Clinical Efficacy of Pitavastatin, a New 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase Inhibitor, in Patients with Hyperlipidemia

Dose-finding study using the double-blind, three-group parallel comparison

Yasushi Saito[a], Nobuhiro Yamada[b], Tamio Teramoto[c], Hiroshige Itakura[d], Yoshiya Hata[e], Noriaki Nakaya[f], Hiroshi Mabuchi[g], Motoo Tushima[h], Jun Sasaki[i], Yuichiro Goto[j], and Nobuya Ogawa[k]

The Second Department of Internal Medicine, School of Medicine, Chiba University[a], Chiba (Japan), Institute of Clinical Medicine, School of Medicine, Tsukuba University[b], Tsukuba (Japan), Department of Internal Medicine, School of Medicine, Teikyo University[c], Tokyo (Japan), The National Health and Nutrition Research Laboratory[d], Tokyo (Japan), School of Medicine, Kyorin University[e], Tokyo (Japan), Fussa National Health Insurance Hospital[f], Fussa (Japan), The Second Department of Internal Medicine, School of Medicine, Kanazawa University[g], Kanazawa (Japan), Department of Arteriosclerotic and Metabolic Medicine, National Cardiovascular Disease Center[h], Osaka (Japan), The Second Department of Internal Medicine, School of Medicine, Fukuoka University[i], Fukuoka (Japan), School of Medicine, Tokai University[j], Isehara (Japan), and School of Medicine, Ehime University[k], Matsuyama (Japan)

Summary

Pitavastatin (CAS 147526-32-7, NK-104), the first totally synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor discovered in Japan, was examined. Pitavastatin significantly decreased the serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) at doses of 1 mg/day or more, and significant dose-dependence of the effect of this drug was observed within the dose range from 1 mg/day to 4 mg/day. It also significantly decreased the serum levels of triglycerides (TG) within this dose range. There was no dose-dependence of the incidence of adverse reactions to pitavastatin.

Key words

- **CAS 147526-32-7**
- **HMG-CoA reductase inhibitor**
- **Hyperlipidemia**
- **NK-104**
- **Pitavastatin, dose-finding study, effects on total cholesterol and LDL cholesterol**

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Zusammenfassung

Klinische Wirksamkeit von Pitavastatin, einem neuen 3-Hydroxy-3-Methylglutaryl-Coenzym A-Reduktase-Inhibitor, bei Patienten mit Hyperlipidämie / Doppelblinde Dosisfindungsstudie mit Drei-Gruppen-Parallelvergleich

Pitavastatin(CAS 147526-32-7, NK-104), der erste, vollständig synthetische 3-Hydroxy-3-Methylglutaryl-Coenzym A (HMG-CoA)-Reduktase-Inhibitor, der in Japan entdeckt wurde, wurde untersucht. Pitavastatin senkte signifikant die Serumkonzentration von Gesamt- und LDL-Cholesterin (LDL: low density lipoprotein) bei einer Dosierung von 1 mg/Tag oder mehr. Signifikante, dosisabhängige Arzneimitteleffekte wurden innerhalb eines Dosisbereichs von 1–4 mg/Tag beobachtet. Außerdem wuden die Triglyzerid-(TG) Serum konzentrationen innerhalb dieses Dosisbereichs signifikant gesenkt. Eine Dosisabhängigkeit in bezug auf die Häufigkeit Pitavastatin-induzierter Nebenwirkungen wurde nicht beobachtet.

1. Introduction

It is widely known that hyperlipidemia, especially hypercholesterolemia, is a critical risk factor for the development/worsening of atherosclerosis. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) play a central role in the treatment of patients with hypercholesterolemia. The results of large-scale clinical trials of statins have confirmed that the onset of cardiovascular disease and cerebral infarction as well as death from these diseases can be inhibited by decreasing the serum level of cholesterol [1–5].

As mentioned in the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP II) Guidelines [6], the Guidelines of the European Atherosclerosis Association [7] and the Japanese Guidelines for Treatment of Hyperlipidemia [8], it is necessary to use a drug with a stronger cholesterol-lowering action for the primary prevention of cardiovascular disease and cerebral infarction in patients with major risk factors such as glucose intolerance and for secondary prevention in patients with cardiovascular events or a history of such events. If a single drug were available for this purpose, it would be of great therapeutic benefit.

Pitavastatin ((+)-monocalcium bis {(3R,5S,6S)-7-[2-cyclopropyl- 4- (4- fluorophenyl)- 3- quinolyl]- 3,5- dihydroxy-6-heptenoate}, CAS 147526-32-7, NK-104[1)]) is the first totally synthetic HMG-CoA reductase inhibitor discovered in Japan (Nissan Chemical Industries, Ltd. and Kowa Co. Ltd., Tokyo, Japan). Pitavastatin is a strong HMG-CoA reductase inhibitor and causes a marked decrease of serum cholesterol and triglycerides through upregulation of hepatocellular LDL (low density lipoprotein) receptor expression and inhibition of hepatocellular VLDL (very low density lipoprotein) release [9-13]. In addition, pitavastatin has been shown to inhibit the proliferation of endothelial smooth muscle cells and to prevent vascular endothelial thickening at sites of atherosclerosis [14]. Pitavastatin is, therefore, thought to be a promising agent for the inhibition of atherosclerotic diseases.

In phase I single-dose and multiple-dose clinical studies, pitavastatin was well tolerated, showed good absorption and was little metabolized. In a phase I step IV trial in adult male volunteers with serum total cholesterol levels of ≥ 200 mg/dl, the cholesterol level was decreased by 20–30 % after treatment with pitavastatin, and the effect of the drug appeared to be dose-dependent. It was also confirmed that pitavastatin showed no significant toxicity. In a subsequent early phase II clinical trial in patients with hyperlipidemia, pitavastatin was administered at a dose of 4 mg/day once daily for 8 weeks; it decreased the low density lipoprotein cholesterol (LDL-C) level by about 47 % and was well tolerated.

Based on the results of these clinical trials, we recently conducted a multicenter, double-blind, dose-finding trial of pitavastatin, in which the drug was administered for 12 weeks at doses of 1, 2 and 4 mg/day once daily to assess the dose-response relationship and estimate the recommended clinical dose for treatment of hyperlipidemia.

2. Patients and methods

This study protocol was approved by the Institutional Review Board (IRB) of each participating institution. This study was performed in accordance with applicable Good Clinical Practice(GCP) and International Conference on Harmonization (ICH) guidelines and under the principles of the World Medical Assembly Declaration of Helsinki.

2.1. Patients

Prior to the start of the study, the patients were given a full explanation of the study, and voluntary written informed consent to participate in the study was obtained after it was confirmed that the patients had fully understood the details of the study.

273 patients with hyperlipidemia with serum total cholesterol levels ≥ 220 mg/dl, aged 25–75 years, were given pitavas-

[1)] Manufacturer: Nissan Chemical Industries, Ltd., Tokyo (Japan).

tatin. The study consisted of a 4-week or longer run-in period, a 12-week treatment period using 3 dose levels (1, 2 or 4 mg/day once daily after dinner) and a 4-week post-treatment follow-up period.

During the treatment period, the patients were assigned at random to either of the three dose groups and the results were assessed by the double-blind parallel comparison method. During the run-in period and post-treatment follow-up period, placebo tablets (2 tablets after dinner) were administered when it was necessary.

There were 90, 90 and 86 evaluable patients in the 1, 2 and 4 mg groups, respectively. Patients were allowed to use concomitantly those drugs that were thought to have no influence on serum lipids. They maintained their usual diet and activities throughout the study period.

2.2. Drugs

Testing drugs were prepared by Kowa Company, Tokyo (Japan). Pitavastatin calcium tablets were prepared for the study: 1 mg tablets (Lot No. AE015T), 2 mg tablets (Lot No. AE025T) and placebo tablets (Lot No. AE005T), all tablets being identical in appearance. Administration groups were allocated randomly to the 1 mg group (1 mg tablet and placebo tablet), 2 mg group (2 mg tablet and placebo tablet) or 4 mg group (two 2 mg tablets). In each group, drugs were administered to the patients in the order of the assigned number.

2.3. Parameters assessed

Fasting blood samples were collected during the run-in (-4 weeks), treatment (0, 4, 8, 12 weeks) and follow-up (+4 weeks) periods. Serum lipids, biochemistry tests, serum antibody tests and endocrine tests were performed by one laboratory.

Total cholesterol (TC) and triglycerides (TG) were measured by enzymatic methods [15,16]. High-density lipoprotein cholesterol (HDL-C) was measured directly using a precipitation method [17]. LDL-C was calculated using Friedewald's formula [18].

To assess pharmacokinetics, blood was collected at the end of the 12 weeks of treatment, and the plasma concentrations of unchanged pitavastatin and its major metabolite (a lactone) were determined by another laboratory.

Evaluation of safety was based on the incidence of adverse events/reactions, the incidence of laboratory abnormalities, changes in blood pressure, pulse rate and weight.

2.4. Statistical procedures

Results are expressed as the means ± SD. Regression analysis was performed for the primary endpoint of efficacy (the percent change of TC at the last assessment) and Tukey's multiple comparison test was done among groups. To estimate the optimum dose, the dose-response pattern was explored using three dose-response relationship patterns [(1, 0, -1), (2, -1, -1), and (1, 1, -2)] and analysis of variance. If there were imbalances that were considered to possibly have an impact on the evaluation of some factors, adjusted analysis was performed. For other serum lipids, regression analysis was also performed.

For the assessment of safety, the dose-dependence of the incidence of adverse reactions was examined by the Cochrane-Armitage (CA) test [19].

Differences were considered to be statistically significant when a one-sided probability of less than 0.05 was found for the dose-response relationship and when a two-sided probability of less than 0.05 was found for other parameters.

3. Results

3.1. Clinical profile

There was no imbalance between the 3 dose groups with regard to age, sex ratio, WHO classification for hyperlipidemia, weight or height, although imbalances were noted with regard to the familial hypercholesterolemia (FH) and baseline serum lipid levels (TC, TG, HDL-C and LDL-C).

3.2. Serum lipid levels

3.2.1. Total cholesterol

The percent change in TC levels on completion of treatment was –23.0 % in the 1 mg group, –29.1 % in the 2 mg group and –32.5 % in the 4 mg group (Table 1, Fig. 1), showing a dose-dependent decrease. In simple

Table 1: Mean percent change and mean change from baseline values of lipid variables at the end of the treatment period.

	1 mg	2 mg	4 mg	Tukey	ANOVA
Total Cholesterol				1 mg:2 mg p<0.001	(LINEAR) p<0.001
Baseline (mg/dl),(n)	288.2±53.5(90)	281.4±40.9(90)	298.6±67.4(86)	1 mg:4 mg p<0.001	(1-23) p<0.001
Mean % change, (n)	–23.0±9.1(84)	–29.1±8.5(82)	–32.5±9.5(85)	2 mg:4 mg p<0.036	(12-3) p<0.001
LDL Cholesterol				1 mg:2 mg p<0.001	(LINEAR) p<0.001
Baseline(mg/dl),(n)	204.8±54.9(88)	198.7±42.3(81)	217.3±70.3(81)	1 mg:4 mg p<0.001	(1-23) p<0.001
Mean % change, (n)	–33.6±11.9(81)	–41.8±10.2(73)	–47.2±12.5(77)	2 mg:4 mg p<0.014	(12-3) p<0.001
Triglycerides				1 mg:2 mg p<0.574	(LINEAR) p<0.229
Baseline (mg/dl),(n)	147.3±86.7(89)	193.6±172.8(89)	167.5±106.6(85)	1 mg:4 mg p<0.451	(1-23) p<0.202
Mean % change, (n)	–7.7±40.0(83)	–13.6±33.0(80)	–14.7±39.1(83)	2 mg:4 mg p<0.981	(12-3) p<0.422
[≧ 150 mg/dl][a)]				1 mg:2 mg p<0.792	(LINEAR) p<0.306
Baseline (mg/dl),(n)	227.3±87.6(35)	306.6±211.9(39)	275.1±93.9(33)	1 mg:4 mg p<0.868	(1-23) p<0.469
Mean % change, (n)	–26.8±28.7(33)	–22.3±27.4(35)	–30.4±29.2(33)	2 mg:4 mg p<0.476	(12-3) p<0.169
HDL Cholesterol				1 mg:2 mg p<0.825	(LINEAR) p<0.239
Baseline (mg/dl),(n)	55.0±16.6(90)	49.6±15.5(90)	51.3±17.1(86)	1 mg:4 mg p<0.757	(1-23) p<0.474
M.change (mg/dl), (n)	6.8±9.5(84)	5.9±9.5(82)	7.9±10.1(85)	2 mg:4 mg p<0.396	(12-3) p<0.123

[a)] Patients with a baseline TG level of ≥ 150 mg/dl. Tukey: multiple comparison, ANOVA: Study of Contrast (One-Sided)

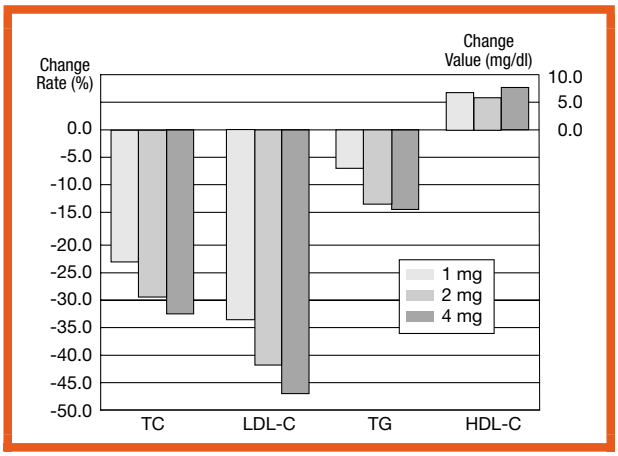

Fig. 1: Mean percent change and mean change from baseline values of lipid valuables at the end of the treatment period. TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride, HDL-C: High-density lipoprotein cholesterol.

regression analysis using the dose-response pattern of a linear decrease, a significant dose-response relationship was observed ($p < 0.001$). Tukey's multiple comparison test showed significant differences among all combinations of the groups. In analysis of variance using three-response patterns, there were significant differences among these patterns ($p < 0.001$).

When analysis of covariance was performed using the baseline serum lipid levels that showed imbalance among the 3 groups as the covariates, the dose-response relationship for the percent change in TC levels was found not to be influenced by the difference in baseline serum lipid levels.

3.2.2. LDL cholesterol

The percent change in LDL-C levels was -33.6 % in the 1 mg group, –41.8 % in the 2 mg group and –47.2 % in the 4 mg group on completion of treatment and a significant dose-dependence ($p < 0.001$) was found (Table 1, Fig 1). Similar trends to those for TC were shown by multiple comparison and paired comparison tests.

3.2.3. Triglycerides

The percent change in TG levels on completion of treatment was –7.7 % in the 1 mg group, –13.6 % in the 2 mg group and –14.7 % in the 4 mg group. Although there were significant percent reductions of TG in the 2 mg and 4 mg groups, no dose-response relationship was found. Among patients with a baseline TG level of ≥ 150 mg/dl, the percent change in TG on completion of treatment was –26.8 % in the 1 mg group, –22.3 % in the 2 mg group and –30.4 % in the 4 mg group (Table 1, Fig 1). Although there were significant percent reductions of TG in all groups, no significant dose-dependence was observed (Table 1).

3.2.4. HDL cholesterol

The mean absolute change of the HDL-C levels from the baseline value was 6.8 mg/dl, 5.9 mg/dl and 7.9 mg/dl in the 1, 2 and 4 mg groups, respectively, on completion of treatment (Table 1, Fig 1). Although HDL-C increased significantly in all groups, no dose-dependence of the response was observed.

3.3. Safety

Pitavastatin was well tolerated in this study. No serious adverse clinical events or changes in laboratory values were attributable to pitavastatin.

3.3.1. Symptoms and clinical signs

Five subjects out of 88 (5.6 %), 4 out of 86 (4.7 %) and 5 out of 86 (5.8 %) in the 1 mg, 2 mg and 4 mg treated groups complained of clinical events, such as rash, constipation and abdominal pain. There was no relationship between the dose of pitavastatin and the type of symptom/sign reported.

3.3.2. Laboratory abnormalities

The elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatine phosphokinase (CK), which were common laboratory abnormalities in statins, were 2.3 %, 3.8 % and 5.4 %, respectively. There were no significant differences among the three dose groups. No patient had elevations in ALT or AST equivalent to > 3 times the upper limit of normal or CK equivalent to > 10 times the upper limit of normal.

3.4. Pharmacokinetics

On week 12, the plasma concentrations of unchanged pitavastatin and the lactone metabolite showed an increase with the dose although wide variations were noted according to the interval from the time of the dosing on the previous day.

4. Discussion

Pitavastatin, a newly developed HMG-CoA reductase inhibitor, exerted a potent lipid lowering effect in patients with hyperlipidemia in the present dose-response, double-blind study. Pitavastatin (1 mg, 2 mg, 4 mg) consistently reduced TC and LDL-C levels in a dose-dependent manner and significantly reduced the levels of TG in patients with high triglyceridemia. As for HDL-C, pitavastatin moderately increased it by 10 % at each dose level.

These lipid lowering effects of pitavastatin (1 mg, 2 mg, 4 mg) were considered to be comparable to those of atorvastatin (5 mg, 10 mg, 20 mg). The TC and LDL-C reduction rates of pitavastatin were in the range from 23 % to 33 % and from 34 % to 47 %, respectively, while those of atorvastatin were in a range from 25 % to 34 % and from 32 % to 49 %, respectively [20].

It is well known that LDL-C reduction is associated with a stabilization of the lipid plaque and prevention of coronary vascular events. The powerful effect of pitavastatin on LDL-C levels was considered to contribute to the treatment of patients with primary hypercholesterolemia.

Furthermore, its effects on TG and HDL-C are also considered to contribute to the suppression of coronary vascular events.

Pitavastatin reduced TG from 22 % to 30 % in patients with high levels of TG. Although its effect on HDL-C was mild, the 10 % increase from baseline levels is of clinical significance.

The safety of pitavastatin is comparable with that reported for other statins. ALT, AST and CK were found to increase moderately and no patients had clinically significant elevations in ALT or AST equivalent to > 3 times the upper limit of normal or CK equivalent to > 10 times the upper limit of normal.

In conclusion, pitavastatin was shown in this study to be well-tolerated and effective in producing substantial TC and LDL-C reductions in patients with primary hypercholesterolemia in a dose-dependent manner. Pitavastatin was also shown to significantly reduce the serum levels of TG and to increase those of HDL-C.

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Correspondence:
Prof. Yasushi Saito, MD,
Second Department of Internal Medicine,
Chiba University,
1-8-1 Inohana, Chuo-ku, Chiba-shi,
Chiba, 260-0856 (Japan)
E-mail: yasushi@intmed02.m.chiba-u.ac.jp