Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

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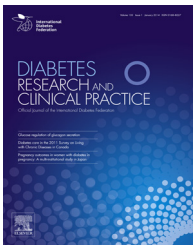

Switching from atorvastatin to rosuvastatin lowers small, dense low-density lipoprotein cholesterol levels in Japanese hypercholesterolemic patients with type 2 diabetes mellitus

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ARTICLE INFO

Article history:
Received 4 July 2015
Received in revised form
9 October 2015
Accepted 9 October 2015
Available online 9 November 2015

Keywords:
LDL cholesterol
Rosuvastatin
Type 2 diabetes mellitus

ABSTRACT

Aims: This open-label, randomized, parallel-group comparative study compared the efficacy of rosuvastatin (5 mg/day) and atorvastatin (10 mg/day) for reduction of small dense low-density lipoprotein cholesterol (sd LDL-C) levels in Japanese patients with type 2 diabetes mellitus (T2DM).

Methods: Patients with T2DM and hypercholesterolemia with detectable sd LDL-C after receiving 10 mg/day atorvastatin for ≥24 weeks were randomly assigned to receive rosuvastatin (5 mg/day; switched treatment) or atorvastatin (10 mg/day; continued treatment) for 12 weeks. The primary endpoints were changes in sd LDL-C levels and sd LDL-C/total LDL-C ratio evaluated using the LipoPhor AS® system.

Results: There were no significant percent changes from baseline for LDL-C levels between the switched (n = 55) and the continued treatment group (n = 56). However, the former group exhibited a statistically significant reduction from baseline of sd LDL-C levels, sd LDL-C/total LDL-C ratio compared with the latter group (−3.8 mg/dL vs. −1.4 mg/dL, p = 0.014; −2.3% vs. −0.6%, p = 0.004, respectively). Multiple regression analysis among all subjects revealed that independent factors contributing to the reduction in sd LDL-C levels were a change in LDL-C (p = 0.003) and triglyceride (TG) levels (p = 0.006), treatment group (the switched group = 1, the continued group = 0; standard coefficient = −1.2, p = 0.034) and baseline glycated hemoglobin A1c (HbA1c) (p = 0.045), respectively.

Conclusion: Switching from 10 mg atorvastatin to 5 mg rosuvastatin may be a useful therapeutic option to reduce sd LDL-C levels in Japanese hypercholesterolemic patients with T2DM.

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1. Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) is an independent risk factor for coronary heart disease (CHD); however, large CHD prevention trials have demonstrated that reducing LDL-C with intensive HMG-CoA reductase inhibitor (statins) treatment regimens does not prevent the majority of CHD events [1]. Indeed, increased LDL-C concentrations do not completely predict plaque formation.

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http://dx.doi.org/10.1016/j.diabres.2015.10.013
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Compared to large buoyant LDL (lb LDL), small dense LDL (sd LDL) are thought to be more atherogenic as a result of their better penetration of the arterial wall, lower binding affinity for the LDL receptor, longer plasma half-life, and weaker resistance to oxidative stress [2,3]. Several studies have reported a 2- to 3-fold increase in the risk of CHD in patients with sd LDL [4–6].

In particular, it has been reported that sd LDL is predominant in patients with type 2 diabetes mellitus (T2DM) [7,8], which is a well-known independent risk factor for CHD. Since it has been reported that increased sd LDL-C levels without high LDL-C levels are involved in the development of arteriosclerosis due to lipid abnormalities in patients with T2DM, management of these lipoproteins in this patient group will be of increasing importance in the future.

Both rosuvastatin and atorvastatin are potent statins that exert a powerful lipid-lowering effect in high-risk patients, including those with T2DM who require active control of their lipid levels. Although atorvastatin is widely used across the world, rosuvastatin has come into widespread clinical use in Western countries because it has been reported to exhibit a stronger LDL-C lowering effect and a higher rate of achievement of therapeutic goals than atorvastatin [9,10].

Also, in Japan, several reports have demonstrated that 5 mg rosuvastatin once daily resulted in more effective lowering of LDL-C levels and a higher rate of achieving therapeutic goals than 10 mg atorvastatin once daily; both doses are the standard drug dose used in Japan [11–13]. A previous study reported that the maximal dose of rosuvastatin (40 mg) is significantly more effective than the maximal dose of atorvastatin (80 mg) in lowering sd LDL-C [13]. In addition, a recent meta-analysis of randomized trials demonstrated that rosuvastatin is more effective at reducing sd LDL levels than atorvastatin [14].

However, few reports have compared the two most standard doses of these statins with regard to their effects on lowering sd LDL-C and the LDL subfraction distribution in the Japanese population with T2DM [11]. Therefore, in this study, we prospectively compared changes in sd LDL-C levels and subfraction distribution, evaluated using the LipoPhor AS® system, resulting from switching treatment from 10 mg atorvastatin to 5 mg rosuvastatin in Japanese patients with T2DM.

2. Methods

2.1. Ethics statement

This study was conducted in accordance with the Good Clinical Practice, International Conference on Harmonization guidelines, and applicable laws and regulations. The study protocol was approved by the ethics committee of the Fukuiken Saiseikai Hospital. After receiving a full explanation of the study, all patients provided written informed consent before enrollment. This study is registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; Japan), number UMIN000009169.

2.2. Study population and outcome measures

First, a total of 230 outpatient subjects with T2DM who were currently receiving 10 mg atorvastatin once daily for ≥24 weeks for treatment of hyper-LDL cholesterolemia (≥120 mg/dL) were screened for study eligibility. A fasting blood sample was taken from all patients to detect sd LDL-C using the LipoPhor AS® system. Next, 129 subjects with detectable sd LDL-C were enrolled in the randomization protocol. At the time of enrollment, the baseline characteristics and clinical data of the patients were collected. Thereafter, a total of 18 subjects were excluded either because they refused to participate in the study or they met one of the following exclusion criteria: thyroid or gastrointestinal diseases; fasting triglyceride levels ≥4.5 mmol/L (400 mg/dL); chronic disease requiring continuous use of steroids, immunosuppressants, or loop diuretics; history of cerebrovascular or cardiac disorder within 12 weeks; uncontrolled severe hypertension (systolic blood pressure ≥170 mm Hg and/or diastolic blood pressure ≥95 mm Hg); serum creatinine exceeding the upper limit of normal; macroalbuminuria (albumin/creatinine ratio ≥300 mg/g serum creatinine); or elevated aspartate aminotransferase and/or alanine aminotransferase (3 times the upper limit of normal). Additionally, subjects with malignant tumors, unstable psychiatric disorders, severe trauma, and/or infection were excluded, as were those who were considered unlikely to comply with study requirements.

Finally, 111 eligible patients were randomly assigned to receive either rosuvastatin at 5 mg/day (switched treatment; $n = 55$) or atorvastatin at 10 mg/day (continued treatment; $n = 56$) for 12 weeks. Use of other lipid-lowering agents (other statins, fibrate, anion exchange resins, cholesterol transporter inhibitors, etc.) was prohibited during the study period. At the time of randomization, dietary guidance was provided for all 111 eligible patients by a national registered dietitian at the hospital. The dietitian checked meals and gave the participants diet counseling relevant to diabetes and hypercholesterolemia, such as calorie and cholesterol restriction (~300 mg/day).

Randomization was performed using the subjects' identification number on their medical chart; that is, patients with even or odd second to last digits of their identification number were assigned to the switched or continued treatment group, respectively.

The primary endpoints were changes in sd LDL-C levels and sd LDL-C/total LDL-C ratios from baseline between the two treatment groups. The secondary endpoints were changes in mid-band LDL-C levels, mid-band LDL-C/total LDL-C ratio, sd LDL-C/lb LDL-C ratio, and the percent change of routine lipid parameters (LDL-C, total cholesterol, high-density lipoprotein cholesterol [HDL-C], triglycerides [TG]) from baseline between the two treatment groups. Levels of lb LDL-C were calculated by subtracting sd LDL-C and mid-band LDL-C levels from total LDL-C. Levels of lb LDL-C estimated by this method were reported to be well correlated with the values determined by ultracentrifugation ($r = 0.858$, $p < 0.0001$) [15]. The sd LDL-C/lb LDL-C ratio was calculated as a surrogate marker for LDL particle size [16]. To assess safety, the incidence and details of adverse events and laboratory abnormalities were investigated.

Compliance with treatment was assessed at 4, 8, and 12 weeks by interview. Any change in the dosage regimen of concomitant medications was prohibited during the study period. Laboratory tests (including biochemistry tests, hematology tests, urinalysis, serum lipids, and other parameters)

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