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Long-term treatment with pitavastatin (NK-104), a new HMG-CoA reductase inhibitor, of patients with heterozygous familial hypercholesterolemia

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Abstract

The clinical efficacy and safety of pitavastatin (NK-104), a novel HMG-CoA reductase inhibitor, during long-term treatment, were examined in 25 patients (male/female = 11/14, mean age = 53 ± 13 (mean ± SD) years) with heterozygous familial hypercholesterolemia (FH). After a period on placebo of > 4 weeks, 2 mg/day of pitavastatin was administered for 8 weeks, and the dose was increased to 4 mg/day for up to 104 weeks. Total cholesterol (TC) decreased by 31% from the initial value of 340 ± 57 to 237 ± 40 mg/dl ($P < 0.0001$) at week 8. During treatment with the higher dose, TC decreased even further to 212 ± 35 mg/dl at week 12; it decreased by 37% from the initial value ($P < 0.0001$). Similarly, the baseline low-density lipoprotein (LDL)-cholesterol (LDL-C) decreased by 41% at week 8, and by 49% at week 12, from 267 ± 61 mg/dl at baseline. These findings indicate a dose-dependent effect of the drug on TC and LDL-C concentrations. To examine whether the levels of circulating matrix metalloproteinases (MMPs) and their endogenous inhibitors (tissue inhibitors of metalloproteinases: TIMPs) are altered during lipid-lowering therapy, we also measured their plasma levels. The mean levels of MMP-2 and -3 were significantly increased. No significant alteration was found in MMP-9, TIMP-1 and -2 levels. As for the safety of pitavastatin, adverse reactions were observed in one case (4%) of subjective and objective symptoms. The effects of pitavastatin on TC and LDL-C were stable during long treatment of patients with heterozygous FH.

Keywords: NK-104; Pitavastatin; Familial hypercholesterolemia (FH); Long-term treatment; Cytochrome P-450; Matrix metalloproteinase (MMP)

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disease characterized by severe hypercholesterolemia due to increased levels of plasma low-density lipoprotein (LDL) [1] and by premature coronary artery disease (CAD), even in the absence of other coronary risk factors [2]. Epidemiological studies indicate the prevalence of heterozygous FH is about 1 in 500 in the general population. Usually asymptomatic, severe CAD associated with untreated FH results in sudden death in over half of male and 15% of female heterozygotes < 60 years of age [1].

Treatment of FH is aimed at reducing the levels LDL-cholesterol (LDL-C) to retard progression of atherosclerotic lesions and thereby decrease the risk of CAD. However, many patients with FH do not respond

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adequately to single-agent therapy with a hydroxymethyl glutaryl (HMG)-CoA reductase inhibitor.

Pitavastatin, (previously named itavastatin or nisvastatin, Kowa Company Ltd., Tokyo) is a new, totally synthetic HMG-CoA reductase inhibitor. Compared with pravastatin and simvastatin, pitavastatin possesses a 10-fold higher cholesterol-lowering effect. Furthermore, pitavastatin lowers triglycerides (TG) levels at the same doses used for cholesterol reduction, which is not observed with pravastatin or simvastatin [3,4]. In an animal study, pitavastatin suppressed balloon-injury-induced neointimal thickening by inhibiting intimal smooth muscle cell growth and extracellular matrix accumulation [5]. And, this potent agent is hardly metabolized via the cytochrome P-450 mediated pathway in humans [6,7].

In the present study, we evaluated the clinical efficacy and safety of pitavastatin, administered for 76–104 weeks, in patients with heterozygous FH. We have already reported the early results of this study [8].

Matrix metalloproteinases (MMPs) and their endogenous inhibitors tissue inhibitors of metalloproteinases (TIMPs) play a central role in the extracellular matrix metabolism. Recent pathological studies have shown MMPs and TIMPs are involved in the development of atherosclerotic lesions [9–11]. However, the clinical significance of their circulating forms remains uncertain. To examine whether the circulating levels of MMPs and TIMPs changed during lipid-lowering therapy, we also measured their plasma levels.

2. Methods

2.1. Study patients

Initially, the study population consisted of 36 patients with heterozygous FH. All patients fulfilled our diagnostic criteria; i.e. primary hypercholesterolemia (>230 mg/dl) with tendon xanthoma or first-degree relatives of previously diagnosed heterozygous FH patients. Of the initially enrolled 36 patients, 25 who had been under continuous pitavastatin therapy over 76 weeks were reported in this study. Achilles' tendon xanthoma was observed in 21 patients and xanthelasma in four. The body mass index was 24.6 ± 3.2 kg/m^2 (mean $\pm$SD). CAD had already been documented in six patients (24%), and one patient had cerebral vascular disease. Six patients (24%) were hypertensive. Although four patients (16%) had impaired glucose tolerance, only one required insulin therapy. Of the 25 patients who finished this study, eight were given only pitavastatin, and the remaining 17 patients were administered other drugs in combination with pitavastatin: disopyramide ($n=2$), mexiletine ($n=1$), diltiazem ($n=4$), benidipine ($n=2$), amlodipine ($n=2$), nisoldipine ($n=1$), isosorbide dinitrate ($n=5$), transdermal nitroglycerin ($n=1$), aspirin ($n=3$). The dosages of coadministered drugs were maintained during the study period.

2.2. Study protocol

All patients were instructed to follow the National Cholesterol Education Program Step II diet [12]. After >4 weeks on placebo (in three patients who had previously been treated with probucol, confirmation of baseline lipid levels was obtained after 8 weeks on placebo), 2 mg of pitavastatin was administered once, daily, in the evenings, for 8 weeks. Afterward, the dosage was increased to 4 mg for 68–96 weeks. Blood samples for lipid and lipoprotein analysis were collected before the start of treatment (baseline), at weeks 8, 12, 28, 52 and the last week during treatment for 76–104 weeks (mean $\pm$SD $= 96 \pm 9$ weeks). Serum cholesterol and TG levels were determined by enzymatic methods [13], and high-density lipoprotein cholesterol (HDL-C) levels were directly measured by a polyanion-polymer/detergent (PPD) method (Daiichi, Tokyo) as described elsewhere [14]. LDL-C levels were calculated by the Friedewald formula [15]. Serum levels of apolipoprotein AI, AII, B, CII, CIII and E were determined by immunoturbidimetry as described before [16]. Plasma levels of MMP-2, -3, -9, TIMP-1 and -2 were determined by a one-step sandwich enzyme immunoassay (EIA) using commercially available kits with monoclonal antibodies against each substance (Fuji Chemical Industries Ltd., Toyama, Japan) [17]. Written informed consent to participate in the study was obtained from each patient before entry into the study, and the Institutional Review Board of each institution (see Appendix A) had approved the study protocol.

2.3. Statistical analysis

Repeated measurements ANOVA was used for analyses of serial changes in each variable, and then compared using the Student's paired t-test for parametric variables. Because serum TG and Lp (a) levels were significantly skewed, logarithmic transformation was applied before these parametric analyses. For parameters showing a non-Gaussian distribution, the Kruskal–Wallis H-test was used for analyses of serial changes in each variable with post-hoc analysis using the Bonferroni correction for multiple comparisons. All statistical analyses were performed with the Stat View 5.0 system (Abacus Concepts, Berkeley, CA). A P value of <0.05 was considered statistically significant. All values are shown as the mean $\pm$SD.

3. Results

3.1. LDL cholesterol

Mean levels of LDL-C decreased ($P < 0.0001$) by 41% after 8 weeks on pitavastatin at a dose of 2 mg/day, and then decreased even further ($P < 0.0001$; −49% from baseline) after 4 more weeks on pitavastatin at a dose of 4 mg/day. Both at week 52 and at the last week (weeks 76 and 104) LDL-C levels were 44% lower compared with the baseline value (Table 1).

3.2. Total cholesterol (TC)

After 8 weeks on pitavastatin at a dose of 2 mg/day, TC decreased by 31% ($P < 0.0001$) from the baseline value of 340±57 mg/dl. When the dose of pitavastatin was increased to 4 mg/day, further decreases by 37% from the baseline value and by 9% from the TC values at week 8 were observed at week 12 ($P < 0.0001$). At week 52 and at the last week (weeks 76 and 104) of treatment, the TC values were 31 and 33% lower than the baseline value, respectively (Table 1).

3.3. HDL cholesterol

Serum HDL-C levels increased significantly during pitavastatin therapy (repeated measurements ANOVA $P = 0.035$). Values at baseline, week 28, 52 and at the last week (weeks 76 and 104) were 48±8, 52±11, 54±12 and 51±9 mg/dl, respectively (Table 1).

3.4. Triglycerides

The same as in the early report of this study [8], patients were divided into two groups according to their TG levels before treatment (<150 or ≥ 150 mg/dl) and their responses were compared with pitavastatin treatment. In the group with ≥ 150 mg/dl TG, these were significantly reduced at week 52 and at the last week (weeks 76 and 104) (Table 1). Seven patients whose pretreatment TG levels were ≥ 150 mg/dl showed 38% reduction at the last week from the baseline level of 379±204 mg/dl. In all patients, TG values were significantly reduced at weeks 12, 28, 52 and at the last week (Table 1).

3.5. Apolipoproteins

The mean levels of apolipoproteins AI and AII were significantly increased. In contrast, those of apolipoproteins B, C-II, -III and E were significantly decreased along with reductions of LDL-C and TG. Changes in apolipoprotein levels are shown in Table 1. The mean change of apolipoproteins AI, AII, B, CII, CIII and E at the last week (weeks 76 and 104) from the baseline levels were +12, +9, −34, −13, +1 and −27%, respectively. Both apolipoprotein B and E levels decreased promptly and significantly during pitavastatin therapy in a dose-dependent manner. In the group with <150 mg/dl TG before treatment, apolipoprotein E levels at weeks 0 and 52 and at the last week were 6.4±1.5, 4.8±0.8 and 4.9±0.8 mg/dl, respectively. In the group with ≥ 150 mg/dl TG, the apolipoprotein E levels at weeks 0 and 52 and at the last week were 11.8±4.0, 6.3±1.0 and 6.1±1.1 mg/dl, respectively.

3.6. Lipoprotein (a)

The level of Lp (a) tended to increase during treatment. The evaluation at baseline, week 52 and the last week were 26.4±27.7, 28.2±27.3 and 27.4±31.1 mg/dl, respectively.

3.7. Matrix metalloproteinases

As shown in Table 2, the levels of MMP-2 and -3 were increased significantly (Kruskal–Wallis H-test $P < 0.0001$, $P = 0.026$, respectively) during pitavastatin therapy. There were no significant changes in MMP-9, TIMP-1 and -2 levels. The level of TIMP-2 tended to decrease ($P = 0.071$). Although Kruskal–Wallis H-test showed a statistically significant increase in MMP-3, the level of significance was weak when assessed by the Bonferroni correction.

3.8. Adverse events

Pitavastatin was well tolerated. In the 25 patients who had been under continuous pitavastatin therapy for more than 76 weeks, adverse reactions were observed in only one case (4%). The patient experienced hypoesthesia in his fingers.

Compared with the baseline values, statistically significant differences were detected in serum alanine aminotransferase (ALT) at week 12, and of lactate dehydrogenase (LDH) at weeks 28 and 52 and at the last week (Table 3). But the difference in ALT between week 0 and the last week was not significant. In LDH, although the difference between week 0 and the last week was significant, the highest value was not higher than twice the upper limit of the normal range. There were no significant changes in asparate amino transferase or creatinine kinase.

Among the 11 patients, who did not finish treatment, adverse reactions occurred in three patients. One with subjective and objective symptoms (epigastric discomfort), and two with abnormal values in laboratory tests. Of these two patients, one, a 45-year-old man showed a decrease of blood testosterone from 366.5 at baseline to 243.4 ng/dl, at week 100. The other, a 32-year-old man, showed a decrease of blood testosterone from 356.0 at

Table 1
Effects of NK-104 on lipids and apolipoprotein levels in heterozygous FH

	Baseline	Week 8	Week 12	Week 28	Week 52	Week 96	ANOVA
Cholesterol (mg/dl)							
Total	340±57	237±40****	212±35****	220±38****	231±40****	222±25****	$P < 0.0001$
		−31% (−187−−51 mg/dl)	−37% (−233−−49 mg/dl)	−36% (−225−−54 mg/dl)	−31% (−181−−14 mg/dl)	−33% (−230−−13 mg/dl)	
LDL	267±61	158±36****	135±30****	144±39****	153±37****	146±26****	$P < 0.0001$
		−41% (−190−−52 mg/dl)	−49% (−223−−45 mg/dl)	−47% (−221−−60 mg/dl)	−44% (−187−−32 mg/dl)	−44% (−230−−34 mg/dl)	
HDL	48±8	50±10	50±9	52±11*	54±12**	51±9	$P = 0.035$
		+5% (−14−+19 mg/dl)	+4% (−18−+13 mg/dl)	+9% (−10−+16 mg/dl)	+11% (−8−+21 mg/dl)	+6% (−16−+13 mg/dl)	
Triglycerides (mg/dl)							
All patients	179±164	154±139	140±128*	133±103**	122±85***	129±78*	$P = 0.0007$
		±0% (−413−+448 mg/dl)	−12% (−388−+328 mg/dl)	−22% (−438−+208 mg/dl)	−24% (−461−+39 mg/dl)	−9% (−462−+113 mg/dl)	
Baseline level ≥ 150	379±204	274±206	270±172	230±132	205±108*	205±102*	$P = 0.027$
		−11% (−413−+448 mg/dl)	−16% (−388−+328 mg/dl)	−26% (−438−+208 mg/dl)	−40% (−461−−4 mg/dl)	−38% (−462−+3 mg/dl)	
Baseline level < 150	101±22	104±52	89±55	84±28**	86±35**	99±41	$P = 0.032$
		+4% (−83−+168 mg/dl)	−10% (−81−+189 mg/dl)	−20% (−66−+32 mg/dl)	−17% (−56−+39 mg/dl)	+3% (−56−+113 mg/dl)	
Apolipoprotein (mg/dl)							
AI	129±22	142±21**	139±21*	148±23***	147±23***	142±23**	$P = 0.0002$
		+13% (−33−+48 mg/dl)	+10% (−32−+48 mg/dl)	+17% (−21−+49 mg/dl)	+16% (−33−+54 mg/dl)	+12% (−42−+45 mg/dl)	
AII	32±6	34±6*	34±7	35±6*	35±7*	35±6*	$P = 0.080$
		+7% (−11−+9 mg/dl)	+7% (−12−+10 mg/dl)	+10% (−10−+11 mg/dl)	+9% (−11−+10 mg/dl)	+9% (−13−+10 mg/dl)	
B	189±39	127±26****	111±23****	113±24****	119±27****	121±23****	$P < 0.0001$
		−33% (−129−−12 mg/dl)	−40% (−155−−12 mg/dl)	−41% (−147−−18 mg/dl)	−36% (−120−+7 mg/dl)	−34% (−136−+1 mg/dl)	
CII	5.8±3.1	4.6±1.6**	4.4±1.6**	4.4±1.3**	4.6±1.9**	4.6±1.9**	$P < 0.0001$
		−17% (−7.8−+1.4 mg/dl)	−19% (−8.5−+1.6 mg/dl)	−19% (−9.4−+1.0 mg/dl)	−15% (−7.5−+1.2 mg/dl)	−13% (−7.4−+2.2 mg/dl)	
CIII	12.8±6.8	11.6±5.0	10.9±5.4	11.1±5.0	10.6±4.7	11.9±4.5	$P = 0.021$
		−4% (−15.4−+8.2 mg/dl)	−11% (−15.5−+9.4 mg/dl)	−11% (−17.8−+9.0 mg/dl)	−11% (−21.1−+4.8 mg/dl)	+1% (−18.5−+7.0 mg/dl)	
E	7.9±3.4	5.6±1.7***	5.3±1.5****	5.1±1.1***	5.2±1.1***	5.3±1.0***	$P < 0.0001$
		−25% (−10.9−+2.9 mg/dl)	−29% (−10.2−+1.8 mg/dl)	−33% (−12.1−±0 mg/dl)	−29% (−12.5−+0.8 mg/dl)	−27% (−12.2−+1.3 mg/dl)	

All values are expressed as the mean±SD. LDL, low-density lipoprotein; HDL, high-density lipoprotein. The average response is given in the line below the values and expressed as a percentage and the range is given in parentheses.

* $P < 0.05$,

** $P < 0.01$,

*** $P < 0.001$,

**** $P < 0.0001$ vs. week 0.

Table 2
Changes in MMPs and TIMPs

	Normal range	Baseline	Week 28	Week 52	Week 96	K–W test[a]
MMP-2	367–770	238±137	313±147	390±151*	541±243*	$P < 0.0001$
MMP-3	≤130	36±44	33±22	42±66	46±26	$P = 0.026$
MMP-9	12–71	21±7	27±16	23±9	29±17	$P = 0.469$
TIMP-1	108–223	74±37	94±47	88±53	100±59	$P = 0.458$
TIMP-2	26–110	77±69	93±100	64±64	38±47	$P = 0.071$

All values are expressed as the mean±SD (ng/ml). MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase.
[a] K–W test denotes Kruskal–Wallis *H*-test. Because MMPs and TIMPs values showed non-Gaussian distribution, Kruskal–Wallis *H*-test was used for analyses of serial changes in each variable.
* $P < 0.01$ vs. baseline by the Bonferroni correction.

week 28 to 224.2 ng/dl at week 76. Because of inappropriate sample conditions, these two patients were excluded from the final analysis of data.

4. Discussion

FH is associated with a marked increase in cardiovascular risk, and current drug-therapy regimens are often insufficient to achieve the primary or secondary prevention lipid targets necessary to increase life expectancy in these patients [18,19]. The most powerful drugs used to lower plasma cholesterol in FH today are the HMG-CoA reductase inhibitors (Statins) [20]. This class of agents acts primarily in the liver where they inhibit de novo cholesterol synthesis. The regulatory response to these agents is to increase LDL receptor expression, which in turn leads to a lower plasma LDL-C concentration. Despite the efficacy of these agents, patients may still require additional therapy to achieve the desired cholesterol concentration.

Three previous studies on the effect of atorvastatin at the dose of 80 mg/day, on lipoprotein levels in heterozygous FH showed dramatic reductions in LDL-C, in the order of 41–57% [21–23]. In this study, pitavastatin monotherapy for FH patients reduced LDL-C levels by 40–42% and by 40–50% at a dose of 2 and 4 mg/day, respectively, which were similar to the decreases attained with atorvastatin. A significant decrease of TC levels was also obtained, and the levels were maintained at low values during treatment. The results obtained with long-term pitavastatin monotherapy seem to be very promising, because greater reductions in LDL-C can be expected when used in combination with bile-acid binding resin.

In the present study, we observed significant reductions in TG. The mechanisms of reduction of TG have not been clarified, but it is suggested that pitavastatin can reduce the secretion of VLDL and apolipoprotein B from the liver. Arad et al. showed that the HMG-CoA reductase inhibitor lovastatin can reduce the rate of entry of apolipoprotein B-containing lipoproteins into plasma, either as VLDL or as directly secreted LDL [24]; thus, the reduction of TG appears to be a relatively common phenomenon resulting from strong inhibition of HMG-CoA reductase. In this study, both apolipoproteins B and E decreased significantly and in a dose-dependent manner during pitavastatin therapy. Even in the group with pretreatment TG levels of <150 mg/dl, apolipoprotein E levels were significantly lower at the last week compared to baseline values. These findings suggest that endogenous TG rich lipoproteins, including VLDL and intermediate-density lipoprotein (IDL), were reduced by pitavastatin therapy.

The HDL-C level increased significantly during the study period. Apolipoprotein AI, which is a major component of HDL, also increased significantly during long-term treatment with pitavastatin.

Among the three previous studies on the effects of atorvastatin in FH [21–23], only one [21] showed

Table 3
Changes in liver enzymes and creatine kinase during NK-104 therapy

Enzymes	Normal range	Baseline	Week 8	Week 12	Week 28	Week 52	Week 96
AST	10–40	22±8	23±8	23±8	25±8	24±8	23±6
ALT	5–45	21±13	24±13	24±11*	25±12	24±11	21±8
LDH	220–430	288±67	299±47	305±59	324±67*	319±53**	315±42**
CPK	50–230	150±272	118±81	146±113	136±96	144±118	119±85

All values are expressed as the mean±SD (IU/L). AST, asparate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine kinase.
* $P < 0.05$,
** $P < 0.01$ vs. baseline.

significant elevation in HDL cholesterol levels. While another study, provided evidence for a negative dose-response effect of atorvastatin on HDL-C and apo AI compared to simvastatin [25].

It is known that serum VLDL and IDL levels are elevated in heterozygous FH [1,26]. These lipoproteins, which contain apolipoproteins CII and E, have been reported to be pro-atherogenic, the same as LDL [27]. In this study, the serum levels of apolipoproteins CII and E were decreased. Thus, it is indicated that pitavastatin reduces the serum levels of VLDL–IDL as well as that of LDL.

The levels of circulating MMP-2 and -3 changed significantly during pitavastatin therapy. The significant increase of MMP-2 and -3 we observed in our patients has not been reported before. In a previous study (unpublished data), we measured plasma MMP-2 levels during lipid-lowering therapy with pravastatin. After treatment for 19 weeks, the level of MMP-2 was significantly increased (+14.9%). Thus, it is likely that the increase of MMP-2 level is not an effect unique to pitavastatin, but a relatively common phenomenon resulting from HMG-CoA reductase inhibition.

Recently, it has been reported that peripheral blood levels of MMP-2 and -9 in patients with CAD, especially in acute coronary syndrome, were significantly higher compared to control subjects [28]. But, during this long-term study, there was no evidence of any increase in the incidence of acute coronary syndrome. In our previous study, in contrast, circulating MMP-2 and -3 levels were significantly lower in patients with stable coronary atherosclerosis, compared with healthy control subjects [17]. HMG-CoA reductase inhibitors might increase bone mineral density in human beings and thereby decrease the risk of osteoporotic fractures [29]. And MMP is highly expressed in the matrix in fibrous tissue surrounding areas of ossification [30]. Taken together, our current findings might reflect the effect of HMG-CoA reductase inhibitors in the process of bone formation. So far, there has been little information regarding the role of circulating MMPs and TIMPs. Further studies are required to clarify this issue.

Long-term pitavastatin therapy was well tolerated during the present study; adverse reactions were observed in 4% (1/25) of the patients. Previous studies showed that the frequency of adverse reactions ranged from 0 to 17.8% in the treatment of FH with atorvastatin [21–23]. These results suggest that pitavastatin therapy is at least similar and potentially safer than atorvastatin, even during long-term treatment.

Simvastatin, lovastatin, and atorvastatin have been shown to be metabolized predominantly through the cytochrome P-450 CYP3A4 pathway, while fluvastatin is metabolized by the cytochrome P-450 CYP2C system, and pravastatin by sulfation and possibly other mechanisms [31,32]. This indicates that the metabolism of these statins can be expected to change, when other compounds that inhibit these pathways, such as erythromycin [33] or itraconazole [34], are coadministered. Preliminary reports have indicated that pitavastatin shows good absorption and a relatively long half-life. Like atorvastatin, the greater cholesterol reduction attained with pitavastatin appears to be due to a greater or more prolonged inhibition of HMG-CoA reductase. Moreover, it has been shown that pitavastatin is hardly metabolized by cytochrome P-450 [6,7]. In in vitro studies, although CYP2C9 and CYP2C8 are considered as the key enzymes responsible for the metabolism of pitavastatin, no inhibitory effect by pitavastatin on CYP mediated 4-hydroxylation of tolbutamide (CYP2C9) was detected [6,7]. In the matter of drug interaction, this property of pitavastatin appears to be promising. Detailed investigation is required to solve this issue.

We could conclude that long-term pitavastatin therapy is effective and safe for FH patients.

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