Effect of statins on lipoprotein (a) in dyslipidemic patients

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INTRODUCTION
Cardiovascular disease (CVD), is the leading cause of mortality in India and the second most common cause worldwide. Due to its increased incidence, the National and International guidelines on cardiac health, target a down-regulation of low-density lipoprotein cholesterol (LDL-C) as a treatment for atherosclerotic CVD. But after the CARE study noted that many patients suffering from cardiovascular events have normal plasma cholesterol levels, the need to identify non-classical and independent risk factors of CVD and develop suitable therapies to minimize their risk became a part of cardiovascular research.

Lipoprotein (a) (Lp(a)) is a circulating lipoprotein composed of liver-derived apo(a) covalently bound to apo(b). It is also similar in lipid composition to apo(b) of LDL. The PRIME study established Lp(a) as a predictor of coronary heart disease. Later increased Lp(a) (>30 mg/dl in many studies) was identified as an independent risk factor for CVD.

Elevated Lp(a) levels in plasma act synergistically with those of LDL-C to increase CVD risk. The LDL-C lowering effect of HMG CoA reductase inhibitors (statins) has been well-documented, but the effect of statins on Lp(a) levels has not been well-established by clinical studies. Although there are some studies that show combination therapies of statins and niacin to reduce Lp(a) levels, statin monotherapy is here to stay as the preferred treatment of hyperlipidemias and prophylaxis for CVD in developing countries like India. Contradictory findings have been reported concerning variations in Lp(a) levels after statin treatment. This calls for a better understanding of statin monotherapies on Lp(a) levels.

Objectives
The following study is aimed at a comparative analysis of the effect of three major statins; simvastatin, atorvastatin, and rosuvastatin, on serum Lp(a) levels among dyslipidemic patients without CVD.
METHODS

Study population

A prospective, randomized, open-label interventional study was conducted in treatment-naive dyslipidemic patients visiting the tertiary care center (Rajah Muthiah Medical College and Hospital, Chidambaram, Tamil Nadu, India) for a routine master health check-up. Patients were screened to assess their eligibility to participate in the study.

Inclusion criteria

1. Patients aged between 40 and 70 years
2. Patients who have read, signed, and agreed to the items listed in the informed consent form

Exclusion criteria

1. Patients having an allergy, hypersensitivity, or intolerance to statins or their derivatives
2. Any patient who has a previous history of substance abuse or dependency
3. Pregnant/lactating women
4. Patients with a history of any of the following:
   • Hepatic or renal impairment
   • Presence of uncontrolled or untreated hypertension or diabetes mellitus
   • Cardiovascular diseases like congestive heart failure. The presence of CVD was assessed by the World Health Organization protocol, which includes a detailed questionnaire and 12-lead electrocardiography
   • Active cancer within the last 5 years or a diagnosis of cancer within the last 5 years
   • Fibromyalgia, myopathy, rhabdomyolysis, unexplained muscle pain or weakness, and/or discontinuation of a statin because of myalgia.

Materials and Methods

The study was approved by the Institutional Human Ethics Committee and was carried out strictly in accordance with International Conference on Harmonization Good Clinical Practice guidelines. Informed consent was obtained from all the patients before their enrollment into the study. It was a 12 weeks study with 85 patients who fulfilled the eligibility criteria. They were randomly assigned to one of the three treatment groups. Group A (n=28) received simvastatin 20 mg once daily (OD); Group B (n=29) received atorvastatin 10 mg OD; and Group C (n=28) received rosuvastatin 5 mg OD. The dosage for each statin in this study was determined based on previous dose efficacy studies. All the study drugs were generic products marketed by Micro Labs Limited, Bangalore, India. The patients were asked to take their study medication every day at bedtime after food. The following flowchart illustrates the movement of study patients through the study (Figure 1).

All patients in the study received their respective study drug for a period of 12 weeks, during which the patients had to make a total of three visits (0, 4th and 12th week). At their first visit, before administration of the study drug, the baseline lipid profile including total cholesterol (TC), LDL, high-density lipoprotein (HDL) and triglycerides (TGL) and Lp(a) values in serum, were recorded. During their second and third visit (4th and 12th week), the patients underwent general physical examination and were assessed for compliance to study medication and any adverse drug reactions. Blood samples were collected for lipid profile analysis and Lp(a) estimation.

Investigations

For the estimation of lipid parameters, about 5 ml of blood was drawn by venipuncture under aseptic conditions in a sterile vacutainer after a fasting period of 12 hrs overnight. Serum was immediately separated by centrifugation (10 mins at approximate 15,000 rpm) and stored at 2~4°C and analyzed for Lp(a) and lipid profile every 10 days. Determination of Lp(a) was done using an in-vitro latex reagent (Manufactured by Biolatex, Spain; Marketed by Diatek, Kolkata, West Bengal, India) by means of particle-enhanced turbidimetric immunoassay method.

TC, HDL and TGL in serum were measured by enzymatic methods using commercially available kits (Biosystems S.A. Barcelona). LDL was calculated by Friedewald’s

Figure 1: The movement of the patients in the three parallel groups of this study and the number of patients who were lost in follow-up at each visit.
formula. All laboratory investigations were carried out following Good Laboratory Practice, at the Department of Biochemistry in Annamalai University, Chidambaram, Tamil Nadu, India.

Statistical methods

The randomization of patients into the three parallel groups was done by an online computer algorithm. The sample size was approved by the Institutional Ethics Committee and was determined by the number of patients visiting the outpatient department for a master health check-up and who fulfilled the eligibility criteria of this study. Descriptive data are expressed as mean±standard deviation. One-way ANOVA was applied for analysis of all the lipid parameters in each group; significance p<0.001. Duncan’s Multiple Range Test was applied for analysis of Lp(a) levels among the three groups; significance p<0.05. All statistical analysis was performed using SPSS version 17.0 (SPSS, Inc., Chicago, Illinois).

RESULTS

Of the 85 patients who were enrolled in the study, a total of 66 patients completed the 12 weeks statin therapy as per the study specifications. Data from patients who completed all the three study visits, 22 in Group A, 23 in Group B and 21 in Group C, were only taken up for statistical analysis. The mean age of the three study groups was almost the same. The ratio of male to female patients in each group was not even. There were about 50% more males than females in each group. The average weight and body mass index of patients in each group at the start of the study was also quite similar for all the three groups. The lipid profile of all the three groups were also similar, except for TGL and Lp(a) values that showed a small variance of 10% between each other. Thus, all the three groups share similar physical and clinical conditions before the start of their respective therapy (Table 1).

After 12 weeks of therapy, atorvastatin was found to be most effective in reducing serum Lp(a) levels. There was an average of 18.73% (p≤0.05) reduction in serum Lp(a) levels from the baseline. This reduction was more significant in the first 4 weeks of atorvastatin therapy, with about 14.65% (p≤0.05) reduction from baseline. Group A patients, treated with simvastatin 20 mg/day also showed little reduction in the serum Lp(a) levels, but it was not significant. On the contrary, Group C patients, treated with rosuvastatin, showed an increase in serum Lp(a) levels throughout the study period. Though this percentage of increase is insignificant, it is noteworthy (Table 2).

Patients who received rosuvastatin 5 mg showed a reduction in the mean serum TC levels by 53.18% (p<0.001) from baseline. Patients who received atorvastatin 10 mg and simvastatin 20 mg had a reduction in average serum TC by 45.40% (p<0.001) and 34.80% (p<0.001) respectively. Patients after atorvastatin therapy showed a significant reduction in average serum LDL levels from baseline after 4 weeks and 12 weeks by 65.47% (p<0.001) and 88.87% (p<0.001) respectively. Similar effect was produced by rosuvastatin on the LDL levels (Table 3).

Considering the mean serum HDL levels, the rosuvastatin group showed a substantial increase by 51.66% (p<0.001) at 4 weeks of therapy. Whereas, this increase in percentage, fell back to 27.23% (p<0.001) at the end of 12 weeks of treatment, the simvastatin and atorvastatin groups showed 38.21% (p<0.001) and 45.10% (p<0.001) increase in serum HDL levels respectively at the end of study period. TGL levels were reduced by all the three groups significantly. No adverse drug reactions were reported during or after this study.

DISCUSSION

CVD is recognized as a dreaded scourge in both developed and developing countries especially after studies established

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Group A (simvastatin 20 mg/day)</th>
<th>Group B (atorvastatin 10 mg/day)</th>
<th>Group C (rosuvastatin 5 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.5±6.7</td>
<td>47.9±7.1</td>
<td>50.8±6.1</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>13 (59.1)</td>
<td>15 (65.2)</td>
<td>12 (57.1)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>9 (40.9)</td>
<td>8 (34.8)</td>
<td>9 (42.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.5±8.6</td>
<td>76.3±8.3</td>
<td>73.4±8.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.3±3.6</td>
<td>29.8±4.2</td>
<td>29.8±3.6</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>222.8±6.9</td>
<td>219.7±10.1</td>
<td>223.4±12.5</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>143.6±8.9</td>
<td>144.0±11.3</td>
<td>145.6±10.2</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>43.2±6.9</td>
<td>39.3±9.7</td>
<td>43.3±9.1</td>
</tr>
<tr>
<td>TGL (mg/dl)</td>
<td>179.5±8.4</td>
<td>181.5±11.9</td>
<td>173.2±22.1</td>
</tr>
<tr>
<td>Lp (a) (mg/dl)</td>
<td>35.7±5.7</td>
<td>39.1±6.2</td>
<td>38.2±5.4</td>
</tr>
</tbody>
</table>

**Values are expressed in mean±SD, BMI: Body mass index, TC: Total cholesterol, LDL: Low density lipoproteins, HDL: High density lipoproteins, TGL: Triglycerides, Lp(a): Lipoprotein (a)**
its role as the leading cause of mortality in India and International community. Although LDL-C has been highlighted as the primary lipid that causes atherosclerotic CVD, the mystery shrouding CVD is not totally resolved. To trace, identify and scrutinize, other non-classical, independent risk factors of CVD, is still a challenge facing the medical professionals.

Lp(a), has been identified as one such independent risk factor for CVD. Owing to our poor knowledge of the metabolic paths of Lp(a), particularly with respect to the catabolism, pharmaceutical science has not yet developed drugs that are able to reduce elevated Lp(a) concentrations to the desired levels. This comparative study of statins was primarily aimed at studying the effect of statins on Lp(a) levels. Although Lp(a) is structurally similar to an LDL moiety, we can’t conclusively explain why it has a contradictory effect in case of rosuvastatin similar to an LDL moiety, we can’t conclusively explain why it has a contradictory effect in case of rosuvastatin which carries an upper hand over rest of the lipid parameters. Further, Hernandez et al. (2011) demonstrated a similar effect in his randomized control trial, that a 12 weeks monotherapy of atorvastatin effectively reduced serum Lp(a) concentration.

**Table 2: Variation in Lp(a) levels at 4 weeks and 12 weeks of treatment period across the three groups.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Visit 1 (baseline)</th>
<th>Visit 2 (4 weeks)</th>
<th>Visit 3 (12 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n=22) (simvastatin 20 mg/day)</td>
<td>35.77±5.78^a</td>
<td>34.86±5.27^a ↓ (2.55%)</td>
<td>34.63±6.26^a ↓ (3.15%)</td>
</tr>
<tr>
<td>Group B (n=23) (atorvastatin 10 mg/day)</td>
<td>39.17±6.23^b</td>
<td>33.43±4.73^a ↓ (14.65%)</td>
<td>31.83±4.93^a ↓ (18.73%)</td>
</tr>
<tr>
<td>Group C (n=21) (rosuvastatin 5 mg/day)</td>
<td>38.24±5.44^b</td>
<td>39.29±5.7^a ↑ (2.75%)</td>
<td>41.52±5.65^a ↑ (8.58%)</td>
</tr>
</tbody>
</table>

**Values are expressed in mean (mg/dl) and ±SD with the percentage variation at 4 weeks and 12 weeks of treatment from baseline. Values not sharing a common superscript differ significantly at p≤0.05. DMRT: Duncan’ multiple range test, SD: Standard deviation, Lp(a): Lipoprotein (a).**

**Table 3: Variations in lipid profile and serum Lp(a) levels at 4 weeks and 12 weeks of treatment period across the three groups.**

<table>
<thead>
<tr>
<th>Lipid profile (mg/dl)</th>
<th>Group A (n=22) simvastatin 20 mg/d</th>
<th>Mean±SD (% variation)</th>
<th>Group B (n=23) atorvastatin 10 mg/d</th>
<th>Group C (n=21) rosuvastatin 5 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>195.27±7.8 ↓ (23.61%)#</td>
<td>182.23±7.1 ↓ (34.80%)#</td>
<td>186.17±9.5 ↓ (29.26%)#</td>
<td>167.7±9.4 ↓ (45.40%)#</td>
</tr>
<tr>
<td>LDL</td>
<td>106.27±8.4 ↓ (49.80%)#</td>
<td>93.59±7.8 ↓ (66.59%)#</td>
<td>94.83±7.8 ↓ (65.47%)#</td>
<td>83.26±7.2 ↓ (88.87%)#</td>
</tr>
<tr>
<td>HDL</td>
<td>58.31±9.5 ↑ (35.30%)#</td>
<td>59.6±9.9 ↑ (38.21%)#</td>
<td>60.65±9.2 ↑ (59.17%)#</td>
<td>55.23±8.9 ↑ (45.10%)#</td>
</tr>
<tr>
<td>TGL</td>
<td>153.45±10.6 ↑ (27.88%)#</td>
<td>145.18±6.9 ↑ (36.63%)#</td>
<td>153.48±9.7 ↑ (29.50%)#</td>
<td>146.04±9.8 ↑ (37.39%)#</td>
</tr>
<tr>
<td>Lp (a)</td>
<td>34.86±5.2 ↓ (2.55%)^a</td>
<td>34.64±6.3 ↓ (3.15%)^a</td>
<td>33.44±4.7 ↓ (14.65%)^a</td>
<td>31.83±4.9 ↓ (18.73%)^a</td>
</tr>
</tbody>
</table>

**Values are expressed in mean (mg/dl) and ±SD with the percentage variation at 4 weeks and 12 weeks of treatment from baseline. #Significance p≤0.001, compared to baseline, ns: Not significant (p≥0.05), TC: Total cholesterol, LDL: Low density lipoproteins, HDL: High density lipoproteins, TGL: Triglycerides, Lp(a): Lipoprotein (a), SD: Standard deviation.**
CONCLUSION

Lp(a) is a proven independent risk factor of CVD, yet it is not being screened for, in general population and LDL levels are still considered as the primary target for controlling CVD. Although there are many other lipid lowering therapies, like nicotinic acid, fibrates and bile acid sequestrates, statins have stood the test of time as the first line therapy for hypercholesterolemia. Combination therapies of statins can only supplement the use of statins but cannot supplant them. In developing countries like India, where pharmacoeconomics plays a major role in the choice of drugs, long-term statin monotherapy is preferred for a better prognosis in CVD patients and for a better prophylaxis in patients identified with a high risk of CVD. This study findings may be limited by its sample size owing to time and financial constraints. But still, this study clearly shows that atorvastatin monotherapy may be a better choice for patients with a high risk of CVD, when compared to other statin monotherapies.

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REFERENCES


