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Multicenter collaborative randomized parallel group comparative study of pitavastatin and atorvastatin in Japanese hypercholesterolemic patients Collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study)

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Abstract

Aims: To compare the efficacy and safety of pitavastatin and atorvastatin in Japanese patients with hypercholesterolemia.
Methods and results: Japanese patients with total cholesterol (TC) ≥ 220 mg/dL were randomized to receive pitavastatin 2 mg ($n = 126$) or atorvastatin 10 mg ($n = 125$) for 12 weeks. The primary endpoint was percent change from baseline in non-HDL-C level after 12 weeks of treatment. Reduction of non-HDL-C by pitavastatin treatment (39.0%, $P = 0.456$ vs. atorvastatin) was non-inferior to that by atorvastatin (40.3%). Both pitavastatin and atorvastatin also significantly reduced LDL-C by 42.6% and 44.1%, TC by 29.7% and 31.1%, and TG by 17.3% and 10.7%, respectively, at 12 weeks without intergroup differences. HDL-C showed a significant increase at 12 weeks with pitavastatin treatment (3.2%, $P = 0.033$ vs. baseline) but not with atorvastatin treatment (1.7%, $P = 0.221$ vs. baseline). Waist circumference, body weight and BMI were significantly correlated with percent reduction of non-HDL-C in the atorvastatin group, whereas pitavastatin showed consistent reduction of non-HDL-C regardless of the body size. In patients with metabolic syndrome, LDL-C was reduced significantly more in patients receiving pitavastatin when compared with those receiving atorvastatin. AST, ALT and γGTP increased significantly in patients receiving atorvastatin but not in those receiving pitavastatin. Both treatments were well tolerated.
Conclusion: Pitavastatin 2 mg and atorvastatin 10 mg are equally effective in improving the lipid profile and were well tolerated in Japanese patients with hypercholesterolemia.

Keywords: Statins; Non-HDL-cholesterol; Obesity; Metabolic syndrome; Hepatic enzymes

1. Introduction

Clinical trials have shown that individuals with elevated low-density lipoprotein cholesterol (LDL-C) have an increased risk of coronary heart disease (CHD), and that LDL-C reduction with statin therapy reduces CHD morbidity

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and mortality rates in patients with or without established CHD [1,2]. At present, different types of statins are clinically available. The choice of statin is usually based on the individual pharmacological properties, such as efficacy in LDL-C reduction and metabolic dependence on hepatic enzymes.

In addition to LDL, some species of triglyceride-rich lipoproteins are also known to be atherogenic; notable among those are cholesterol-enriched remnant lipoproteins. Moreover, very low-density lipoprotein (VLDL) cholesterol serves as a marker for atherogenic VLDL remnants. Non-high-density lipoprotein (HDL) cholesterol, representing the sum of VLDL-C and LDL-C, therefore constitutes "atherogenic cholesterol" and is proposed as a secondary target of lipid-lowering therapy for CHD prevention [3,4].

Metabolic syndrome and type 2 diabetes, important risk factors for development of cardiovascular disease, often are accompanied by an atherogenic lipid profile represented by elevated triglyceride and low HDL-C, resulting in high non-HDL-C levels. Thus, a preferable characteristic for a statin in the treatment of metabolic syndrome and type 2 diabetes would be to reduce non-HDL-C, elevate HDL-C and effectively lower LDL-C. Atorvastatin, a potent LDL-C lowering agent currently marketed, reduces non-HDL-C by 36% (CARDS: 10 mg daily), and has been shown to prevent cardiovascular events in various populations at high risk of arteriosclerotic disease [5,6].

Pitavastatin is a newly developed synthetic statin clinically available in Japan and Korea. Pitavastatin 2 mg daily, a mid-strength dose, lowers LDL-C by 42% [7]. It was also reported that pitavastatin reduces triglyceride (TG) and remnant lipoproteins cholesterol by 29% and 31%, respectively, and increases HDL-C by 10% in Japanese diabetic patients [8]. A double-blind comparative study of pitavastatin vs. pravastatin revealed that pitavastatin 2 mg daily was twice as effective at lowering TC and LDL-C as pravastatin 10 mg daily [9]. Pitavastatin also exhibits unique pharmacokinetic properties; it is lipophilic, but unlike atorvastatin which is metabolized by CYP3A4, its metabolism is not dependent on cytochrome P450 [10].

The aim of this study is to prove that reduction of non-HDL-C by pitavastatin treatment is non-inferior to atorvastatin treatment in a multicenter collaborative randomized parallel group comparative study. In addition, the effects on other lipid parameters, the relationship between lipid-lowering efficacy and body mass index, and safety were evaluated.

2. Methods

2.1. Study design

Collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA) study was a randomized, multicentered, open-label study comparing the efficacy and safety of pitavastatin with that of atorvastatin in Japanese patients with hypercholesterolemia. Patients were recruited from 39 primary care and specialist centers in Chiba, Tochigi, Kanagawa and Shizuoka prefectures, Japan. Following a 4-week dietary lead-in period, eligible patients were randomized into 2 groups in a 1:1 ratio to receive either 2 mg pitavastatin or 10 mg atorvastatin once a day for 12 weeks (see Supplementary Fig. 1). Patient registration and randomization were done using a centralized system of Internet Data and Information Center for Medical Research (http://indice.umin.ac.jp/) as part of the University Hospital Medical Information Network. The randomization was stratified by age, diabetes mellitus, and familial hypercholesterolemia. Use of statins and fibrates was discontinued during the lead-in period to eliminate any effects of premedication. During the study period, administration of fibrates, other statins, probucol and cyclosporine (because of drug–drug interaction) [11] was prohibited. No changes were made in types or doses of medications used to treat hypertension or diabetes, or permitted lipid-lowering drugs (*i.e.* eicosapentaenoic acid). No changes were made in lifestyle guidance, including exercise and diet, throughout the lead-in and dosing periods.

2.2. Patients

Eligible patients were men and women aged 20 or older with hypercholesterolemia (TC $\geq$ 220 mg/dL) and TG < 400 mg/dL, including familial hypercholesterolemia during the lead-in period. Major exclusion criteria, besides the medication prohibitions noted above, included the following: patients with a past history of hypersensitivity to statins; patients with hepatic dysfunction [aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq$ 100 IU/L], suspected hepatic metabolism disorders or biliary obstruction (acute hepatitis, acute exacerbation of chronic hepatitis, liver cirrhosis, liver cancer and jaundice), or renal dysfunction (serum creatinine $\geq$ 1.5 mg/dL); pregnant women, women who may be pregnant, and breast-feeding women; patients with poorly controlled diabetes (HbA1c > 8.0%).

The study was conducted in accordance with the principles of the Helsinki Declaration developed by the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October 2000 and the "Ethical guidelines for clinical studies" issued by the Ministry of Health, Labor and Welfare of Japan in 2003, with local Ethics Committee approval being obtained at each center. All patients were fully informed and written consent was obtained. An independent monitoring committee was organized to discuss study continuation and protocol modification.

2.3. Assessment

The following information was obtained during the dietary lead-in period before randomization: gender; age; height; body weight; waist circumference; menopause (women only); familial hypercholesterolemia; concomitant diseases;