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Lipid-Lowering Efficacy and Safety of a New Generic Rosuvastatin in Koreans: an 8-Week Randomized Comparative Study with a Proprietary Rosuvastatin

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ABSTRACT

Objective: The aim of this study was to investigate whether a new generic rosuvastatin is non-inferior to a proprietary one in terms of lipid-lowering efficacy. We also evaluated its non-lipid effects including adverse events.

Methods: One-hundred and fifty-eight patients with cardiovascular risks requiring pharmacological lipid-lowering therapy were screened. After a 4-week run-in period, 126 individuals who met the lipid criteria for drug therapy were randomly assigned to receive the new generic or proprietary rosuvastatin 10 mg daily for 8 weeks. The primary outcome variables were low-density lipoprotein-cholesterol (LDL-C) reduction and LDL-C target achievement. Hematological and biochemical parameters and adverse events were assessed.

Results: After 8 weeks of drug treatment, the mean percentage change in LDL-C was not different between the groups (−45.5%±19.9% and −45.1%±19.0% for generic and proprietary rosuvastatin, respectively; p=0.38). The LDL-C target achievement rate was similar between the groups (75.0% and 77.1% for generic and proprietary rosuvastatin, respectively; p=0.79). The percentage change in the other lipid profiles was not significantly different. Although generic- and proprietary rosuvastatins modestly affected creatine kinase and blood pressure, respectively, the changes were all within normal ranges. Incidence of adverse events did not differ between the receivers of the 2 formulations.

Conclusion: The new generic rosuvastatin was non-inferior to the proprietary rosuvastatin in terms of lipid-lowering efficacy. The rosuvastatin formulations did not exhibit clinically significant non-lipid effects with good safety profiles. Our study provides comprehensive data regarding 2 rosuvastatin formulations in East Asian subjects.

Trial Registration: ClinicalTrials.gov Identifier: NCT03949374

Keywords: Rosuvastatin calcium; Cholesterol, LDL; Blood pressure; Hematology; Alanine transaminase

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INTRODUCTION

In the field of cardiovascular preventive medicine, statins have become an indispensable component. For several reasons, including cost-effectiveness, generic medications frequently replace proprietary medications. However, studies investigating the efficacy and safety of this class of medication are not sufficient. It has been reported that substituting generic for proprietary statin did not lead to any changes in efficacy and adverse events.[1] Nevertheless, even after the introduction of several generic statins, a comprehensive evaluation of these formulations has not been commonly performed.

Lately, statins are being widely used in Asian countries. Appropriate use of statins in East Asians is a medical issue because it has been reported that this population is more sensitive to statins than other ethnicities.[2,3] A few studies have shown that the responsiveness to low-dose statin is higher than expected in East Asians. However, comprehensive data on the efficacy and safety of statins, especially generic statins, are limited in East Asians. We aimed to investigate whether a new generic rosuvastatin is non-inferior to a proprietary one in terms of low-density lipoprotein-cholesterol (LDL-C)-lowering efficacy. We hypothesized that there would be no difference in LDL-C lowering efficacy of the two formulations. In addition, we assessed the effects of both rosuvastatin formulations on other lipid profiles and hematological and biochemical parameters. Finally, safety outcomes were also evaluated.

MATERIALS AND METHODS

1. Study participants

All participants provided written informed consent. Men and women aged 19 to 80 years were initially screened from October 2015 to April 2018. Statin-naïve individuals or those who were taking statins but provided consent to discontinue the medications for 4 weeks were eligible for the study. The participants had a variety of cardiovascular risks and required pharmacological lipid-lowering therapy according to the 2015 Korean Guidelines for the Management of Dyslipidemia.[4] After a 4-week run-in period, individuals who met the lipid criteria requiring pharmacotherapy were enrolled in the study. The exclusion criteria included history of acute coronary syndrome, cerebrovascular diseases, percutaneous coronary intervention, and coronary artery bypass graft in the past 3 months; uncontrolled hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg); uncontrolled diabetes mellitus (hemoglobin A1c ≥9%); thyroid dysfunction; serum creatinine or transaminase level ≥2× the upper limit of normal; history of myopathy or creatine kinase level >2× the upper limit of normal; drug or alcohol abuse; hypersensitivity against the test medication; and pregnant or breast-feeding women or women of childbearing potential who are not using contraceptives.

2. Study design

This was a 12-week (4 weeks of wash-out/lifestyle changes and 8 weeks of drug treatment), randomized, open-label, active-control study. The protocol was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea (No. 4-2015-0730; ClinicalTrials.gov identifier: NCT03949374). At the screening visit, the participants were interviewed about their medical history, and they underwent a physical examination and laboratory assessment. Individuals who met the inclusion criteria after the run-in period were randomly assigned to receive one of the following 2 regimens: a new generic rosuvastatin 10 mg (Rovasro; Whan In

Pharm Co., Ltd., Seoul, Korea) or proprietary rosuvastatin 10 mg daily (Crestor; AstraZeneca Korea, Seoul, Korea). Thereafter, the participants were followed-up at the end of week 8 for efficacy and tolerability. During the study, medications affecting patients' blood pressure were not changed.

Fasting blood samples were collected at randomization and at the end of week 8 of drug treatment. The samples were analyzed within 4 h of collection by a local laboratory certified by the Korean Society of Laboratory Medicine. Tolerability assessments were performed based on reported adverse events, history taking, physical examination, and laboratory evaluations. Drug-related adverse events were defined as any adverse events assessed by the investigators as "possibly related" or "related" to the study medication. Serious adverse events included death or events that are life-threatening, resulting in hospitalization or prolonging it, disability or permanent damage, or birth defect.

3. Statistical analysis

Primary outcome variables were percentage change and target achievement rate in the level of LDL-C from baseline to week 8 of drug treatment. The LDL-C target was defined as <70 mg/dL for the very high risk group, <100 mg/dL for the high risk group, <130 mg/dL for the moderate risk group, and <160 mg/dL for the low risk group.[4] Secondary outcome variables included percentage change in the level of total cholesterol, triglyceride, high-density lipoprotein-cholesterol (HDL-C), apolipoprotein (Apo)-B, Apo-A1, and high-sensitivity C-reactive protein (hsCRP). In addition, changes in blood pressure, hematologic parameters such as white blood cell count, hemoglobin level, and platelet count, and biochemical parameters such as creatinine, aspartate aminotransferase, alanine aminotransferase, and creatine kinase levels were compared before and after treatment with each formulation. A minimum of 50 participants were required per group, assuming a power of 80% and margin of 9.0 to report non-inferiority of the new generic rosuvastatin. A difference of 9%±16% (mean±standard deviation) in LDL-C between the groups was defined as significant. In expectation of a 20% dropout rate, at least 63 individuals per group were needed for the study. Efficacy analysis was performed in the population that underwent a follow-up test for laboratory values (full analysis set). Tolerability analysis was conducted for all the participants who took either of the 2 formulations at least once (safety set).

Continuous data are reported as mean±standard deviation, whereas categorical data are presented as frequency and percentage. Group differences in categorical variables were examined using the chi-square test, and those in continuous variables were assessed using Student's t-test. Paired t-test was used to evaluate the differences before and after treatment in each group. Differences between the 2 groups were considered significant when the p-value was <0.05 (2-sided). All data were analyzed using SAS software 9.3 (SAS Korea, Seoul, Korea).

RESULTS

1. Baseline characteristics

A total of 158 patients were screened and 126 of them were randomized. After the run-in period, 32 patients who did not meet the inclusion criteria were excluded. Of the 126 randomized patients, 121 were included in the full analysis set. Among the 5 dropped-out patients, 3 in the Rovasro group and 1 in the Crestor group did not undergo laboratory

Table 1. Baseline characteristics of the study population (full analysis set)

Characteristics	Total (n=121)	Rovasro® (n=60)	Crestor® (n=61)	p
Male	56 (46.3)	26 (43.3)	30 (49.2)	0.52
Age	59.0±7.1	60.3±10.6	57.6±9.6	0.14
Hypertension	72 (59.5)	35 (58.3)	36 (59.0)	>0.99
Diabetes mellitus	15 (12.4)	9 (15.0)	6 (9.8)	0.56
Smoking	21 (17.4)	8 (13.3)	13 (21.3)	0.25
Hypercholesterolemia	69 (57.0)	34 (56.7)	35 (57.4)	0.94
Risk status				0.67
Very high	36 (29.8)	17 (28.3)	19 (31.2)	
High	13 (10.7)	8 (13.3)	5 (8.20)	
Moderate	48 (39.7)	25 (41.7)	23 (37.7)	
Low	24 (19.8)	10 (16.7)	14 (23.0)	
BMI (kg/m²)	25.2±2.0	25.5±2.9	24.8±3.2	0.21

Data are presented as number (%) or mean±standard deviation.
BMI, body mass index.

tests, whereas one in the Crestor group did not take the test medication. The clinical characteristics of the participants included in the full analysis set are shown in **Table 1**. The mean age was 59 years; 56 (26%) of the patients were male; 15 (12%) had diabetes mellitus. The mean baseline LDL-C level was 156 mg/dL (**Table 2**). Thirty-six (30%) and 13 (11%) patients belonged to the very high- and high-risk groups, respectively. Clinical variables did not differ between the 2 groups.

Table 2. Changes in lipid profiles and hsCRP after treatment (full analysis set)

Laboratory values	Rovasro® (n=60)	Crestor® (n=61)	p
LDL-C (mg/dL)			
Before	157±31	155±29	
After	84±29	84±28	
% change	−45.5±19.9	−45.1±19.0	0.38
LDL-C target achievement (%)	45 (75.0)	47 (77.1)	0.79
TC (mg/dL)			
Before	238±35	238±34	
After	160±35	161±32	
% change	−32.3±14.6	−31.7±12.8	0.41
TG (mg/dL)			
Before	158±74	150±78	
After	120±51	122±72	
% change	−16.2±36.9	−12.2±38.5	0.48
HDL-C (mg/dL)			
Before	48.8±10.3	51.5±12.8	
After	51.6±11.6	53.1±12.9	
% change	6.4±15.4	4.6±17.3	0.65
Apo-B (mg/dL)			
Before	135±20	132±21	
After	83±21	82±20	
% change	−38.0±15.4	−36.9±16.3	0.47
Apo-A1 (mg/dL)			
Before	148±27	150±24	
After	153±30	154±25	
% change	3.9±12.7	3.6±13.1	0.84
CRP (mg/L)			
Before	2.49±4.92	1.46±1.64	
After	2.11±3.78	1.68±2.58	
% change	77.1±399.8	61.4±277.7	0.70

The *p*-value for the inter-group comparison using the 2-sample *t*-test or Wilcoxon's rank sum test.
TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Apo-B, apolipoprotein B; Apo-A1, apolipoprotein A1; CRP, C-reactive protein.

2. Changes in the lipid and other clinical parameters

After 8 weeks of drug treatment, the mean percentage of change in LDL-C was not different between the 2 groups (−45.5%±19.9% and −45.1%±19.0% in the Rovasro and Crestor groups, respectively; *p*=0.38). The LDL-C target achievement rate was similar between the groups (75.0% and 77.1% in the Rovasro and Crestor groups, respectively; *p*=0.79). The percentage change in the level of total cholesterol, triglyceride, HDL-C, Apo-B, Apo-A1, and hsCRP was not significantly different between the groups (**Table 2**). The systolic and diastolic blood pressure did not change in the Rovasro group (from 127±12 to 126±16 mmHg, *p*=not significant), whereas those in the Crestor group decreased after drug treatment (from 129±15 o 125±14 mmHg, *p*=0.02).

2. Safety outcomes including hematologic and biochemical parameters

Hemoglobin level (from 14.3±1.5 to 14.0±1.4 g/dL in the Rovasro group, *p*=0.006; from 14.5±1.4 to 14.3±1.3 g/dL in the Crestor group, *p*=0.008, reference 13–17 g/dL) and platelet count slightly decreased in both groups (from 261±50 to 250±51 ×10^3/μL in the Rovasro group, *p*<0.001; from 257±51 to 245±58 ×10^3/μL in the Crestor group, *p*<0.001, reference 150–400 ×10^3/μL). However, all the values were within the normal range. Although alanine aminotransferase levels did not change in the Rovasro group (from 25.1±15.8 to 26.9±16.1 IU/L, *p*=not significant), they increased in the Crestor group (from 21.3±10.8 to 25.6±13.3 IU/L, *p*=0.003, reference 5–46 IU/L). On the contrary, creatine kinase levels increased in the Rovasro group (from 106±60 to 152±234 IU/L, *p*=0.009), but did not change in the Crestor group (from 119±86 to 118±94 IU/L, *p*=0.90, reference 44–245 IU/L). However, no participant in any of the groups showed an increase in alanine aminotransferase or creatine kinase levels by more than 10-fold the upper limit of normal.

The number of adverse events was 18 and 12 in the Rovasro and Crestor groups, respectively. The number of patients who experienced any adverse events was not different between the 2 groups (15 [23.8%] and 12 [19.3%] in the Rovasro and Crestor groups, respectively, *p*=0.55). The proportion of patients who had drug-related adverse events was 9.7%–14.3%, whereas that of patients who had serious adverse events was 1.6%–3.2%; both were similar in the 2 groups. One serious event in the Rovasro group was prostate cancer, whereas 2 serious events in the Crestor group were pyelonephritis and arthritis. The most common events developed during the study were associated with the musculoskeletal and nerve systems, and the head and neck region in the order of frequency. Incidences of the adverse events including muscular or neurological systems were not significantly different between the 2 groups (**Table 3**).

DISCUSSION

In this study, the generic rosuvastatin was non-inferior to the proprietary rosuvastatin in terms of LDL-C reduction and target achievement rate. The efficacy in terms of changes in other lipid values was similar for the 2 rosuvastatin formulations. Only a few non-lipid parameters showed differential changes after treatment with the 2 rosuvastatin formulations: the generic rosuvastatin modestly increased creatine kinase, whereas the proprietary one decreased blood pressure and elevated liver enzyme slightly. The safety profiles including the number of patients with adverse events were not different between the receivers of the 2 formulations.

LDL-C reduction by rosuvastatin 10 mg has been reported to be approximately 46% in a pooled analysis of data mostly from Western countries.[5] In the present study, LDL-C reduction was

Table 3. Adverse events (safety set)

Adverse events	Rovasro® (n=63)		Crestor® (n=62)		p
	No. of subjects (%)	No. of events	No. of subjects (%)	No. of events	
Any adverse events	15 (23.8)	18	12 (19.3)	12	0.70*
Drug-related adverse events	9 (14.3)	9	6 (9.7)	6	0.60*
Serious adverse events	1 (1.6)	1	2 (3.2)	2	0.62
Musculoskeletal	5 (7.9)	6	3 (4.8)	3	0.72
Myalgia	4 (6.4)	4	2 (3.2)	2	
Neck pain	1 (1.6)	1	0 (0)	0	
Arthralgia	0 (0)	0	1 (1.6)	1	
Nervous system	3 (4.8)	3	4 (6.4)	4	0.72
Dizziness	2 (3.2)	2	2 (3.2)	2	
Headache	1 (1.6)	1	2 (3.2)	2	
Head and neck	1 (1.6)	1	3 (4.8)	3	0.36
Facial edema	0 (0)	0	1 (1.61)	1	
Erythema of eyelid	1 (16)	1	1 (1.6)	1	
Blurred vision	0 (0)	0	1 (1.6)	1	
Chest	2 (3.2)	2	1 (1.6)	1	>0.99
Chest pain	1 (1.6)	1	0 (0)	0	
Cough	0 (0)	0	1 (1.6)	1	
Dyspnea	1 (1.6)	1	0 (0)	0	
Gastrointestinal	1 (1.6)	1	0 (0)	0	>0.99
Constipation	1 (1.6)	1	0 (0)	0	
Infection	1 (1.6)	1	1 (1.6)	1	>0.99
Nasopharyngitis	1 (1.6)	1	0 (0)	0	
Pyelonephritis	0 (0)	0	1 (1.6)	1	
Laboratory abnormalities	1 (1.6)	3	0 (0)	0	>0.99
Liver enzyme elevation	1 (1.6)	1	0 (0)	0	
Creatine kinase elevation	1 (1.6)	1	0 (0)	0	
Gamma-glutamyltransferase elevation	1 (1.6)	1	0 (0)	0	

The p-values with asterisk are from χ^2 test. Other p-values are from Fisher's exact test.

approximately 45% in both groups, which was highly similar to that of the above-mentioned data. In previous studies performed in Korean population, the values ranged from 42.9% to 52.0%.[6-10] The LDL-C target achievement rate in our study was 75.0%–77.1%. In previous studies in Korea, the target achievement rate was relatively variable and ranged from 67.5% to 94.0%.[7-10] The cardiovascular risk status and baseline LDL-C of study populations varied in the studies, and the differences in the target achievement rates might be associated with these factors. Although studies analyzing the effect of generic rosuvastatin have not been common, one report from West Asia has showed that the generic one was efficacious and safe.[11]

The generic rosuvastatin used in our study did not exhibit a significant effect on blood pressure, whereas the proprietary one reduced blood pressure although it was not large. The blood pressure-lowering effect of statins reported to date has not been consistent. Simvastatin or atorvastatin use was associated with lower blood pressure, whereas rosuvastatin use was not. However, these findings have limited power as the studies were not elaborately designed.[12,13] Likewise, a few studies have shown that rosuvastatin, alone or in combination with valsartan, modestly reduced blood pressure.[14,15] In our study, the effect of the rosuvastatin formulations on serum creatinine level was not significant. Although several studies have been conducted in this regard, the effects of statins including rosuvastatin on renal function have not been consistent either. A study performed in Japan revealed that atorvastatin and fluvastatin increased serum creatinine level.[16] Furthermore, rosuvastatin has been demonstrated to be associated with acute kidney injury in Chinese patients undergoing cardiac surgery.[17] In contrast, a meta-analysis reported that rosuvastatin can inhibit contrast nephropathy.[18] Taken together, high-quality evidence regarding the influence of statin on renal function is still insufficient.[19]

In previous studies performed in Koreans, the incidence of treatment-emergent adverse events with rosuvastatin ranged from 7.6% to 23.7%,[6,8,9,14,20] whereas that of drug-related adverse events was from 1.7% to 5.6%.[6,8,9] In addition, the incidence of drug-related serious adverse events has been very low and ranged from 0% to 1.5% in Korean studies.[9,10,14] An increase in liver enzyme by > 3 times the upper limit of normal after rosuvastatin use was rare, with 0.5%–1.3%.[6,7] Conversely, an increase in creatine kinase by >5 or 10 times the upper limit of normal was observed in nearly none or 2.6% of Korean study populations.[6,8]

Our study has a few potential limitations. First, the sample size of our study was not sufficient to assess and compare the non-lipid effect and safety of the 2 rosuvastatin formulations. However, the primary purpose of the study was to examine the non-inferiority of the generic rosuvastatin in terms of lipid-lowering effect and we achieved this aim. Second, although our study described and compared the effect of 2 rosuvastatin formulations in Koreans, it is not clear whether our findings in this population are different from or similar to those in other ethnicities. However, no study has assessed the complete effect of generic rosuvastatin, particularly in East Asians, and the present study provides specific data in this regard. Third, data regarding differences of antihypertensive medications between the 2 groups, blood pressure lowering in hypertensive patients, and changes in diastolic blood pressure were not available. Further data on these issues might have given more insight on test medication.

In conclusion, the new generic rosuvastatin was non-inferior to the proprietary rosuvastatin in terms of lipid-lowering efficacy. Both rosuvastatin formulations did not exhibit clinically significant non-lipid effects, but presented good safety profiles. These results provide comprehensive data regarding the effects of 2 rosuvastatin formulations in East Asian subjects.

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