Effects of Rosuvastatin on Low-Density Lipoprotein Cholesterol and Plasma Lipids in Asian Patients with Hypercholesterolemia

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Aims: Rosuvastatin is more efficacious than other statins in lowering low-density lipoprotein cholesterol (LDL-C). Studies showing higher blood levels in Asians have resulted in concerns regarding increased adverse drug reactions. This study aimed to evaluate the efficacy and safety of rosuvastatin in hypercholesterolemic Asian patients.

Methods: This retrospective observational study was conducted on statin-naive patients and statin-switch patients. Patients were treated with rosuvastatin for ≥8 weeks. Primary outcomes were changes in LDL-C levels and proportions of patients achieving their goals (primary prevention, LDL-C ≤ 130 mg/dL; secondary prevention, LDL-C ≤ 100 mg/dL).

Results: Of 1007 hypercholesterolemic patients, 483 were statin-naive (LDL-C 161 ± 40.8 mg/dL) and 524 were statin-switch patients (LDL-C 132.7 ± 36.9 mg/dL). In statin-naive patients, rosuvastatin significantly reduced LDL-C, total cholesterol, and triglycerides by 39.9%, 28.8%, and 9.2%, respectively (p < 0.001). Eighty-one percent of these patients achieved LDL-C goals. In the statin-switch cohort, LDL-C, total cholesterol, and triglycerides levels were significantly reduced by 24.5%, 16.6%, and 3.8%, respectively (p < 0.001). Achievement of target LDL-C levels increased from 29% to 72.9%. There was no significant adverse drug reaction.

Conclusion: Rosuvastatin was well tolerated and effective in lowering LDL-C in hypercholesterolemic Asian patients. Patients whose LDL-C levels were suboptimal on other statins improved their levels and more achieved LDL-C goals after switching to rosuvastatin.


Key words: Cardiovascular disease, Lipids, Rosuvastatin, Asian patients

Introduction

Reducing low-density lipoprotein cholesterol (LDL-C) to target levels is the primary therapeutic goal of lipid-lowering therapy in hypercholesterolemic individuals at risk of cardiovascular events. The beneficial effects of statins on lowering LDL-C have been shown in multiple landmark trials and meta-analysis to be effective in lowering cardiovascular endpoints; however, many patients do not achieve target lipid levels, depriving them of the maximum benefit of statin therapy. More recent studies have shown the ability to achieve further cardiovascular endpoint reduction with even lower LDL-C levels, suggesting the need for more effective lipid-lowering therapeutic management.

Statin monotherapy is generally well tolerated with few adverse events, most being mild and transient in nature. Myopathy and hepatic damage are the two major but uncommon adverse events. Acute pharmacokinetic studies have shown that Asians may have higher blood levels of rosuvastatin than Caucasians but whether this results in more adverse events has not been demonstrated.

This study was aimed to evaluate the efficacy and safety of rosuvastatin in lowering LDL-C in hypercholesterolemic Asian patients.
Materials and Methods

Study Design

A retrospective observational study was performed to evaluate the efficacy and safety of rosuvastatin in lowering plasma LDL-C and the achievement of LDL-C goals in two groups of patients in clinical practice: statin-naive and statin-switch hypercholesterolemic patients. The statin-naive patients were patients not previously treated with any statin and the primary objective was to evaluate the LDL-C-lowering efficacy of rosuvastatin in these patients. Secondary objectives included safety assessments of rosuvastatin therapy and evaluation of the efficacy of rosuvastatin in modifying other plasma lipids, such as total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides. The study was approved by the Independent Ethics Committee of Gleneagles and Mt Elizabeth Hospitals.

Study Subjects and Procedures

Eligible subjects were men and women aged 18 years or above who had hypercholesterolemia and had to have lipid-lowering therapy for primary and secondary prevention. Secondary prevention patients include those with coronary artery disease, peripheral vascular disease, cerebrovascular disease, renovascular disease, and diabetes mellitus. The patients were either: (i) statin-naive patients whose LDL-C level was ≥135 mg/dL; or (ii) patients who had been previously treated with atorvastatin, simvastatin, or other statins for at least 8 weeks but whose LDL-C level control remained suboptimal. All patients were treated with rosuvastatin for 8 or more weeks in clinical practice. The rosuvastatin doses were decided by the attending clinicians. Blood samples for biochemistry tests were obtained after 10 hours of fasting. Laboratory determinations of plasma total cholesterol, triglycerides, LDL-C (calculated), HDL-C, serum creatine kinase (CK), and alanine aminotransferase (ALT) were performed at accredited laboratories in Singapore.

Evaluation of Efficacy

The lipid-lowering efficacy of rosuvastatin was evaluated by: (i) the changes in LDL-C from baseline levels and (ii) the percentage of patients achieving the US National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) target\(^\text{13}\) LDL-C levels, set at ≤130 mg/dL for primary prevention patients and ≤100 mg/dL for secondary prevention patients. Other lipid variables analyzed were changes in total cholesterol, HDL-C, and triglycerides from baseline levels.

Evaluation of Safety

The safety of rosuvastatin therapy was evaluated by clinical assessments and blood samples of liver and muscle enzymes when clinically indicated. Serum CK and ALT measurements were taken by the attending clinicians on a case-by-case basis. An elevation of serum CK to >10 times the upper normal limit (UNL) values (120 U/L: range, 12–80 U/L for males, 10–55 U/L for females) and elevation of ALT to >3 times UNL (25 U/L: range, 8–20 U/L) were considered clinically important. The proportions of patients having different raised levels of serum CK or ALT at anytime during the 8 or more weeks of rosuvastatin therapy were computed and assessed for clinical relevance.

Statistical Analysis

All data were analyzed using the SAS Version 9.1 system (SAS Institute Inc., Cary, NC, USA). Demographic and baseline characteristics of patients were analyzed using descriptive statistics. All efficacy and safety measures were analyzed using analysis of covariance with baseline measurements as covariates. For all comparisons, statistical significance was assumed at a two-tailed value of \( p \leq 0.05 \). The results are presented as the mean ± SD.

Results

Patients’ Demographics and Baseline Clinical Characteristics

A total of 1007 hypercholesterolemic patients treated with rosuvastatin for 8 or more weeks during the period April 2004 to February 2006 were studied. In the statin-naive group, there were 483 patients (266 men, 217 women; age, 57.9 ± 12.4 years) with a pre-treatment LDL-C level of 161 ± 40.8 mg/dL. In the statin-switch cohort, there were 524 patients (318 men, 206 women; age, 61.6 ± 10.5 years) with a pre-switch LDL-C level of 132.7 ± 36.9 mg/dL. Demographic and baseline clinical characteristics of the patients are shown in Table 1, 2, 3, respectively.

In the statin-naive group, there were slightly more primary prevention patients (55.9%; 270/483) than secondary prevention patients (44.1%; 213/483). Hypertension was a risk factor for the majority (55.4%) of primary prevention patients. Other risk factors included smoking (20.7%), a family history of coronary artery disease, cerebrovascular disease and peripheral vascular disease (25.2%), and low HDL-C (21.5%). Secondary prevention patients had mainly coronary artery disease (58.7%) and/or diabetes mellitus (53.5%). A minority had peripheral vascular disease (2.3%), cerebrovascular disease (7.5%), or reno-
Lipid-Modifying Efficacy of Rosuvastatin

Table 1. Demographic characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Naive Patients</th>
<th>Switch Patients</th>
<th>All</th>
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<tbody>
<tr>
<td></td>
<td>Primary</td>
<td>Secondary</td>
<td>All</td>
</tr>
<tr>
<td>Sex</td>
<td>Male, n (%)</td>
<td>139 (51.5)</td>
<td>266 (55.1)</td>
</tr>
<tr>
<td></td>
<td>Female, n (%)</td>
<td>131 (48.5)</td>
<td>217 (44.9)</td>
</tr>
<tr>
<td></td>
<td>All, n</td>
<td>270</td>
<td>483</td>
</tr>
<tr>
<td>Race</td>
<td>Chinese, n (%)</td>
<td>233 (86.3)</td>
<td>402 (83.2)</td>
</tr>
<tr>
<td></td>
<td>Malay, n (%)</td>
<td>8 (3.0)</td>
<td>16 (3.3)</td>
</tr>
<tr>
<td></td>
<td>Indian, n (%)</td>
<td>9 (3.3)</td>
<td>23 (4.8)</td>
</tr>
<tr>
<td></td>
<td>Other, n (%)</td>
<td>20 (7.4)</td>
<td>42 (8.7)</td>
</tr>
<tr>
<td></td>
<td>All, n</td>
<td>270</td>
<td>483</td>
</tr>
<tr>
<td>Age</td>
<td>Mean ± SD</td>
<td>57.9 ± 12.4</td>
<td>61.6 ± 10.5</td>
</tr>
<tr>
<td></td>
<td>Min–Max</td>
<td>19–90</td>
<td>32–90</td>
</tr>
</tbody>
</table>

Table 2. Secondary prevention: vascular disease and diabetes patients (n=547)

<table>
<thead>
<tr>
<th></th>
<th>Naive Patients</th>
<th>Switch Patients</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>125 (58.7)</td>
<td>244 (73.1)</td>
<td>369 (67.5)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>5 (2.3)</td>
<td>10 (3.0)</td>
<td>15 (2.7)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>16 (7.5)</td>
<td>23 (6.9)</td>
<td>39 (7.1)</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>12 (5.6)</td>
<td>24 (7.2)</td>
<td>36 (6.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>114 (53.5)</td>
<td>150 (44.9)</td>
<td>264 (48.3)</td>
</tr>
</tbody>
</table>

vascular disease (5.6%).

The statin-switch cohort was predominantly secondary prevention patients (63.7%). Most of the secondary prevention patients had coronary artery disease (73.1%) and/or diabetes mellitus (44.9%). Other risk-associated conditions in these secondary prevention patients included peripheral vascular disease (3.0%), cerebrovascular disease (6.9%), and renovascular disease (7.2%). As with the statin-naive group, hypertension was a risk factor for the majority (56.8%) of primary prevention statin-switch patients. Other risk factors identified were a family history of coronary artery disease, cerebrovascular disease or peripheral vascular disease (27.4%), smoking (23.7%), low HDL-C (28.4%) and obesity (4.7%).

Lipid-Lowering Efficacy

Statin-Naïve Cohort

In the statin-naive cohort, LDL-C levels were reduced by 39.9% from 161 ± 40.8 mg/dL to 92.2 ± 32.3 mg/dL (p < 0.001) after treatment with rosuvastatin for 38.4 ± 30.6 weeks. The total cholesterol levels were reduced by 28.8% from 258.3 ± 72.7 mg/dL to 180 ± 52.7 mg/dL (p < 0.001). There was a significant reduction (9.2%) of triglycerides from 153.9 ± 74.1 mg/dL to 126.3 ± 58.9 mg/dL (p < 0.001). No difference in HDL-C levels was observed. The patients were predominantly treated with 10 mg/day dose of rosuvastatin (92.8%).

Eighty-one percent (391/483) of statin-naive patients achieved their respective LDL-C target goals for primary prevention and secondary prevention after 8 or more weeks of rosuvastatin therapy (Fig. 1). Of these patients, 79.9% (358/448) achieved targets on 10 mg rosuvastatin. There was no difference in the achievement of target levels between patients with primary or secondary prevention (81.1% in primary prevention vs. 80.8% in secondary prevention).
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Statin-Switch Cohort

In the statin-switch cohort, 521 patients were treated with other statins for a period of 140.1 ± 122.9 weeks. The majority of these patients were switched from atorvastatin (59.4%; 311/524) and simvastatin (27.9%; 146/524), with 12.8% (67/524) switched from other statins. Most patients (95.2%; 499/524) were switched to an equivalent or lower dose of rosuvastatin. The doses (mean ± SD) of rosuvastatin administered to those who switched from an equivalent or higher dose of atorvastatin and simvastatin were 10.8 ± 3.5 mg and 10.4 ± 3.4 mg, respectively. Only 4.8% of statin-switch patients required their doses to be increased.

The changes in LDL-C, total cholesterol, HDL-C, and triglycerides from pre-switch levels are shown in Fig. 2. LDL-C levels were significantly reduced by 24.5% from 132.7 ± 36.9 mg/dL to 97.6 ± 35.1 mg/dL (p < 0.001) while total cholesterol levels decreased by 16.6% from 220 ± 68.9 mg/dL to 179.4 ± 55.5 mg/dL (p < 0.001). The triglycerides were significantly reduced by 3.8% from 144.7 ± 70.3 mg/dL to 127.8 ± 57.2 mg/dL (p < 0.001). No significant change in HDL-C levels was observed in all switch groups. Improvements in LDL-C in patients who switched from atorvastatin were similar to those who switched from simvastatin. In switch from atorvastatin patients, LDL-C levels were significantly reduced by 22.5% from 133.6 ± 37.2 mg/dL to 100.8 ± 35.8 mg/dL (p < 0.001). In patients who switched from simvastatin, LDL-C levels were significantly reduced by 26% from 128.8 ± 35.5 mg/dL to 92.8 ± 32.3 mg/dL (p < 0.001).

Before statin-switch, only 29% of these patients (35.3% in primary prevention and 25.5% in secondary prevention) had achieved ATP III defined LDL-C targets. After switching to rosuvastatin, 72.9% of patients (75.8% in primary prevention and 71.3% in secondary prevention) managed to achieve their target goals (Fig. 3). There was no difference in the achievements of targets between groups switched from atorvastatin, simvastatin, and other statins. The percentage of patients achieving target goals ranged from 73.9% to 78% for primary prevention patients and 65% to 81.8% for secondary prevention patients.

Safety - Elevations of Serum CK and ALT Levels

Serum CK levels were assessed in 264 patients during rosuvastatin therapy. No patient had rhabdomyolysis or myositis. Of all patients assessed, 85.2% had normal CK levels (<192 U/L), 13.6% had levels 1–2 times UNL (192–384 U/L), and only 1.1% had levels 2–4 times UNL (384–768 U/L). The change in

Fig. 1. Percent of primary and secondary prevention naive patients who achieved the various LDL-C target goals after 8 or more weeks of rosuvastatin therapy.

Treatment goals were ≤130 mg/dL for primary prevention and ≤100 mg/dL for secondary prevention. In addition, an optional goal of ≤100 mg/dL and ≤70 mg/dL was set for primary and secondary prevention patients, respectively.
Fig. 2. Percent change in plasma total cholesterol, LDL-C, HDL-C and triglycerides after 8 or more weeks of rosuvastatin therapy in three treatment groups representing patients who had switched over from atorvastatin, simvastatin and other statins. Values below the X-axis represent reduction; those above X-axis represent increase. The dose (mean ± SD) of rosuvastatin administered to those who switched from an equivalent or higher dose of atorvastatin and simvastatin were 10.8 ± 3.5 mg and 10.4 ± 3.4 mg, respectively.

Fig. 3. Percent of primary and secondary prevention statin-switch patients who achieved LDL-C target goals before and after switching to rosuvastatin. Treatment goal was ≤130 mg/dL for primary prevention and ≤100 mg/dL for secondary prevention. Before switching, primary prevention patients on atorvastatin and simvastatin were administered doses (mean ± SD) of 10.9 ± 4.0 mg and 16.8 ± 11.1 mg of the respective drug. Correspondingly, secondary prevention patients received 11.8 ± 4.2 mg and 14.1 ± 6.3 mg of the same drugs, respectively. After switching, primary prevention patients switched from atorvastatin and simvastatin received 10.9 ± 3.2 mg and 10.0 ± 2.5 mg of rosuvastatin, respectively. Secondary prevention patients in the corresponding switch groups received 11.3 ± 3.7 mg and 10.8 ± 3.8 mg of rosuvastatin, respectively.
CK was insignificant for both statin-naive and statin-switch cohorts and no patient had serum CK elevated to more than 10 times UNL.

Serum ALT levels were determined for 757 patients while on rosuvastatin therapy. Of all patients assessed, 81.4% had normal ALT, 16.9% had ALT levels ≤2 times that of UNL, and 1.7% had levels ≥2 times UNL. Rosuvastatin did not lead to any significant change in ALT levels in both statin-naive and switch patients.

**Discussion**

This study documents the use of rosuvastatin in Asian patients in clinical practice. The demographics of our patients are typical of those requiring cardiovascular disease prevention therapy.

In patients not previously treated with statins, there was a significant 39.9% reduction in LDL-C, which is remarkably similar to the 33–56.8% reported in other studies involving mainly Caucasian or Japanese patients. This study also shows that most primary and secondary prevention hypercholesterolemic statin-naive patients were able to achieve their therapeutic LDL-C goals with the 10 mg starting dose of rosuvastatin.

A high proportion of hypercholesterolemic patients on other statin therapies do not achieve target lipid levels. In our statin-switch patients, 70.1% were not at goal despite being treated with other statins. This study showed that the achievement of therapeutic LDL-C goals for these patients was achieved by switching to rosuvastatin. Although most patients were switched to an equivalent or even a lower dose of rosuvastatin, they could still achieve their target LDL-C goals. Most statin-switch patients in this study achieved LDL-C goals with 10 mg/day rosuvastatin.

In contrast to other studies, there was no significant change in HDL-C levels. In our practice, rosuvastatin is mainly used in patients with high LDL-C levels. The baseline HDL-C in our patient cohort was quite high at 53.6 ± 13.3 mg/dL and 52.2 ± 12.7 mg/dL for statin-naive and statin-switch patients, respectively. It has been shown that in patients with high HDL-C, rosuvastatin may not be as effective in increasing HDL-C as in those with low HDL-C.

In our study, no muscle or liver safety concerns were observed during rosuvastatin treatment. This is consistent with similar safety findings reported in other studies on rosuvastatin. There have been concerns that increased plasma levels of rosuvastatin in Asians, as shown in single-dose pharmacokinetic studies, may lead to increased adverse drug effects. However, our study did not reveal any increased adverse effects in our patients and the safety and lipid-lowering efficacy was shown to be similar to other studies predominantly using Caucasians. Acute dose studies may not reflect blood levels after chronic therapy and blood levels may not reflect tissue drug levels. The higher hydrophilicity of rosuvastatin as compared to older statins and its higher selectivity for cells (such as hepatocytes) that express active transporters with high affinity for organic anions may also mean that uptake of the drug by peripheral tissues such as skeletal muscles is restricted due to lower passive diffusion of the drug.

This study is the longest follow-up of patients in any statin study in Asia and represents a multiethnic population living in South East Asia. A limited number of studies have evaluated the effects of rosuvastatin in Asian populations. These studies contribute significantly to the database on the effects of rosuvastatin in Asians; however, the other two published studies (DISCOVERY-Asia and IRIS) and our study differ in their purpose, population emphasis and design.

DISCOVERY-Asia is a randomized open-label clinical trial with a 12-week duration of therapy and follow-up to establish the efficacy of a fixed starting dose of rosuvastatin and atorvastatin. Patients were predominantly from North Asia (79%), with the majority being Chinese from China.

The IRIS study is a 6-week randomized trial to document the efficacy of rosuvastatin compared to atorvastatin at fixed doses in South Asians in the United States and Canada, who had been exposed to the dietary and other environmental habits of these countries.

Our study is a clinical observational study to evaluate the clinical practice of using rosuvastatin in Singaporean patients, who live in South East Asia. It is the longest follow-up of patients in any statin study in Asia, which is critical for the assessment of efficacy and side effects in clinical practice. The South East Asian population in this study is multiethnic (Chinese, Malay, Indian and others), and the number of South East Asian patients on rosuvastatin in this study (n = 1,007) is much more than in DISCOVERY-Asia (n = 313). There were no constraints on starting doses in this study.

Unlike the DISCOVERY-Asia and IRIS studies, patients in this study were prespecified into primary and secondary prevention groups. The efficacy of switching to rosuvastatin from other statins and relating the switch response to the initial dose and type of statin were also studied, which were not included in DISCOVERY-Asia or IRIS.
In our study, the similar lipid-lowering efficacy of rosuvastatin, with the absence of any adverse drug effects, in our Asian population compared to Caucasians suggests that rosuvastatin can be used effectively and safely in Asians and Caucasians.

**Limitations of the Study**

The limitations of this study are those inherent to retrospective observational studies. One limitation is that we do not have data on patients who stopped treatment before 8 weeks of rosuvastatin therapy. However, the main aim of this study was to observe the real-world clinical practice of using rosuvastatin for at least 8 weeks in hyperlipidemic patients in Asian patients in Singapore.

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**Disclosure**

The four authors are members of AstraZeneca Singapore Pte Ltd Cardiology Advisory Board and receive nominal fees for their consultation.

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