Post-marketing Study of Clinical Experience of Atorvastatin 80 mg vs 40 mg in Indian Patients with Acute Coronary Syndrome- A Randomized, Multi-centre Study (CURE-ACS)

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Abstract

Objective: To generate comparative clinical data in Indian patients with acute coronary syndrome (ACS) in terms of safety and efficacy of atorvastatin 80 mg vis-à-vis atorvastatin 40 mg

Materials and Methods: A total of 236 patients with diagnosed ACS (with TIMI Risk score ≥ 3) within preceding 10 days were randomized to receive either atorvastatin 80 mg or atorvastatin 40 mg once daily for 12 weeks. Out of 236 patients, data for 173 was analyzed who had both baseline and post-baseline lipid assessment. The primary end point of the trial was percentage change in LDL-C at the end of treatment from baseline. Other end points were change in high sensitivity C reactive protein, incidence of increase in liver enzymes ≥3 times upper limit of normal and incidence of myotoxicity (with or without elevation of creatinine phosphokinase) at the end of treatment.

Results: A dose-dependent response was observed with greater reduction of LDL- C in atorvastatin 80 mg (27.5% vs 19.04%) than that of atorvastatin 40 mg group. Both the treatment groups had a significant reduction (p<0.001) in LDL-C at the end of 6 and 12 weeks in comparison to baseline. hs-CRP was also significantly reduced (p<0.001) in both the treatment groups i.e. atorvastatin 80 mg (76.15%) and atorvastatin 40 mg (84.4%) from baseline at the end of 12 weeks. Both doses of atorvastatin were well tolerated. No patient had elevation of (≥ 3 times of upper limit of normal) liver enzymes or creatinine phosphokinase. One patient on atorvastatin 80 mg complained of myalgia. There were no dose-related differences in incidence of adverse events between two treatment groups.

Conclusion: The CURE-ACS trial indicated that atorvastatin 80 mg was more effective than atorvastatin 40 mg in terms of reduction in LDL cholesterol and was as safe and well tolerated as 40 mg dose in Indian patients with ACS.

Introduction

Coronary artery disease (CAD) rates were identical in India and the US (United States) till 1968.1 During the past 3 decades, CAD rates have doubled in India, whereas these rates have halved in most developed countries, especially the US.2 As a result of these opposing trends, CAD rates are now 4-fold higher in India compared to the U.S.1 Though contemporary mortality data from India are unavailable, the totality of the data reviewed suggests that an epidemic of CAD is already set in.1

Furthermore, the urban population in India is projected to double by the year 2020. Therefore, the CAD burden in India is likely to increase exponentially due to changing lifestyle and urbanization of villages.3 Angiographic studies show that aggressive cholesterol reduction by a variety of methods, as opposed to dietary modifications alone, results in increased rates of plaque regression and stabilization.4

The results of the TNT5 and IDEAL6 trials established the important role for intensive statin therapy in the management of patients with stable CAD, and extend the observations from PROVE IT TIMI 227 in ACS patients to patients with stable disease.

The MIRACL5 trial demonstrated that treatment with atorvastatin 80 mg daily, initiated early after presentation with ACS and maintained for 16 weeks, resulted in a significant reduction of early recurrent ischemic events, including both cardiac events and stroke when compared with treatment with placebo.

Atorvastatin 80 mg has been extensively used in management of ACS and stable CHD patients in the western world. Such patients benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels. In the Indian context, there is no data about usage of atorvastatin 80 mg either in ACS patients or stable CHD patients. This may be due to safety concerns of usage of higher dosage of statins in Indian patients.

In order to generate reliable data and build a confidence for usage of intensive lipid lowering therapy in patients with acute coronary syndrome, the current ‘clinical experience’ trial was planned. Hypothesis of this trial was that high dose atorvastatin i.e. 80 mg would be as safe and tolerable and would be more effective in terms of LDL-C lowering than atorvastatin 40 mg.

The study objective was to evaluate safety and efficacy of atorvastatin 80 vis-à-vis atorvastatin 40 mg in Indian patients with acute coronary syndrome and generate relevant clinical data.

Methods

Study design

The Cure-ACS, a multi-centre study, was conducted at

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7 cardiology centers spread across India from October 2009 to December 2010. The study was conducted according to the protocol and in accordance with the Ethical guidelines by ICMR. The study design was multicenter, open-label, randomized, controlled, comparative, parallel group. The study was conducted at each trial site after receiving approval from institutional ethics committee and DCGI (Drug Controller General of India). The study was registered in clinical trial registry - India (CTRI/2009/091/000687).

**Patient population**

Diagnosed or hospitalized patients within 10 days of acute coronary syndrome with TIMI score ≥ 3 of either gender in the age group of 18-75 years were screened to check their eligibility for enrolment in the study. Written informed consent was obtained from each patient before screening. At the time of screening, these patients needed to be in a stable condition without heart failure. At the time of screening, laboratory investigations which included complete blood count (CBC), liver function tests, serum creatinine, lipid profile, creatinine phosphokinase and hs-CRP were performed. ECG recordings of patients were also done at screening.

**Patients meeting any one of the following criterion were excluded from the study**

1. Current therapy with highest therapeutic dose of any statin including atorvastatin 80 mg
2. Coronary artery bypass grafting (CABG) within the previous 2 months or scheduled to undergo bypass surgery
3. Liver dysfunction (ALT and/or AST more than 2 times uLN)
4. Creatinine phosphokinase (CPK) elevation more than 3 times the ULN
5. Renal impairment (Serum creatinine levels more than 2.0 mg/dl)
6. Patients on drugs which are strong inhibitors of cytochrome p450 3 A4 enzymes like macrolid antibiotics (such as erythromycin, roxithromycin etc.),azole antifungals (ketoconazole, fluconazole etc.), cyclosporine, gemfibrozil etc.

**Study visit schedule and treatment plan**

In this study, there were total 4 study visits: Screening visit (Day -5 to 0), Enrolment Visit (Day 2), Follow-up visit 1 (Day 44) and Follow-up visit 2 (Day 86). Enrolled patients were provided allocated study medications for three months and they were evaluated during study period at the end of 6 weeks and 12 weeks for safety and efficacy evaluation.

Lipid profile, liver function tests, creatinine phosphokinase, hs-CRP were repeated at the end of 6 weeks. Laboratory investigations, performed at the time of screening were repeated at the end of study.

All the blood biochemistry was done by Metropolis Healthcare Ltd., Mumbai. Metropolis is a NABL (National Accreditation Board for Testing and Calibration Laboratories), CAP (College of American Pathologists) accredited Central Laboratory providing clinical trial services. A well-qualified ICH-GCP (International Conference on Harmonization- Good Clinical Practice), GLP (Good Laboratory Practice) trained project management team with extensive clinical trial laboratory experience was involved in conduct of the blood biochemistry investigations. Standardized methods were used uniformly for blood sample collection, transfer and testing.

**Patients were evaluated based on the following endpoints**

Primary endpoint: Percentage change in LDL-C at the end of treatment (12 weeks) from baseline

Secondary end points
1. Percentage change in hs-CRP at the end of treatment (12 weeks) from baseline
2. Incidence of myotoxicity (i.e. evidence of muscle pain, soreness, weakness and/or cramps with or without CPK elevation) at the end of treatment (12 weeks)
3. Incidence of increase in liver enzymes (ALT and AST) ≥ 3 times UNL at the end of treatment (12 weeks)

The following other safety parameters were also evaluated:

Any other adverse effects that were reported voluntarily, observed and enquired during the study.

Any clinically significant change in the value of laboratory, vital signs and physical examination during the study was compared to baseline.

**Statistical analysis**

**Sample size**

Desired sample size for the study taking a standard deviation of 2.7 for LDL-C from the study10 for a power of 80% for 5% level of significance was a minimum of 80 patients per treatment arm which could detect even a small difference of 1.20 between two treatments in the primary endpoint (i.e. LDL-C).

Clinical trials like HPS (Heart Protection Study), 4S (Scandinavian Simvastatin Survival Study) etc. have documented how much reduction in relative risk for major coronary events can be achieved from a given lowering of LDL-C. They indicate that for every 1% reduction in LDL-C levels, relative risk for major CHD events is reduced by approximately 1%.11

That means even a small difference in LDL-C reduction can contribute significantly in reducing cardiovascular mortality.

In our study, we had a total of 173 evaluable patients.

**Method of randomization**

Patients meeting eligibility criteria were enrolled in the study and randomized in 1:1 ratio to receive either atorvastatin (Lipicure) 80 mg or atorvastatin (Lipicure) 40mg. Patients were assigned to the study arm using a computer generated randomization sheet. The block randomization was done for 50 patients at each centre.

Randomization allocation concealment was maintained. Randomization sequence was generated by medical monitor of sponsor and patients were enrolled and randomized by principal investigators at their respective trial sites.

Data generated at the end of treatment period was considered as end point data. In case any patient failed to complete the trial, the last set of data generated was considered as end point data. Evaluation of efficacy and safety was done as per full analysis set, which consisted of all randomized patients who at least completed the first follow-up visit. Analysis of data was done by applying Wilcoxon test for within group comparison and Mann-Whitney test was applied for comparison between the groups. The level of significance was 5%.

**Results**

A total of 236 patients were randomized to either atorvastatin 40 mg (n=116) or atorvastatin 80 mg (n=120). Number of patients lost to follow-up immediately after randomization and not completed even the first follow-up visit on day 44 were 27 (n=12 and 15 in atorvastatin 40 mg and 80 mg respectively). Number of patients with protocol non compliance was 36 (n= 11 and 25 in atorvastatin 40 mg and 80 mg respectively). Protocol non-
compliance was defined as: Patients failing to visit the study centre for assessment on scheduled date with allowed window period of ± 4 days. Difference of 10% in non-compliance between two treatment groups was because of more no. of patients did not turn up for follow-up visits with allowed window period of ± 4 days in atorvastatin 80 mg.

These patients were excluded from the analysis. Data of 173 evaluable patients (n= 93 of atorvastatin 40 mg and n=80 of atorvastatin 80 mg) was analysed (Figure 1).

Table 1 shows baseline characteristics of patients. Majority of patients in both treatment groups were male (80% and 84% from atorvastatin 40 mg and 80 mg respectively). Patients from both groups had matching baseline characteristics in terms of age, gender, weight and body mass index.

More number of patients from atorvastatin 80 mg group had concomitant hypertension (73.75% vs 53.76%) and diabetes mellitus (41.25% vs.30.11%) than that of atorvastatin 40 mg.

Prior statin therapy [n (%)]
- Other illness [n (%)]
- Hypothyroidism [n (%)]
- Hypertension [n (%)]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Atorvastatin 40 (n=93)</th>
<th>Atorvastatin 80 (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean± SD)</td>
<td>55.12±10.25</td>
<td>57.83±9.49</td>
</tr>
<tr>
<td>Male [n [%]]</td>
<td>74 (79.57)</td>
<td>67 (83.75)</td>
</tr>
<tr>
<td>Female [n [%]]</td>
<td>19 (20.43)</td>
<td>13 (16.25)</td>
</tr>
<tr>
<td>Weight (Kg; mean± SD)</td>
<td>69.04±14.32</td>
<td>69.11±14.34</td>
</tr>
<tr>
<td>BMI (Kg/m²; mean± SD)</td>
<td>25.05±4.15</td>
<td>25.05±4.14</td>
</tr>
</tbody>
</table>

Concomitant Illness

| Hypertension [n [%]] | 50 (53.76) | 59 (73.75) |
| Diabetes mellitus [n [%]] | 28 (30.11) | 33 (41.25) |
| Peripheral Vascular Disease [n [%]] | 1 (1.08) | 0 (0) |
| Hypothyroidism [n [%]] | 2 (2.15) | 2 (2.5) |
| Other illness [n [%]] | 9 (9.68) | 17 (21.25) |
| Prior statin therapy [n [%]] | 36 (38.71) | 39 (48.75) |

Table 1: Overall disposition of patients

Fig. 1: Overall patient characteristics

Table 2: Evaluation of primary and secondary endpoints (n=173)

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Treatment Groups</th>
<th>Mean±SD</th>
<th>95% CI</th>
<th>% Reduction from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Atorvastatin 40</td>
<td>80.95±26.19</td>
<td>75.54-86.35</td>
<td>-</td>
</tr>
<tr>
<td>LDL-C (mg/dl) (Primary end point)</td>
<td>Atorvastatin 40</td>
<td>80.46±24.87</td>
<td>74.92-86.01</td>
<td>-</td>
</tr>
<tr>
<td>Day 44</td>
<td>Atorvastatin 40</td>
<td>66.61±21.25</td>
<td>62.23-70.99</td>
<td>17.72% (p&lt;0.001)</td>
</tr>
<tr>
<td>Day 86</td>
<td>Atorvastatin 40</td>
<td>59.44±18.14</td>
<td>59.0-63.48</td>
<td>26.12% (p&lt;0.001)</td>
</tr>
<tr>
<td>p value 0.024 for LDL-C reduction on Day 86 between Liprice 40mg and Liprice 80 mg</td>
<td>Atorvastatin 80</td>
<td>65.54±22.84</td>
<td>60.83-70.25</td>
<td>19.04% (p&lt;0.001)</td>
</tr>
<tr>
<td>hs-CRP (mg/L) (Secondary end point)</td>
<td>Atorvastatin 40</td>
<td>58.33±18.11</td>
<td>29.0-62.36</td>
<td>27.5% (p&lt;0.001)</td>
</tr>
<tr>
<td>Day 44</td>
<td>Atorvastatin 40</td>
<td>14.23±24.59</td>
<td>9.13-19.33</td>
<td>-</td>
</tr>
<tr>
<td>Day 86</td>
<td>Atorvastatin 40</td>
<td>13.92±21.76</td>
<td>9.08-18.77</td>
<td>-</td>
</tr>
<tr>
<td>p value 0.045 for hs-CRP reduction on Day 86 between Atorvastatin 40mg and Atorvastatin 80 mg</td>
<td>Atorvastatin 40</td>
<td>3.24±8.35</td>
<td>1.48-4.99</td>
<td>77.73% (p&lt;0.001)</td>
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<tr>
<td>Day 86</td>
<td>Atorvastatin 40</td>
<td>2.64±5.14</td>
<td>1.47-3.80</td>
<td>81.03% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin 80</td>
<td>2.22±3.45</td>
<td>1.51-2.94</td>
<td>84.4% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin 80</td>
<td>3.32±3.59</td>
<td>0.25-6.39</td>
<td>76.15% (p&lt;0.001)</td>
</tr>
</tbody>
</table>
Discussion

Since their introduction in the late 1980s, statins have established a prominent place in therapeutics as a class of drugs that can achieve relatively large reductions in plasma cholesterol levels and thereby, ameliorate vascular atherosclerosis and reduce cardiovascular morbidity and mortality. These beneficial effects result from their ability to reduce endogenous cholesterol biosynthesis and increase the expression of low density lipoprotein (LDL) receptors, which are responsible for LDL-Cholesterol uptake and clearance from plasma. However, the statins vary in their pharmacological characteristics and dose-related efficacy in reducing LDL-C. Among the statins, atorvastatin exhibits a number of pharmacokinetics characteristics that are different to the other members of the class. For example, it is the only statin with a metabolite that has an ability to inhibit HMG-CoA reductase that is equivalent to that of the parent compound.

The widespread use of statins has resulted in significant benefit for patients with coronary artery disease. Over the last decade or so, large, randomized clinical trials have consistently shown that statins reduce mortality and morbidity from cardiovascular disease, whether used as primary or secondary prevention. When used in acute coronary syndromes and stable coronary artery, statins in high dose can lead to a significant reduction of clinical adverse events. Furthermore, the benefits of statin therapy can be extended beyond their lipid lowering ability, with proven effect on platelet adhesion, thrombosis, endothelial function, inflammation and plaque stability.

The Cure-ACS study was specifically designed to evaluate the safety and efficacy of high dose (80 mg) of atorvastatin in Indian patients with high risk acute coronary syndrome.

The results of this study confirmed the hypothesis that increased dose of atorvastatin results in incremental reduction in LDL-C. The reduction in LDL cholesterol would translate in more reduction in ischemic events. In this study, baseline LDL-C was relatively low in both treatment groups in contrast to that of reported in previous studies like PROVE IT TIMI 22. One of the reasons for baseline low LDL-C in this study may be prior statin therapy in almost 40-50% patients before enrolment in the study.

In the PROVE IT TIMI 22 trial, intensive therapy with high dose atorvastatin 80 mg resulted in a median LDL-C level of 62 mg/dl, as compared with a level of 95 mg/dl for standard dose (40mg) pravastatin. Despite relatively low baseline levels of LDL-C (80.46 ± 24.87 mg/dl) in our study, 12 weeks of atorvastatin 80 mg produced a significant reduction to mean level of 58.33 ± 18.1 mg/dl (27.5%), a level lower than that achieved with active treatment in the Scandinavian Simvastatin Survival study survival study (4S), PROVE IT TIMI 22 trial.

The majority of trials on statin therapy in the last decade have examined the effect of lowering LDL-C by 25-40%. In the 4S study, the mean LDL-C reduction was 35%. A sub-study of the PROVE IT TIMI 22, in which patients with prior acute coronary syndrome, treated with intensive atorvastatin therapy, were divided in different groups depending on the specific LDL-C levels attained (>80-100 mg/dl, > 60-80 mg/dl, 40-60 mg/dl and ≤ 40 mg/dl), indicated that the lowest occurrence of cardiovascular events was in the groups with the lowest LDL-C levels (26.1%, 22.2%, 20.4% and 20.4% respectively) for various groups.

Our finding reinforce the strategy outlined in the update to the NCEP clinical practice guidelines aimed at achieving the lowest LDL-C levels possible, particularly in high risk patients with CHD. In our study, a statistically non-significant increase in HDL-C at the end of 12 weeks of treatment from baseline was observed in atorvastatin 40 mg and atorvastatin 80 mg (2.28% vs 0.38% respectively) groups. With regard to HDL-C levels, there appears to be a trend in some trials towards a lesser increases in this parameter as the atorvastatin dosage is increased.

In the STELLAR trial, average increases in HDL-C levels were 4.8-5.7% with dosage of 10-20 mg/day, 4.4% with 40 mg/day and 2.1% with atorvastatin 80 mg/day. Patients from both treatment groups had significant reduction in hs-CRP at the end of 12 weeks. A significant reduction in hs-CRP was observed in both treatment groups. Both doses (40 mg and 80 mg) of atorvastatin were very well tolerated. No hepatotoxicity was reported in any of the patients treated. Except in a single case who complained of myalgia in atorvastatin 80 mg group all others tolerated it very well. In none of the patients clinically significant elevation of creatinine phosphokinase was observed.

In this study, there were no dose-related differences in incidence of adverse events between two treatment groups. As the study was neither planned nor powered to compare reduction in ischemic events, it is not possible to comment on these parameters.

Conclusion

The Cure-ACS study is the only study comparing high doses of atorvastatin (80 mg vs 40 mg) in Indian patients with acute coronary syndrome. Based on the results of the study, it is concluded that atorvastatin 80 mg is as safe and tolerable as 40 mg. Atorvastatin 80 mg was found be more effective than atorvastatin 40 mg in terms of reduction in LDL cholesterol. Patients presenting with acute coronary syndrome within preceding 10 days can safely be started on high dose (80 mg) of atorvastatin.

Limitations of Study

- This was not a double –blind study.
- Duration of study was short i.e. 12 weeks. Though this study duration was adequate to evaluate change in primary efficacy endpoint i.e. LDL-C and secondary endpoint (hs-CRP), it was inadequate to evaluate long-term safety of high dose of atorvastatin.
- Primary efficacy endpoint in the study was not a hard clinical endpoint but a surrogate endpoint.

Conflict of Interest

- Lead principal investigator and other principal investigators received a financial aid from Intas Pharmaceuticals Ltd. for conducting the study.
- Dr. Hanmant Barkate and Dr. R.C. Rane are full time employees of Intas Pharmaceuticals Ltd.
- Dr. Chhavi Jindal is an ex-employee of Intas Pharmaceuticals Ltd.

Source of Funding

This work was financially supported by Intas Pharmaceuticals Limited, Ahmedabad (India).

Note: Brand of atorvastatin used in this trial was Lipicure®, manufactured and supplied by Intas Pharmaceuticals Ltd., Ahmedabad.

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References