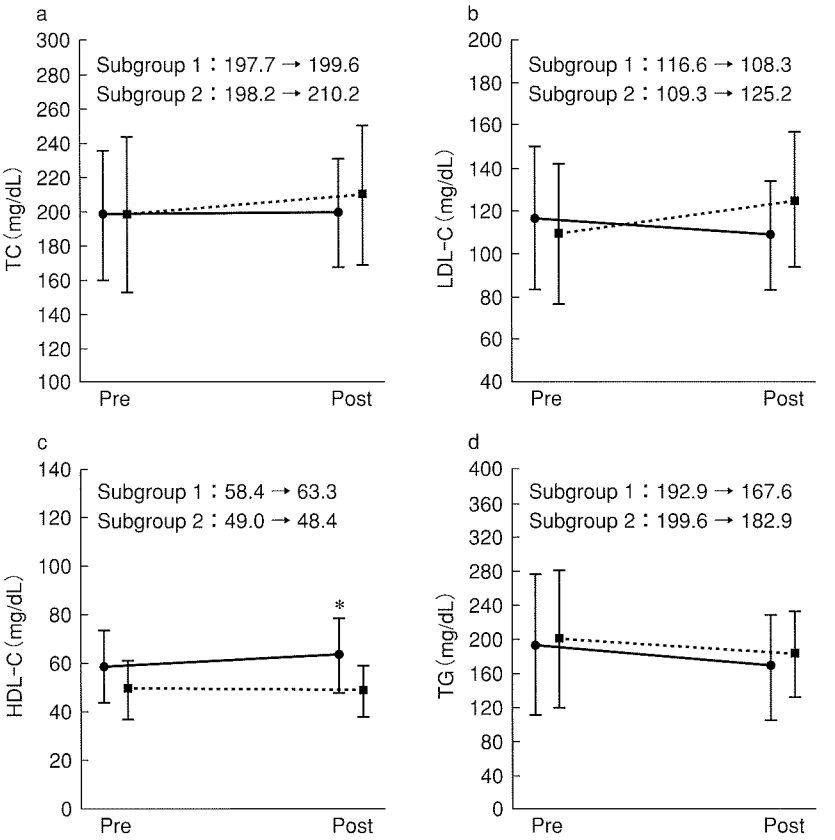

Fig. 2 Serum levels of lipids and lipoproteins in Subgroup 1 ($n = 17$) and Subgroup 2 ($n = 11$) patients

● Subgroup 1, ■ Subgroup 2

a : TC(total cholesterol), b : LDL-C(LDL cholesterol), c : HDL-C(HDL cholesterol), d : TG(triglyceride)

*: $p < 0.05$ vs Pre

2 Lipid Values

Changes in serum lipid, lipoprotein concentrations in both groups are listed in **Table 2**. Total cholesterol, LDL-C, and TG levels at baseline did not differ between the two groups. At follow-up, there were no significant differences in total cholesterol, LDL-C and triglycerides between the two groups. The level of HDL-C at baseline and follow-up was higher in the Group 1 than Group 2 ($p < 0.05$). The levels of total cholesterol, LDL-C, HDL-C and trigrycerides did not change during treatment in both groups. Changes in total cholesterol, LDL-C, HDL-C and trigrycerides levels did not differ between the two groups.

In the patients with diabetes mellitus, there were no significant differences in total cholesterol, LDL-C, HDL-C and triglycerides levels at baseline between the two subgroups (**Fig. 2**). The HDL-C level at follow-up was higher in Subgroup 1 ($n = 17$) than Subgroup 2 ($n = 11$) ($p < 0.05$). Change in HDL-C level was significantly increased during treatment in Subgroup 1 ($p < 0.05$) and also changes in total cholesterol, LDL-C and triglycerides except HDL-C did not differ between the two

Table 3 Changes in apolipoprotein values

		Group 1 ($n = 52$)	Subgroup 1 ($n = 17$)
At baseline	Apolipoprotein A-I (mg/dL)	152.5 ± 25.7	148.4 ± 19.8
	Apolipoprotein A-II (mg/dL)	29.7 ± 3.3	28.7 ± 2.9
	Apolipoprotein B (mg/dL)	95.1 ± 22.4	99.1 ± 20.4
At follow-up	Apolipoprotein A-I (mg/dL)	150.5 ± 24.0	150.8 ± 25.2
	Apolipoprotein A-II (mg/dL)	30.2 ± 4.0	29.5 ± 4.6
	Apolipoprotein B (mg/dL)	95.3 ± 21.9	93.6 ± 19.4
Changes in values	% Apolipoprotein A-I	−0.2 ± 9.7	3.4 ± 7.7
	% Apolipoprotein A-II	2.2 ± 10.0	3.9 ± 9.2
	% Apolipoprotein B	1.9 ± 18.2	−4.1 ± 15.1

Values are expressed as the mean ± SD or number of patients

Table 4 Alterations in liver enzymes and creatine kinase in pitavastatin group

		Group 1 ($n = 52$)	Group 2 ($n = 30$)
At baseline	AST(IU/L)	23.6 ± 7.5	21.5 ± 4.5
	ALT(IU/L)	23.1 ± 14.4	21.3 ± 10.9
	LDH(IU/L)	226.0 ± 45.6***	343.5 ± 84.7
	CK(IU/L)	123.5 ± 103.1	98.0 ± 33.8
At follow-up	AST(IU/L)	23.8 ± 7.3	21.3 ± 5.4
	ALT(IU/L)	23.8 ± 14.4	21.8 ± 11.7
	LDH(IU/L)	222.6 ± 48.2***	348.8 ± 94.3
	CK (IU/L)	123.1 ± 74.4	103.2 ± 50.7
Changes in values	% AST	2.5 ± 19.3	0.6 ± 19.7
	% ALT	5.2 ± 28.1	7.2 ± 37.5
	% LDH	−1.2 ± 10.1	1.4 ± 12.3
	% CK	6.7 ± 47.7	5.6 ± 38.1

Values are expressed as the mean ± SD or number of patients.
*** : $p < 0.0001$ vs. Group 2

subgroups.

Changes in serum apolipoprotein concentrations in Group 1 and Subgroup 1 including patients with diabetes mellitus are listed in **Table 3**. The levels of apolipoprotein A-I, A-II and B did not change during treatment in both groups.

3 Safety

Treatment with 10 mg atorvastatin or 2 mg pitavastatin was well tolerated. None of the serious adverse events were considered associated with treatment. There were no adverse events in the study indicative of musculoskeletal or hepatocellular toxicity. Furthermore, no abnormalities including significant elevations in liver enzymes (aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase) or in creatine kinase were noticed during treatment with either statin (**Table 4**). Changes in hemoglobin A_{1C} in patients with diabetic mellitus did not differ during treatment with

Table 5 Changes in hemoglobin A_{1C} in diabetic patients

		Subgroup 1 ($n = 17$)	Subgroup 1 ($n = 11$)
At baseline	Hemoglobin A_{1C} (%)	8.4 ± 1.4	7.5 ± 1.1
At follow-up	Hemoglobin A_{1C} (%)	8.4 ± 1.1[#]	7.3 ± 0.8
Changes in values	%Hemoglobin A_{1C}	0.7 ± 11.5	−2.4 ± 10.4

Values are expressed as the mean ± SD or number of patients.
[#] : $p < 0.05$ vs. Subgroup 2

either statin (**Table 5**).

Ⅲ DISCUSSION

This is the first study to investigate the efficacy and safety of switching from atorvastatin 10 mg to pitavastatin 2 mg daily therapy. In the present study, pitavastatin treatment showed no significant differences in levels of total cholesterol, LDL-C, triglycerides and apolipoprotein B in Group 1 versus Group 2.

Some clinical trials have suggested pitavastatin could increase HDL-C, while atorvastatin influenced this lipid minimally little [10, 11]. An *in-vitro* study demonstrated that pitavastatin increased apoA-I levels more effectively than atorvastatin [12]. Moreover it has been reported that the effect on apoA-I levels observed with atorvastatin in humans may be a result at least in part of enhanced HDL apoA-I catabolism, which is not entirely offset by a concomitant increase in apoA-I production[13]. The present study found no significant difference in the levels of HDL-C, apolipoprotein A-I or A-II during treatment in Group 1. However the level of HDL-C was significantly increased in patients with diabetes mellitus. There is also a negative correlation between pre-HDL cholesterol (before pitavastatin treatment) and ⊿HDL cholesterol and between pre-apolipoprotein A-I and ⊿HDL cholesterol (data was not shown). This suggests the possibility that pitavastatin can increase the level of HDL cholesterol in patients whose level of HDL cholesterol was low.

Over the past two decades, pre-clinical and clinical studies have suggested that statin therapy, especially with atorvastatin produces significant alterations in various cell populations that comprise atherosclerotic vascular lesions. The Treating to New Targets (TNT) study utilizing both low and high doses of atorvastatin in stable nonacute CHD demonstrated a significant decrease in cardiovascular event rates. On the other hand, some previous studies suggested that high levels of serum HDL-C or Apo A-I could contribute to plaque regression and prevention of CHD[14, 15]. The IDEAL study using high doses of atorvastatin and a standard dose of simvastatin suggested the effect of simvastatin on HDL-C would attenuate the difference produced by the improved effect of atorvastatin on LDL-C [16]. Moreover it has been reported that HDL lipoproteins neutralize the proinflammatory activity of C-reactive protein [17]. In the present study, it is suggested that pitavastatin could increase the level of HDL-C in patients who had received atorvastatin when the level of HDL-C of them was low.

In conclusion, the switch to pitavastatin 2 mg in the patients who had received atorvastatin 10 mg made no significant change in the levels of total cholesterol, LDL-C and triglycerides. However the level of HDL-C in patients with diabetes mellitus of Group 1 was significantly increased. Additionally, switching therapy from atorvastatin to pitavastatin resulted in no safety concerns.

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