Comparison of Original and Generic Atorvastatin for the Treatment of Moderate Dyslipidemic Patients

Paiboon Chotnoparatpat, MD
Cardiology Department, Bangkok Metropolitan Medical College and Vajira Hospital, Bangkok, Thailand

Abstract

Objective: This study evaluated and compared the efficacy of generic atorvastatin to original atorvastatin for the treatment of moderate dyslipidemia.

Background: Dyslipidemia is a strong risk factor for coronary artery diseases. Treatment of dyslipidemic patients with statin therapy reduces the risk of cardiovascular disease in both primary and secondary prevention settings. Original atorvastatin can effectively treat dyslipidemia but generic atorvastatin has yet to be proven effective in lowering blood lipids.

Methods and Results: This was a prospective double blind study in 120 moderate dyslipidemic patients treated with 20mg of original or generic atorvastatin for 8 weeks. Patients were randomized to both groups. The study was conducted in five phases, which included two screening periods, one baseline period and two treatment phases. The results showed that there were no statistical differences in LDL-cholesterol or total cholesterol reduction for patients treated with either generic or original atorvastatin (43% vs 46%, 35% vs 35%) respectively.

Conclusion: Generic atorvastatin offers a cost-effective therapeutic choice for dyslipidemic treatment with no statistical difference in its ability to reduce lipids when compared to original atorvastatin. The limitation of this study was that both drugs were evaluated for a short period, thus necessitating longer-term studies for establishing practical therapeutic guidelines in Thai patients.

Note: generic atorvastatin* (Greater phrama mybacin company)

Thai heart J 2008; 21: 008-014
E-Journal: http://www.thaiheartjournal.org

Introduction

Over the past decade, several major randomized clinical trials of low density lipoprotein-cholesterol (LDL-C) lowering have demonstrated that statin therapy reduces the risk of cardiovascular disease in both primary and secondary prevention settings. These trials include the Air Force Coronary Atherosclerosis Prevention Study (AFCAP) (14), the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) (11), the West Of Scotland Coronary Prevention Study (WOSCOPS) (1), the Scandinavian Simvastatin Survival Study (4S) (2), the Cholesterol and Recurrent Event (CARE) Trial, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) (3) Trial, the Pravastatin or atorvastatin Evaluation and Infection Therapy Trial (PROVE-IT) (16).

A consistent finding of these studies is that there is a direct relationship between the magnitude of LDL-C reduction and coronary heart disease risk reduction according to the National Cholesterol Education Program (NCEP) Adult Treatment panel III guidelines (ATP III) (15).

Since 1997, an economic crisis has developed in Thailand with the burden of this economic collapse damaging and affecting the medical arena. Thus, the introduction of generic statins offer a cost-saving therapeutic option, but their efficacy and safety remain to be clarified. The best way to determine the efficacy and safety of generic atorvastatin is to compare the pharmacodynamics to original atorvastatin in treating hypercholesterolemia in Thai patients.
Methods

Population study and definition

This study was approved by the Ethics committee. Patients with moderate hypercholesterolemia, defined as serum LDL-C of > 160 mg/dl but < 250 mg/dl and triglycerides of < 400 mg/dl after 12 hours fasting with one or two major coronary risk factors were asked to participate in this study. The major coronary risk factors were elevated serum cholesterol and LDL-C, elevated blood pressure, cigarette smoking and diabetes mellitus. The exclusion criteria were 1) patients of age < 30 or > 70 years. 2) pregnant or lactating women. 3) patients who received any lipid lowering agents within 8 weeks of the baseline evaluation. 4) patients who received erythromycin, clarithromycin or immunosuppressive agents. 5) patients with any cause of hepatitis. 6) patients with elevated serum creatinine phosphokinase two times above the normal limit. 7) patients with acute coronary syndrome within 3 months. 8) patients with impaired renal function. 9) patients with an allergic history to HMG-CoA Reductase inhibitors (statins) 10) diabetic patients with an acute complication.

The primary endpoint was the percent change of LDL-C from baseline to week 4 and the end of week 8. The secondary endpoint was the percent change of all lipid profiles including total cholesterol, HDL-C and triglycerides from baseline to week 4 and week 8. The side effects of drugs were evaluated by the investigators. Serum transaminase (SGOT, SGPT) and creatinine phosphokinase (CPK) were recorded after the 4th and 8th treatment weeks.

Study design

The study was a prospective double blind study conducted in 5 periods. All patients received dietary advice for cholesterol reduction according to the NCEP III guideline from baseline to the 8th treatment week.

Screening period 1 (-4th week to -2nd week): Patients were assessed and examined in our cardiology clinic for screening inclusion or exclusion criteria. The serum total cholesterol, triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), LDL-C, SGOT, SGPT, CPK and fasting blood sugar (FBS) were checked and the informed consent was obtained.

Screening period 2 (-2nd week to 0 week): Patients had repeated serum cholesterol, TG, LDL-C, HDL-C.

Baseline period (0 week) Total cholesterol, TG, LDL-C, HDL-C measurements were repeated for baseline data.

Treatment period 1 (0 week to 4th week): Patients received 20mg tablets of generic atorvastatin (Greater phrama mybacin company) or original atorvastatin (Pfizer company) randomly. Serum total cholesterol, TG, LDL-C, HDL-C, SGOT, SGPT, CPK were checked after the 4th week of treatment.

Treatment period 2 (4th week to 8th week): Subjects had repeat serum cholesterol, TG, LDL-C, HDL-C, SGOT, SGPT, CPK at the 8th week of treatment.

Sample size calculation and statistical analysis

The equation listed below was designed on the assumption that the two drugs might have the same effect on total cholesterol and LDL- cholesterol reduction with the difference in efficacy of no more than 10%. The sample size in each arm would be at least 28 patients.

\[ N = \frac{2(Z_{\alpha} + Z_{\beta})^2S^2_{pool}}{D^2} \]

Where: \( Z_{\alpha} \) 95% = 1.645, \( Z_{\beta} \) 80 % = .8416 (Z One–tail), \( S^2_{pool} = 223.5, D = 10 \)

The student t-test was used to show the statistical difference between the two drugs. The percent reduction of Total cholesterol, TG, HDL-C, LDL-C from baseline to 4 and 8 weeks by the two drugs were calculated and the student t-test was used to show significant statistical power if the p-value was < 0.05.

Results

One hundred seventy-two outpatients in Vajira Hospital were evaluated for the screening phase. From these patients one hundred twenty patients were enrolled for the baseline and treatment phase with half receiving randomly either generic atorvastatin or the original atorvastatin. Age, sex, body mass index, history of hypertension, diabetes and smoking habit were recorded. There were no statistical differences between the drug groups for these characteristics as shown in Table 1.

Baseline total cholesterol, TG, HDL-C, LDL-C were recorded. There were no statistical differences between the groups in lipid levels as shown in Table 2.
Table 1. The demographic parameters.

<table>
<thead>
<tr>
<th></th>
<th>Generic atorvastatin</th>
<th>Original atorvastatin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number (n)</td>
<td>60</td>
<td>60</td>
<td>ns</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55</td>
<td>54</td>
<td>ns</td>
</tr>
<tr>
<td>Male sex (n)</td>
<td>36</td>
<td>36</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/sq.m)</td>
<td>25</td>
<td>27</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>36</td>
<td>40</td>
<td>ns</td>
</tr>
<tr>
<td>DM (n)</td>
<td>8</td>
<td>8</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>8</td>
<td>9</td>
<td>ns</td>
</tr>
</tbody>
</table>

BMI = body mass index, DM = diabetes mellitus

Table 2. Baseline parameters.

<table>
<thead>
<tr>
<th>Baseline parameter</th>
<th>Generic atorvastatin</th>
<th>Original atorvastatin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>297.2±37.7</td>
<td>296.2±42.4</td>
<td>ns</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>228.6±100.3</td>
<td>227.6±87.5</td>
<td>ns</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>60.0±12.9</td>
<td>57.9±12.5</td>
<td>ns</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>191.5±26.0</td>
<td>192.9±29.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

Table 3. Outcome after 4 weeks of treatment.

<table>
<thead>
<tr>
<th></th>
<th>Generic atorvastatin</th>
<th>Original atorvastatin</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>212.0±34.7</td>
<td>212.3±41.4</td>
<td>ns</td>
</tr>
<tr>
<td>TC Δ %</td>
<td>-28.6</td>
<td>-28.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>189.8±92.0</td>
<td>172.4±68.2</td>
<td>ns</td>
</tr>
<tr>
<td>TG Δ %</td>
<td>-17.1</td>
<td>-24.2</td>
<td>0.5</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>56.7±11.4</td>
<td>55.8±11.5</td>
<td>ns</td>
</tr>
<tr>
<td>HDL Δ %</td>
<td>-6.6</td>
<td>-3.4</td>
<td>0.6</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>120.3±35.2</td>
<td>124.5±37.3</td>
<td>ns</td>
</tr>
<tr>
<td>LDL Δ %</td>
<td>-37.1</td>
<td>-35.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Δ % = % change from baseline
* = p value for the comparison of mean
Table 4. Outcome after 8 weeks of treatment.

<table>
<thead>
<tr>
<th></th>
<th>Generic atorvastatin</th>
<th>Original atorvastatin</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>192.0 ± 30.4</td>
<td>192.4 ± 38.9</td>
<td>ns</td>
</tr>
<tr>
<td>TC Δ%</td>
<td>-35.3</td>
<td>-35.1</td>
<td>ns</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>164.7 ± 66.4</td>
<td>172.5 ± 120.6</td>
<td>ns</td>
</tr>
<tr>
<td>TG Δ%</td>
<td>-27.7</td>
<td>-24.0</td>
<td>ns</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>55.2 ± 11.0</td>
<td>56.5 ± 12.0</td>
<td>ns</td>
</tr>
<tr>
<td>HDL Δ%</td>
<td>-8</td>
<td>-2</td>
<td>0.1</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>107.2 ± 27.1</td>
<td>104.1 ± 31.2</td>
<td>ns</td>
</tr>
<tr>
<td>LDL Δ%</td>
<td>-43.8</td>
<td>-46.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

Δ % = % change from baseline
* = p value for the comparison of mean

After 4 weeks of treatment, the total cholesterol, triglyceride, HDL-C, LDL-C were reduced from baseline as shown in Table 3. The percentage of reduction of total cholesterol, TG, HDL-C, LDL-C, between generic and original atorvastatin were 28 % VS 28%, 17% VS 24%, 6% VS 3%, 37% VS 35%, respectively (Figure 1).

After 8 weeks of treatment, the total cholesterol, TG, HDL-C, LDL-C were lowered as shown in Table 4. The percent change of total cholersterol, TG, HDL-C, LDL-C were 35% VS 35%, 27% VS 24%, 8% VS 2%, 43% VS 46% respectively (Figure 1). All of the patients in both groups achieved their therapeutic goal after 4 weeks of treatment and total cholesterol, TG, LDL-C were slightly reduced further after 8 weeks of treatment.

The side effects in both groups were mild myalgia observed with both drugs (3.3% VS 3.3%), Two-fold elevation of transaminase (SGOT, SGPT) was found in only one case of generic atorvastatin treatment whereas no major side effect with the original atorvastatin treatment was seen.

Discussion

Currently, the treatment of lipid abnormalities is characterized by the primary use of statins to reduce serum levels of LDL-C. Substantial reductions in cardiovascular morbidity and mortality have been achieved by treatment with statins for primary prevention according to the
AFCAP and ASCOT Trials. Atorvastatin is one of the powerful efficacious statins that reduce LDL-C by 43% according to PROVE-IT–AT.

The results of this study showed that there was statistically no difference in total cholesterol or LDL-C reduction for patients treated with generic or original atorvastatin. Generic atorvastatin and original atorvastatin reduced LDL-C by 37% vs 35% respectively after 4 weeks of treatment and remained decreased (LDL-C by 43% vs 46% respectively) at the end of 8 weeks of treatment. Both drugs achieved total cholesterol reduction by 28% and 35% after 4 weeks and 8 weeks of treatment respectively.

There was statistically no difference in TG and HDL-C change after treatment with generic or original atorvastatin (17% vs 24%, 6% vs 3% and 27% vs 24%, 8% vs 2%) after 4 weeks of treatment and 8 weeks of treatment respectively.

All of the patients in this study achieved their therapeutic goal (LDL-C < 130mg/dL) after 8 weeks of each drug treatment. Half of the sample groups had two risk factors suggestive of treatment to a LDL-C level lower than 100mg/dL, according to NCEP, ATP-III guidelines. Therefore, addition of atorvastatin treatment should be offered to these patients to achieve a therapeutic goal.

In our study original atorvastatin and generic atorvastatin lowered LDL-C by 43% - 46%, and this was comparable to other studies. However, our study showed that HDL-C was decreased with both original and generic atorvastatin.

Overall, the statin class is very well tolerated. The safety assessment of statin drugs has focused on peripheral muscle and the liver and in our study mild myalgia was observed with both drugs (3.3% vs 3.3%). A two-fold elevation of transaminase (SGOT, SGPT) was found in only one case of generic atorvastatin treatment and there was no major side effect with original atorvastatin treatment, therefore, the risk for liver toxicity with generic and original atorvastatin therapy, as evidenced by elevated hepatic transaminases was low.

In conclusion generic atorvastatin offers a cost-effective therapeutic choice for dyslipidemic treatment. In addition, future studies aimed at pharmaco-economical cost-saving measures should evaluate the response rate of original and generic atorvastatin at 20 mg/day in a larger sample size as well as evaluate the efficacy of 10 mg/day of original and generic atorvastatin for efficacy.

The limitation of this study was both drugs were evaluated for a short-period, therefore necessitating long-term studies for practical therapeutic guidelines in Thai patients.

References
3. The LIPID Study Group: Design features and baseline characteristics of the LIPID (Long-Term Intervention with Prevastatin in Ischemic Disease) study: a randomized trial in patients with previous acute myocardial infarction and/or unstable angina pectoris. Am J Cardiol 1995; 76: 474-9.


การเปรียบเทียบการรักษาในผู้ป่วยที่มีไขมันในเลือดคัดปรับภูมิระดับปานกลางระหว่าง Generic atorvastatin กับ Original atorvastatin

พิบูลย์ โชคชนมัสกร, พ.บ.
อาจารย์ประจำวิชาวิทยาและฮอร์โมลด ภาควิชาการรักษารักษา
วิทยาลัยแพทยศาสตร์กรุงเทพมหาวิทยาลัย

จุดประสงค์: เพื่อศึกษาผลของการรักษาผู้ป่วยที่มีไขมันในเลือดคัดปรับภูมิระดับปานกลางด้วย generic atorvastatin เปรียบเทียบกับ Original atorvastatin

บททัศน์: การคัดปรับภูมิระดับไขมันในเลือดเป็นปัจจัยหนึ่งที่สำคัญในการส่งผลให้เกิดภาวะระดับไขมันในเลือดคัดปรับภูมิระดับปานกลาง low-density lipoprotein (LDL), ซึ่งนักวิจัยมักจะศึกษาเกี่ยวกับการคัดปรับภูมิระดับผู้ป่วยที่มีไขมันในเลือดคัดปรับภูมิระดับปานกลางด้วย Original atorvastatin หรือ generic atorvastatin ไม่มีการศึกษาถึงส่วนต่างๆของวิธีการและผลการรักษา.

วิธีการและผลการรักษา: การศึกษาเป็น prospective double blind study ในผู้ป่วยที่มีระดับไขมันในเลือดคัดปรับภูมิระดับปานกลาง 120 คน ได้รับการรักษาด้วย 20 มิลลิกรัม ของ original หรือ generic atorvastatin ในช่วงระยะเวลา 8 สัปดาห์ ทั้ง สองกลุ่มแบ่งสูผู้เข้าอยู่ ช่วงคัดกรอง 2 ช่วง ช่วงที่ 1 และ ช่วงที่ 2 ผู้เข้าร่วมและการรักษาติดตามผลทุก 4 สัปดาห์ที่ผ่านมา ผลการศึกษาพบว่า ไม่มีความแตกต่างในอัตราการสูญสารภาพในกลุ่มรักษา LDL-cholesterol และ total cholesterol ในผู้ป่วยที่ได้รับการรักษาด้วย generic กับ original atorvastatin (43% vs 46%, 35% vs 35%) ตามลำดับ.

บทสรุป: Generic atorvastatin กับ Original atorvastatin มี cost-effectiveness ในการรักษาความคัดปรับภูมิระดับไขมันในเลือด โดยไม่มีความแตกต่างในอัตราการสูญสารภาพ แต่ยังคงมีการศึกษาในผู้ป่วยระดับปานกลางได้ต่อไป.

Paiboon Chotnoparatpat, MD