Assessment of the Efficacy and Tolerability of 2 Formulations of Atorvastatin in Korean Adults With Hypercholesterolemia: A Multicenter, Prospective, Open-Label, Randomized Trial

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ABSTRACT

Background: A manufacturer of atorvastatin is seeking marketing approval in Korea of a generic product for adult patients with primary hypercholesterolemia.

Objective: The objective of this study was to compare the efficacy and tolerability of a new generic formulation of atorvastatin (test) with those of an original formulation of atorvastatin (reference) to satisfy regulatory requirements for marketing of the generic product in Korea.

Methods: Patients enrolled were aged 20 to 79 years with documented primary hypercholesterolemia who did not respond adequately to therapeutic lifestyle changes and with a LDL-C level >100 mg/dL from a high-risk group of coronary artery disease patients. Eligible patients were randomized to receive 1 of the 2 formulations of atorvastatin 20 mg per day for 8 weeks. The primary end point was the percent change in LDL-C level from baseline to week 8. Secondary end points included the percent change in total cholesterol, triglycerides, HDL-C level, apolipoprotein B:apolipoprotein A-I ratio, LDL:HDL ratio, LDL-C particle size, high-sensitivity C-reactive protein from baseline to week 8, and achievement rate of the LDL-C goal.

Results: A total of 298 patients (141 men and 157 women; 149 patients in each group; mean [SD] age, 62.4 [9.2] in the test group vs 60.3 [8.9] years in the reference group) were included. LDL-C levels were significantly decreased from baseline to week 8 in both groups, and there was no significant difference in the percent change in LDL-C level between groups (−44.0% [17.2%] in the test group, −45.4% [16.9%] in the reference group; $P = 0.49$). The between-group differences in the percent changes in total cholesterol and triglyceride levels were not statistically significant. In addition, there was no significant difference between the 2 groups in percent changes in HDL-C, apolipoprotein B:apolipoprotein A-I ratio, LDL-C:HDL-C ratio, LDL-C particle size, high-sensitivity C-reactive protein, and the achievement rate of the LDL-C goal. Two (1.3%) patients in the reference group (N = 150) experienced treatment-related serious adverse events (AEs): toxic hepatitis and aggravation of chest pain. Common AEs were cough (4.1%), myalgia (2.1%), and indigestion (1.4%) in the test formulation group and cough (5.3%), creatine kinase elevation (2.7%), and edema (0.7%) in the reference formulation group; however, the differences in overall prevalence of AEs between the 2 treatment groups was not significant ($P = 0.88$).

Conclusions: There were no significant differences observed in the efficacy and tolerability between the test and reference formulations of atorvastatin in these Korean adult patients with primary hypercholesterolemia. ClinicalTrials.gov identifier: NCT01285544. (*Clin Ther*. 2013;35:77–86)

Key words: atorvastatin, efficacy, hypercholesterolemia, tolerability.

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INTRODUCTION

An increased plasma LDL-C level is 1 of the major risk factors of atherosclerotic coronary heart disease and stroke. Lipid-lowering drugs have been shown in many studies to be effective in the prevention of atherosclerotic cardiovascular diseases. In particular, statins, which are a class of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are the drug of choice for the treatment of hypercholesterolemia.[1–5]

Statins inhibit hepatic cholesterol biosynthesis and increase the expression of the hepatic LDL receptor and its activity; this action accelerates the clearance of circulating LDL, which results in a nonlinear, dose-dependent reduction in plasma LDL-C levels.[6] In addition to their lipid-lowering effects, the pleiotropic effects of statins, such as anti-inflammatory and antithrombotic effects and the improvement in endothelial function, have been demonstrated in patients with hypercholesterolemia.[7–10] Statins reportedly reduce cardiovascular events in the primary and secondary prevention of atherosclerotic vascular disease.[11,12]

However, the increased prescription of statins has led to an increase in individual and social economic burdens, and has hindered drug compliance, especially in developing countries. In Korea, a branded formulation of atorvastatin* was approved for the treatment of hypercholesterolemia in 1999. A new generic formulation of atorvastatin† has been developed in Korea and was approved for use by the Korea Food and Drug Administration in 2008.

The current clinical trial was planned to satisfy requirements for the marketing of the generic product for use. Moreover, the objective of this study was to compare the efficacy and tolerability of the new generic formulation with those of the original formulation of atorvastatin in Korean patients with primary hypercholesterolemia.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

Eligible patients were aged 20 to 79 years with documented primary hypercholesterolemia that was not sufficiently responsive to therapeutic lifestyle changes and who had LDL-C levels >100 mg/dL. The inclusion criteria were in accordance with hypercholesterolemia treatment guidelines; coronary artery disease or equivalent group with an LDL-C level ≥100 mg/dL; patients with ≥2 risk factors and LDL-C levels ≥130 mg/dL; and patients with 0 or 1 risk factor and an LDL-C level >160 mg/dL after therapeutic lifestyle changes.

Patients were excluded if 1 of the following applied: therapy with any other investigational drug within 30 days of randomization; a history of hypersensitivity to 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, uncontrolled hypertension, poorly controlled diabetes (glycosylated hemoglobin >9%), unstable angina, or presented with new-onset myocardial infarction (within 6 months), creatinine >2.5 mg/dL, alanine aminotransferase >2 × the upper limit of normal (ULN), aspartate aminotransferase >2 × ULN, or creatine kinase (CK) >2 × ULN; and a history of malignancy or psychosis, chronic liver disease, or drug or alcohol abuse. Women who were pregnant and/or breastfeeding or who failed to use adequate contraception were excluded, as were those using cyclical hormonal contraceptives or intermittent use of hormone replacement therapies.

Study Design

This 8-week, randomized, open-label, parallel-group study was conducted at 5 clinical centers in Korea between September 2008 and July 2009. The study protocol was reviewed and approved by the institutional review boards of all participating centers; all patients provided written informed consent. The study was performed under the guidelines established by the Declaration of Helsinki and Good Clinical Practice Guideline.[13,14]

Patients were assigned, using a block randomization by site and in a 1:1 ratio, to receive the test or reference formulation of atorvastatin 20 mg once daily. The study design is shown in **Figure**. After written consent was received, patients underwent a complete physical examination, a medical history (eg, medical conditions, smoking status, medications), and laboratory assessments at the screening visit (visit 1). Three patients were already taking statin medication and 295 patients were not yet taking any statins. All the patients taking statin medication underwent a 4-week washout period and the others were instructed on therapeutic lifestyle changes during the 4-week period, and then received screening tests. At visit 2, the eligibility of the patients for the inclusion/exclusion criteria was re-examined, and the patients were randomized into a test or reference formulation group with atorvastatin 20 mg/d for 8 weeks. However, patients with coronary heart disease or a risk-equivalent without a history of lipid-

*Lipitor® (Pfizer Inc, New York, New York).
†Lipinon® (Dong-A Pharmaceutical Co, Ltd, Seoul, Korea).