

Original Research

A Phase III, Multicenter, Randomized, Double-blind, Active Comparator Clinical Trial to Compare the Efficacy and Safety of Combination Therapy With Ezetimibe and Rosuvastatin Versus Rosuvastatin Monotherapy in Patients With Hypercholesterolemia: I-ROSETTE (Ildong Rosuvastatin & Ezetimibe for Hypercholesterolemia) Randomized Controlled Trial

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ABSTRACT

Purpose: Combination therapy with ezetimibe and statins is recommended in cases of statin intolerance or insufficiency. The objective of this study was to compare the efficacy and safety of combination therapy with ezetimibe and rosuvastatin versus those of rosuvastatin monotherapy in patients with hypercholesterolemia.

Methods: I-ROSETTE (Ildong ROSuvastatin & ezETimibe for hypercholesterolemia) was an 8-week, double-blind, multicenter, Phase III randomized controlled trial conducted at 20 hospitals in the Republic of Korea. Patients with hypercholesterolemia who required medical treatment according to National Cholesterol Education Program Adult Treatment Panel III guidelines were eligible for participation in the study. Patients were randomly assigned to receive ezetimibe 10 mg/rosuvastatin 20 mg, ezetimibe 10 mg/rosuvastatin 10 mg, ezetimibe 10 mg/rosuvastatin 5 mg, rosuvastatin 20 mg, rosuvastatin 10 mg, or rosuvastatin 5 mg in a 1:1:1:1:1:1 ratio. The primary end point was the difference in the mean percent change from baseline in LDL-C level after 8 weeks of treatment between the ezetimibe/rosuvastatin and rosuvastatin treatment groups. All patients were assessed for adverse events (AEs), clinical laboratory data, and vital signs.

Findings: Of 396 patients, 389 with efficacy data were analyzed. Baseline characteristics among 6 groups were similar. After 8 weeks of double-blind treatment, the percent changes in adjusted mean LDL-C levels at week 8 compared with baseline values were −57.0% (2.1%) and −44.4% (2.1%) in the total ezetimibe/rosuvastatin and total rosuvastatin groups, respectively ($P < 0.001$). The LDL-C-lowering efficacy of each of the ezetimibe/rosuvastatin combinations was superior to

that of each of the respective doses of rosuvastatin. The mean percent change in LDL-C level in all ezetimibe/rosuvastatin combination groups was $>50\%$. The number of patients who achieved target LDL-C levels at week 8 was significantly greater in the ezetimibe/rosuvastatin group (180 [92.3%] of 195 patients) than in the rosuvastatin monotherapy group (155 [79.9%] of 194 patients) ($P < 0.001$). There were no significant differences in the incidence of overall AEs, adverse drug reactions, and serious AEs; laboratory findings, including liver function test results and creatinine kinase levels, were comparable between groups.

Implications: Fixed-dose combinations of ezetimibe/rosuvastatin significantly improved lipid profiles in patients with hypercholesterolemia compared with rosuvastatin monotherapy. All groups treated with rosuvastatin and ezetimibe reported a decrease in mean LDL-C level $>50\%$. The safety and tolerability of ezetimibe/rosuvastatin therapy were comparable with those of rosuvastatin monotherapy. [ClinicalTrials.gov](https://doi.org/10.1016/j.clinthera.2018.04.004) identifier: NCT02749994. (*Clin Ther.* 2018;40:226–241) © 2018 The Authors. Published by Elsevier HS Journals, Inc.

Key words: ezetimibe, hypercholesterolemia, rosuvastatin, single-pill combination.

INTRODUCTION

The American College of Cardiology/American Heart Association guide for the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults in 2013 recommended treatment with moderate- to high-intensity statins for patients with hypercholesterolemia.¹ However, some patients cannot attain LDL-C goals, even with maximal doses of a statin.² In addition, increasing the statin dose increases the risk

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