A comparative study of efficacy and safety of pitavastatin versus atorvastatin in the patients of dyslipidemia in medicine department of a tertiary care teaching hospital

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INTRODUCTION

Cardiovascular diseases (CVDs) are the number one cause of death globally. More people die annually from CVDs than from any other cause. Major risk factors for CVD include dyslipidemia, smoking, hypertension, diabetes, increasing age and obesity. Of all common risk factors for CVD, dyslipidemias are the most significant, accounting for 50% of the population-attributable risk for myocardial infarction, and 25% of the population attributable risk for stroke.

Elevated low-density lipoprotein cholesterol (LDL-C) plays a pivotal role in the development of atherosclerosis and constitutes an independent risk factor for subsequent coronary heart disease (CHD). The results of several landmark studies have established that decreasing LDL-C, using 3-hydroxy 3-methyl glutaryl coenzyme A reductase inhibitors (statins), has a beneficial effect in both primary and secondary prevention of CVD. Hence, this study was done to compare the efficacy and safety of atorvastatin versus pitavastatin in patients of dyslipidemias.

ABSTRACT

Background: Cardiovascular diseases (CVDs) are the major cause of death globally. Dyslipidemia is one of the most significant risk factors for CVD. 3-hydroxy 3-methyl glutaryl coenzyme A reductase inhibitors (statins), which are used for the treatment of dyslipidemia, has a beneficial effect in both primary and secondary prevention of CVD. Hence, this study was done to compare the efficacy and safety of atorvastatin versus pitavastatin in patients of dyslipidemias.

Methods: After obtaining ethical clearance from institution and written informed consent from patients, 100 patients included in the study were randomly allocated to any of the following two groups. (1) Group A: Tablet atorvastatin 10 mg given orally once a day for 12 weeks. (2) Group B: Tablet pitavastatin 2 mg given orally once a day for 12 weeks. The primary endpoint of the study was a comparative assessment of change in lipid profile (triglyceride, low-density lipoprotein [LDL], high-density lipoprotein [HDL]) from baseline and after 12 weeks. The secondary endpoint involved recording all the adverse effects during the study.

Results: Analysis of the baseline and post 12 weeks lipid levels by non-parametric unpaired t-test showed a statistically significant increase in HDL-cholesterol (HDL-C) in Group B as compared to Group A (p=0.028 i.e. p<0.05). However, there was no significant difference between two groups in decreasing LDL-cholesterol (LDL-C) (p=0.615).

Conclusions: In this study, pitavastatin is found to be more efficacious than atorvastatin in increasing HDL-C levels, while as efficacious as atorvastatin in decreasing LDL-C in dyslipidemic patients. Atorvastatin is better tolerated than pitavastatin.

Keywords: Dyslipidemia, Atorvastatin, Pitavastatin

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Epidemiological studies have shown that, in addition to elevated LDL cholesterol levels, low levels of high-density lipoprotein cholesterol (HDL-C) are an independent predictor of the risk of CHD, with a strong inverse association between HDL cholesterol levels and the rates of incident CHD events. New approaches to lipid lowering include new uses of proven treatments and development of novel agents. Studies have consistently shown that the higher the plasma level of HDL-C, the lower the risk of cardiovascular events, suggesting that raising HDL-C may be beneficial.7

Pitavastatin being a newer statin need to be studied and its efficacy in lowering LDL-C need to establish. Findings of LIVES study indicate that pitavastatin has not only a potent LDL-C lowering effect but also a long-term HDL-C elevating effect.8

Very few studies are done to compare atorvastatin and pitavastatin in patients of dyslipidemias. So, this study was done to evaluate the efficacy and safety of atorvastatin versus pitavastatin in patients of dyslipidemias.

METHODS

Study design

This was a randomized, open-label, comparative and prospective 12 weeks study. The study was started only after written approval from Institutional Ethics Committee was obtained. From March 2012 to July 2013, all the patients who fulfilled selection criteria were informed regarding their disease, about this study and its aim. Those patients who were willing to participate in the study were included in the study. Then written and signed informed consent was obtained. During the initial visit, demographic data were entered in case record forms. Complete lipid profile was done for all the patients, and their values recorded in case record form. Eligible patients were randomly assigned to two study groups. Patients were evaluated after 6 weeks for drug compliance and adverse effects and after 12 weeks for repeat lipid levels and adverse effects.

Study groups

The patients included in the study were randomly allocated to any of the following two groups.

- **Group A:** Tablet atorvastatin 10 mg given orally once a day for 12 weeks.
- **Group B:** Tablet pitavastatin 2 mg given orally once a day for 12 weeks.

Study population

Inclusion criteria

Newly diagnosed patients of either sex having uncomplicated dyslipidemia, age above 18 years and LDL-C levels >160 mg/dl, HDL-C level <40 mg/dl in males and <50 mg/dl in females.

Exclusion criteria

Patients having other systemic diseases except diabetes mellitus, hypertension, coronary artery disease and CVD were excluded from the study. Patients who have taken other lipid lowering agents besides statins within previous 1-month and patients having hypersensitivity to statins; pregnant women, lactating mothers, and psychiatric patients were also excluded. Use of concomitant medications known to affect the lipid profile or present a potential safety concern; refusal to give written informed consent voluntarily and any other medical condition that, in the opinion of the investigator, may be an unacceptable additional risk to the patient excludes the participation.

At the end of 12 weeks, outcome was measured by following parameters:

1. Percent increase in HDL-C
2. Percent decrease in LDL-C
3. Percent decrease in triglyceride (TG) and total cholesterol (TC)
4. Percent decrease in LDL-C: HDL-C ratio and TC: LDL-C ratio.

Patients were asked for any adverse events. If it was severe the drug was withdrawn. If required treatment for the adverse events (AE) was given.

Statistical analysis

Distribution of study population into two treatment groups according to age was done and mean and standard deviation (SD) were calculated. Unpaired t-test was used to compare the difference between two study groups and paired t-test was used to see the difference within the study groups. p<0.05 was kept as significant in all the statistical analysis.

RESULTS

Efficacy

Totally 100 patients were enrolled in this study. All the patients were randomly allocated into two treatment groups, atorvastatin (Group A) or pitavastatin (Group B). So, 50 patients were enrolled in each group. Percentage changes in LDL-C, HDL-C, TC, TGs, LDL/HDL ratio and TC/LDL ratio from baseline to 12 weeks were taken as efficacy parameters. Analysis of the baseline and post 12 weeks lipid levels by non-parametric unpaired t-test showed a statistically significant change in HDL-C levels (i.e., HDL-C: p=0.028, in favor of pitavastatin) (Table 1) i.e., the rise in HDL-C levels were statistically significant in the pitavastatin group than the atorvastatin group. However, LDL-C, TC, TG, LDL/HDL ratio and TC/LDL ratio showed no significant change in the
two groups (Tables 2-6). The statistical tests were two-tailed, with the level of significance being taken as p≤0.05.

**Safety**

Both the drugs used in the study were very well-tolerated over 12 weeks. Table 7 displays adverse drug reactions (ADRs) reported in two treatment groups. Severity of ADRs was mild and subsided without treatment.

**DISCUSSION**

Effective maintenance of LDL-C targets is important to reduce cholesterol risk on a long-term basis. However, follow-up studies of established statins showed that as many as 6 out of 10 patients stop taking therapy during the first 6 months of treatment. Statin discontinuation and noncompliance may be due to a variety of factors, including high statin dosage, polypharmacy, lack of titration, intolerance, and complicated treatment regimens.

In large clinical studies, considerable evidence shows that first line statin therapy effectively achieves LDL-C target levels in a wide range of patients. Socioeconomic factors may also affect LDL-C target attainment and maintenance: women, the elderly and ethnic minorities are often undertreated for atherogenic

| Table 1: Comparison of HDL-C levels before and after administration of study drug in both groups. |
|----------------------------------------------------------|-------------------------------------|-------------------------|-------------------------------|----------------------|
| Group | HDL-C at baseline (0 week) Mean (SD) | HDL-C after treatment (12 weeks)* Mean (SD) | % of reduction | p value |
|-------|--------------------------------------|-------------------------------------------|--------------------------|-----------|
| Atorvastatin | 36.22 (10.55) | 39.22 (5.90) | 7.65 | <0.001 |
| Pitavastatin | 32.38 (8.40) | 36.60 (4.72) | 11.54 | <0.001 |

*p=0.028 i.e., p<0.05 by non-parametric unpaired t-test for “after” treatment values between the two groups. HDL-C: High-density lipoprotein cholesterol, SD: Standard deviation

| Table 2: Comparison of LDL-C levels before and after administration of study drug in both groups. |
|----------------------------------------------------------|-------------------------------------|-------------------------|-------------------------------|----------------------|
| Group | LDL-C at baseline (0 week) Mean (SD) | LDL-C after treatment (12 weeks)* Mean (SD) | % of reduction | p value |
|-------|--------------------------------------|-------------------------------------------|--------------------------|-----------|
| Atorvastatin | 149.10 (42.38) | 108.32 (26.23) | 27.36 | <0.001 |
| Pitavastatin | 143.58 (40.58) | 105.60 (27.53) | 26.16 | <0.001 |

*p=0.615 by non-parametric unpaired t-test for “after” treatment values between the two groups. LDL-C: Low-density lipoprotein cholesterol, SD: Standard deviation

| Table 3: Comparison of TC levels before and after administration of study drug in both groups. |
|----------------------------------------------------------|-------------------------------------|-------------------------|-------------------------------|----------------------|
| Group | TC levels at baseline (0 week) Mean (SD) | TC after treatment (12 weeks)* Mean (SD) | % of reduction | p value |
|-------|--------------------------------------|-------------------------------------------|--------------------------|-----------|
| Atorvastatin | 217.61 (61.61) | 176.03 (29.01) | 19.11 | <0.001 |
| Pitavastatin | 209.04 (52.14) | 172.72 (28.61) | 17.38 | <0.001 |

*p=0.567 by non-parametric unpaired t-test for “after” treatment values between the two groups. TC: Total cholesterol, SD: Standard deviation

| Table 4: Comparison of TG levels before and after administration of study drug in both groups. |
|----------------------------------------------------------|-------------------------------------|-------------------------|-------------------------------|----------------------|
| Group | TG levels at baseline (0 week) Mean (SD) | TG after treatment (12 weeks)* Mean (SD) | % of reduction | p value |
|-------|--------------------------------------|-------------------------------------------|--------------------------|-----------|
| Atorvastatin | 200.84 (151.20) | 147.14 (44.83) | 26.74 | 0.002 |
| Pitavastatin | 193.34 (87.18) | 152.54 (34.65) | 21.11 | <0.001 |

*p=0.502 by non-parametric unpaired t-test for “after” treatment values between the two groups. TG: Triglyceride, SD: Standard deviation

| Table 5: Comparison of LDL/HDL ratio before and after administration of study drug in both groups. |
|----------------------------------------------------------|-------------------------------------|-------------------------|-------------------------------|----------------------|
| Group | LDL/HDL levels at baseline (0 week) Mean (SD) | LDL/HDL after treatment (12 weeks)* Mean (SD) | % of reduction | p value |
|-------|--------------------------------------|-------------------------------------------|--------------------------|-----------|
| Atorvastatin | 4.29 (1.29) | 2.80 (0.70) | 34.74 | <0.001 |
| Pitavastatin | 4.50 (1.00) | 2.91 (0.80) | 35.54 | <0.001 |

*p=0.444 by non-parametric unpaired t-test for “after” treatment values between the two groups. LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SD: Standard deviation
We used in our study. Their results show decrease in LDL-C level in the pitavastatin group and atorvastatin group after treatment for 8 weeks were 36.8% and 37.9%, respectively (p=0.61). There was no statistically significant difference between two groups in decreasing LDL-C level. So, above study supports our study. CHIBA study conducted by Yokote et al.\(^{23}\) shows similar effect of LDL-C reduction as in present study.

One another 8 weeks comparative study conducted in Korea\(^{24}\) shows LDL-C reduction was 44.4% in the pitavastatin (2 mg) group and 43.2% in the atorvastatin (10 mg) group, indicating no significant difference between the groups (p=0.41). Hence, this study supports present study. However in above study and CHIBA study reduction in LDL-C is significantly higher than the present study.

A study conducted in Europe by Budinski et al.\(^{25}\) shows LDL-C reductions similar to present study. A study conducted in Thiland\(^{26}\) also supports our study. In JAPAN-ACS study\(^{27}\) LDL-C reduction was equivalent in the pitavastatin and atorvastatin groups (36.2% and 35.8%, respectively, p=0.9) which also supports our study.

The role of HDL-C is still being assessed in lipid-lowering therapy. A meta-analysis done by Brown et al.\(^{28}\) concluded that since HDL-C elevation and LDL-C reduction are statistically independent for moderate percentage changes, these could be considered additive. A study conducted by Cardenas et al.\(^{29}\) also reports the pro-atherogenic properties of low HDL-C concentrations in patients with diabetes or metabolic syndrome.

In the present study, mean increase in HDL-C in atorvastatin group was 7.65% and in pitavastatin group was 11.54%. Both groups show significant difference (p<0.001) in increase in HDL-C level. Unpaired t-test between group A and group B also shows significant difference (p=0.028 i.e. <0.05, in favor of pitavastatin).

The study in Europe\(^{25}\) was conducted in 821 patients which shows no significant difference between atorvastatin and Pitavastatin groups in the percent changes in increase in HDL-C (4% and 3%, respectively, p=0.840). Hence, it contradicts our study. PIAT study\(^{7}\) shows that pitavastatin was significantly superior to atorvastatin with regard to increase in HDL-C levels after 52 weeks (8.8% vs. 3.6%, respectively, p=0.034). So, this study supports our study.

### Table 6: Comparison of TC/LDL ratio before and after administration of study drug in both groups.

| Group   | TC/LDL levels at baseline (0 week) Mean (SD) | TC/LDL after treatment (12 weeks)* Mean (SD) | % of reduction | p value |
|---------|--------------------------------------------|---------------------------------------------|----------------|---------|
| Atorvastatin | 6.33 (2.01)                                  | 4.55 (0.80)                                 | 28.13          | <0.001  |
| Pitavastatin | 6.62 (1.48)                                  | 4.77 (0.85)                                 | 27.95          | <0.001  |

\(*p=0.187\) by non-parametric unpaired t-test for “after” treatment values between the two groups. LDL: Low-density lipoprotein, TC: Total cholesterol, SD: Standard deviation

### Table 7: Number of ADRs reported in both the groups.

| Number of patients | ADR       | Total |
|--------------------|-----------|-------|
| Group A (n=50)     | 2         | Dizziness 5 |
|                    | 2         | Headache 2   |
|                    | 1         | Dyspepsia 1  |
| Group B (n=50)     | 3         | Myalgia 9    |
|                    | 3         | Dizziness 2   |
|                    | 2         | Dyspepsia 2   |
|                    | 1         | Insomnia 1    |

ADRs reported in two treatment groups. Severity of ADRs was mild and subsided without treatment. ADRs: Adverse drug reactions.

As such, there remains a need for an effective, well-tolerated statin that can provide a good balance of cardioprotective benefits and improved multiple lipid parameters over the long-term, using a lower dosage and a simple treatment regimen.

The present study shows that most common age group was between 41 and 60 years. Number of males and females in both the groups were 70 and 30, respectively. So, male patients are more in both the groups.

Pitavastatin was launched in Japan in 2003, South Korea in 2005 and Thailand in 2008. Since then, it has been successfully used in these countries as a first-line statin therapy to treat dyslipidemia in a wide range of patients, including the elderly and those on concurrent medications.\(^{21}\) LDL-C lowering effect of pitavastatin was expected to compare well with the clinically most commonly used other statins.

This study set out to investigate this hypothesis by comparing the pitavastatin (2 mg) with the most commonly used dose of atorvastatin (10 mg).

Atorvastatin is available at a range of doses up to 80 mg/day and has end point studies to demonstrate the effect of LDL-C reduction on outcomes.\(^{22}\) There are very few studies comparing atorvastatin with pitavastatin in patients of dyslipidemia.

In the present study, reduction in LDL-C in the pitavastatin group and atorvastatin group after treatment for 12 weeks were 26.16% and 27.36%, respectively (p=0.62). Similarly in PIAT study conducted by Sasaki et al.\(^{7}\) compared atorvastatin 10 mg versus pitavastatin 2 mg. Doses used were same as problems.\(^{18-20}\) As such, there remains a need for an effective, well-tolerated statin that can provide a good balance of cardioprotective benefits and improved multiple lipid parameters over the long-term, using a lower dosage and a simple treatment regimen.

In above study and CHIBA study reduction in LDL-C is significantly higher than the present study.
CHIBA study\textsuperscript{23} indicated that in patients with metabolic syndrome LDL-C reduction in the pitavastatin group showed a tendency to be significantly superior to that in the atorvastatin group (p=0.050), and the percent change in TG (25.2\%, p<0.001) as well as HDL-C (6.7\%, p=0.019) was statistically significant in the pitavastatin group when compared to atorvastatin.

A study conducted by Budinski et al.\textsuperscript{25} shows mean reduction in TC with atorvastatin was 27.7\% and with pitavastatin was 28.1\% (p=0.684) while in our study mean reduction in TC was 19.11\% and 17.38\%, respectively (p=0.567). Both the studies indicate no significant difference between the groups. In this study mean reduction in TG was 14.1\% and 17.7\% in atorvastatin and pitavastatin groups respectively (p=0.236). So, there is no significant difference between groups in both the studies. In this regard, reference study supports our study.

Regarding safety and tolerability, the overall incidence of AE was more with pitavastatin, and the majority of them were mild to moderate in intensity.

**CONCLUSIONS**

From the results and discussion it can be concluded that pitavastatin and atorvastatin are effective in improving lipid profile in patients of dyslipidemia. Pitavastatin is more effective than atorvastatin in increasing HDL-C while as effective as atorvastatin in reducing LDL-C, TC, TG, LDL-C:HDL-C ratio and TC:LDL-C ratio. Atorvastatin is better tolerated than pitavastatin. However whether these drugs will provide a mortality or morbidity benefit need to be evaluated.

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**Ethical approval:** The study was approved by the Institutional Ethics Committee

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