Research Article

Lipid modifying action of atorvastatin in escalating doses in patients of coronary artery disease

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INTRODUCTION

India is passing through an epidemic of coronary artery disease (CAD) and it is expected to be the most important cause of mortality in India by the year 2015.1 The usual lipid profile prevalent in Indians is relatively low high-density lipoprotein cholesterol (HDL-C) and high triglycerides (TG) with normal or slightly elevated low-density lipoprotein cholesterol (LDL-C).2 Statin-mediated lowering of LDL-C is regarded as the foundation of lipid-modifying therapy. However, this has failed to reduce cardiovascular event rates more than 20-40% relative to placebo indicating the need for comprehensive lipid modification as well as control of non-lipid risk factors to combat the residual risk. Since low levels of HDL-C are established as a strong independent risk factor for cardiovascular disease (CVD), lifestyle modification and pharmacological measures must be taken together to achieve the target.4 Atorvastatin, a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase lowers LDL-C significantly, but has very little impact on HDL-C. It is frequently used in doses 10 mg, 20 mg, 40 mg and 80 mg for different levels of LDL-C elevation at baseline and the magnitude of associated major adverse cardiac event risk in future.

Various studies indicate that statins (which include atorvastatin), tend to decrease LDL-C for an additional 6% on doubling the dose at each level from 10 to 80 mg. This is popularly known as the “Rule of six,” but from literature search no such data for eastern Indian population could be established. Indians are expected to differ in their lipid distribution pattern as compared to their Caucasian counterpart owing partly to different genetic constitution and different lifestyle. Hence, the present study was undertaken to ascertain whether the same rule holds good for our population or not and also to assess the efficacy and tolerability of atorvastatin in escalating doses (10 mg, 20 mg, 40 mg and 80 mg) in modulating the lipid profile in patients of coronary artery disease in eastern Indian population and whether “Rule of six” commonly referred to in context of low-density lipoprotein (LDL) reduction by statins stands true in our population.

METHODS: Patients randomly allocated into four groups (n=632) as per selection criteria. Groups A, B, C, D received atorvastatin 10 mg, 20 mg, 40 mg and 80 mg, respectively once daily at bedtime, for 24 weeks after which evaluation of efficacy and tolerability was done. Comparison between groups performed with one-way ANOVA; p<0.05 considered to be statistically significant.

RESULTS: There was a significant reduction in cholesterol, LDL and triglycerides in all the groups, but between group comparisons did not reveal any significant reduction in lipid parameters between Groups C and D. “Rule of six” was not observed at higher doses of atorvastatin (40, 80 mg). Further, there was significant reduction of high-density lipoprotein (HDL) in Groups C and D, which is not accepted especially in Indian context where it is already low at baseline.

CONCLUSION: In Indian perspective, where HDL is low, and the LDL values are not very high, escalating dose of atorvastatin does not give additional clinical benefit. On the contrary, reduction of HDL itself predicts an adverse cardiovascular outcome. Increased adverse events and burden of cost must be taken into account, while prescribing atorvastatin.

Keywords: Atorvastatin, Low-density lipoprotein, Rule of six

ABSTRACT

Background: A prospective, randomized controlled study with parallel treatment groups carried out to assess efficacy and tolerability of atorvastatin in escalating doses (10 mg, 20 mg, 40 mg and 80 mg) in modulating the lipid profile in patients of coronary artery disease in eastern Indian population and whether “Rule of six” commonly referred to in context of low-density lipoprotein (LDL) reduction by statins stands true in our population.

Methods: Patients randomly allocated into four groups (n=632) as per selection criteria. Groups A, B, C, D received atorvastatin 10 mg, 20 mg, 40 mg and 80 mg, respectively once daily at bedtime, for 24 weeks after which evaluation of efficacy and tolerability was done. Comparison between groups performed with one-way ANOVA; p<0.05 considered to be statistically significant.

Results: There was a significant reduction in cholesterol, LDL and triglycerides in all the groups, but between group comparisons did not reveal any significant reduction in lipid parameters between Groups C and D. “Rule of six” was not observed at higher doses of atorvastatin (40, 80 mg). Further, there was significant reduction of high-density lipoprotein (HDL) in Groups C and D, which is not accepted especially in Indian context where it is already low at baseline.

Conclusion: In Indian perspective, where HDL is low, and the LDL values are not very high, escalating dose of atorvastatin does not give additional clinical benefit. On the contrary, reduction of HDL itself predicts an adverse cardiovascular outcome. Increased adverse events and burden of cost must be taken into account, while prescribing atorvastatin.
tolerability of atorvastatin (10, 20, 40, 80) mg in modifying lipid profile in patients of CAD in our population.

METHODS

The study was conducted in the departments of Cardiology, Biochemistry and Pharmacology of Medical College, Kolkata, West Bengal, India, during the period June 2011-December 2012. The study protocol and procedure was approved by the Institutional Ethics Committee. Written informed consent was taken from each participant in their own language before they entered the study. The patient screening and recruitment was carried out at the cardiology outpatients department. Preliminary groundwork, maintenance of study documents and medications was done in the custody of the principal investigator. All biochemical tests were done by the Department of Biochemistry, which is a National Accreditation Board for Testing and Calibration Laboratories accredited laboratory.

The current study is a prospective, randomized, controlled study with four parallel treatment groups. Patients finally entering the study were randomly allocated into four groups (n=632) according to their baseline LDL-C values. Group A (n=216) (LDL-C 100-149) received ATR-10; Group B (n=198) (LDL-C 150-159) received ATR-20; Group C (n=140) (LDL-C 160-169) received ATR-40; Group D (n=78) (LDL-C ≥170) received ATR-80 for a period of 24 weeks (168 days). The final end-of-study assessment and evaluation of tolerability and efficacy was done on completion of 24 weeks. No further medication was dispensed to the subject although they were advised an optimal medical therapy.

Subject selection criteria

Screening for eligibility of the patient was done based on the following criteria:

Inclusion criteria

- Patients of either sex
- Age 31-75 years
- Known case of CAD which includes:
  - Past history of acute coronary syndrome: both STEMI and NSTEMI,
  - Effort angina with positive tread mill stress test
  - History of coronary revascularization.
- Willingness to give written informed consent.

Exclusion criteria

- Known hypersensitivity to atorvastatin or other statins
- Significant renal impairment (creatinine clearance <60 ml/min)
- Decompensated congestive heart failure
- Clinically significant physical and mental abnormalities
- Abnormal liver function test
- Patients on any drugs, which influence hepatic microsomal enzyme system or drugs, which alter serum lipid profile
- Patients who had received any hypolipidemic drugs within 6 months of entering study
- Any other drug known to interact with or potentially alter the response to the study drugs.

Procedure at different visits

At baseline, the medical history was taken and the potential recruits were subjected to clinical examination to assess their suitability for participation in the study. Baseline investigations such as serum lipid profile, urea, creatinine, transaminase, fasting blood sugar, and electrocardiogram was done. Body weight, resting pulse rate, and blood pressure (BP) were also recorded. Follow-up was done after 12 and 24 weeks or earlier on appearance of any adverse symptoms such as myalgia, and hepatitis. that required thorough assessment of the patient. At each visit, medical history was taken, clinical examination performed including recording of heart rate and BP, study drugs were dispensed as per the dosage schedule and compliance determined. Adverse events were elicited from the history, physical and biochemical examination. Serum transaminase was routinely measured at baseline and at the end while serum creatinine kinase was estimated only in suspected cases of myopathy and considered as significant only when values were ten times the upper limit of normal value.

The final end-of-study assessment and evaluation of tolerability and efficacy was done on completion of 24 weeks. No further medication was dispensed to the subject although they were advised an optimal medical therapy.

Study termination

For an individual subject the study was terminated in the following circumstances:

- On completion of 24 weeks of study medication.
- Missing more than 50% of the scheduled doses or interruption of study medication for more than 3 consecutive doses by the study subject.
- Any other serious complication not related to the study drugs.
- In the event of an adverse event deemed serious enough to warrant withdrawal.
- In the event of protocol violation by study subject e.g., use of non-permitted concomitant medication.
- Any other situation which, in the opinion of the Project Clinician or the Principal Investigator, is not conducive to further continuation of the subject in the study from the viewpoint of the subject’s safety or the sanctity of the trial data.
**Statistical analysis**

The results obtained from the study were presented in the following section in a tabulated manner. The results are expressed in mean±SD. Comparison between the groups was performed with one-way ANOVA. p<0.05 was considered as statistically significant (Graph pad Instat Version 3.05, Graph Pad Software, San Diego, CA, USA).

**RESULTS**

Of 815 patients screened for enrolment in the study, 632 subjects (31-75 years) entered the study, of which 57.8% were male. The mean age was 43.2 years in male and 49.3 years in female. The study was completed by 538 (85.1%) subjects (Table 1).

The most common reason for discontinuation was drop outs, followed by unacceptable adverse events. 190 (88%) patients discontinued therapy due to musculoskeletal pain of which eight belonged to ATR-80 group though evidence was highest in the ATR-80 group (25.6%). Eighteen (20) patients discontinued treatment due to musculoskeletal pain though evidence of myopathy was confirmed in two patients only. However, the reasons for drop-outs were not followed-up (Table 2).

At the end of study period of 24 weeks, individual assessment of biochemical parameters show substantial reduction in TC, LDL-C and TG level in all the arms. The percentage reduction of LDL-C was 28.8%, 34.5%, 39.1% and 41.25% in the four groups (A, B, C, D), respectively. This indicates that though there is increased reduction of LDL-C with increase in dose, the “Rule of six” fades away at higher doses and the percentage increase from previous dose becomes less with higher doses. There was slight increase (1.2%) in HDL level in ATR-10 group; a marginal (1.4%) reduction in HDL in ATR-20 group; (3.7%) reduction in ATR-40 group; maximum (5.4%) reduction in ATR-80 group (Tables 3a-d).

**DISCUSSION**

Increasing tendency toward urbanization, adoption of western lifestyle and obesity threatens a substantial future burden of cardiovascular morbidity and mortality in the developing nations. Dyslipidemia, an important cause of increased cardiovascular risk, is heterogeneous in presentation with elevated LDL-C, increased TG and low HDL-C. Moreover, Indians often present with a characteristic dyslipidemic phenotype that includes low HDL-C, normal or near-normal LDL-C, increased small dense LDL and TG. This phenotype predicts an increased risk of adverse cardiovascular outcome due to accumulation of TG-rich remnants and the more atherogenic small LDL-particles with reduced cardiovascular protection due to low HDL-C.

International guidelines specify target concentrations of LDL-C to reduce the risk of coronary heart disease. In clinical practice, statins are the most commonly used drug in conjunction with lifestyle measures (for example, smoking cessation, increased physical activity and diet modification) to control CVD risk and other appropriate interventions (for example, drugs to control chronic conditions such as high BP and diabetes mellitus). There is a direct relationship between the fall in LDL-C and the reduction in cardiovascular system risk. For every 1% reduction in the LDL-C level, the relative risk for major coronary heart disease events is reduced by approximately 1%.

Statins inhibit HMG CoA reductase, an enzyme involved in cholesterol synthesis. Inhibition of HMG CoA reductase lowers LDL-C levels by slowing down the production of cholesterol in the liver and increasing the liver’s ability to remove the LDL-C already in the blood. Statins reduce LDL by 20-60%, decrease triglycerides by 10-40%, and increase HDL by 5-15%. The “Rule of six” commonly referred to statin monotherapy states that the dose needs to be doubled for each 6% incremental reduction in LDL-C level over the baseline achieved with the starting dose. Clinical evidence substantiates that this “Rule of six,” is a characteristic of all of the statins, including atorvastatin. Though, the western literature supports the “Rule of six” in context to reduction of LDL-C by escalating dose of atorvastatin (10, 20, 40, 80 mg), the same was not reproduced in the present study when the dose was escalated to 40 mg and 80 mg of atorvastatin daily. This could be due to ethnic variation and typical lipid profile of our population. Furthermore, the dose of atorvastatin prescribed was determined on the baseline value of LDL-C of study subjects, which could be another possible explanation of the outcome of the study.

Barter and O’Brien recently reported a study of increasing doses of atorvastatin and simvastatin in 1028 patients with primary hypercholesterolaemia and baseline total cholesterol levels ranging 201-367 mg/dl. After 6 weeks of treatment, 38% of patients achieved the target level with 10 mg of atorvastatin daily. It was only when the former dose was increased to the maximum of 80 mg that 83% of

**Table 1: Distribution of study population according to sex and age in years.**

| Sex   | Age in years | N (%) | Mean age±SD |
|-------|--------------|-------|-------------|
|       | 31-40        | 41-50 | 51-60 | 61-70 | 71-80 |       |
| Male  | 44           | 126   | 105   | 54    | 36    | 365 (57.8) | 43.2±2.23 |
| Female| 15           | 64    | 126   | 38    | 24    | 267 (42.2) | 49.3±1.98  |

SD: Standard deviation
patients achieved the target level after 24 weeks of therapy. Attainment of target cholesterol levels also depends on the baseline level. As expected, higher baseline total cholesterol levels were associated with smaller percentages of patients achieving target levels, even with escalation of the statin dose.15

More than three decades ago, Framingham study16 identified low HDL-C as an independent risk factor for adverse cardiovascular outcome. Data from the study suggests that the risk of CAD in a patient with elevated LDL-C and normal HDL-C is comparable with the risk in a patient with well-controlled LDL-C and low HDL-C. Atorvastatin, in contrast to some other statins, appears to lose its HDL-raising effect at higher doses and even reduces the HDL-C.17,18 In VOYAGER (An individual data meta-analysis of statin therapy in risk groups: effects of rosuvastatin, atorvastatin and simvastatin) a positive relationship between doses of simvastatin/rosuvastatin and HDL has been noted, whereas there is negative relationship between dose of atorvastatin and HDL. Thus greater reduction in HDL-C with increasing doses of atorvastatin might predict an adverse cardiovascular outcome even at the backdrop of controlled LDL-C values. In a study from Gujrat, India, it has been observed that even a smaller dose i.e., 10 mg atorvastatin daily for 8 weeks significantly reduced HDL-C from baseline, although after the treatment period, all the other parameters were well

Table 2: Summary of adverse events between the groups during the study period (causes for discontinuation of therapy).

| Group     | Drop-out | Myalgia | CPK elevation (10 times or more) | Total |
|-----------|----------|---------|---------------------------------|-------|
| ATR-10    | 23       | 3       | -                               | 26 (12) |
| (recruited 216) |          |         |                                 |       |
| ATR-20    | 19       | 4       | -                               | 23 (11.6) |
| (recruited 198) |      |         |                                 |       |
| ATR-40    | 20       | 5       | -                               | 25 (17.9) |
| (recruited 140) |      |         |                                 |       |
| ATR-80    | 12       | 8       | 2                               | 20 (25.6) |
| (recruited 78) |      |         |                                 |       |
| Total     | 632      | 74      | 20                              | 94 (14.9) |

CPK: Creatine phosphokinase

Table 3a: Effects on the lipid profile and serum transaminase of atorvastatin 10 mg after 24 weeks.

| Atorvastatin 10 (n=216) | Cholesterol | LDL | TG | HDL |
|-------------------------|-------------|-----|----|-----|
| Baseline                | 204.3±12.1  | 126.1±11.5 | 176.7±14.1 | 41.3±8.3 |
| 24 weeks                | 164.8±13.4  | 89.8±8.6  | 133.7±12.6 | 41.8±9.6  |
| Mean reduction          | 59.5±6.7    | 36.3±7.2  | 43.0±4.7   | 0.5±0.4   |
| % reduction in 24 weeks | 26.5        | 28.8     | 24.3       | -1.2      |
| p value                 | <0.0001     | <0.0001   | <0.0001    | 0.59      |

Results are expressed as mean±SD (n=216); p<0.05 taken as significant. LDL: Low-density lipoprotein, TG: Triglycerides, HDL: High-density lipoprotein, SD: Standard deviation

Table 3b: Effects on the lipid profile and serum transaminase of atorvastatin 20 mg after 24 weeks.

| Atorvastatin 20 (n =198) | Cholesterol | LDL | TG | HDL |
|--------------------------|-------------|-----|----|-----|
| Baseline                 | 218.3±13.1  | 154.4±6.5 | 184.7±10.8 | 41.6±5.3 |
| 24 weeks                 | 153.4±9.4   | 100.8±8.6 | 136.2±11.2 | 40.9±6.9 |
| Mean reduction           | 64.9±6.9    | 53.6±7.4  | 48.5±4.7   | 0.7±0.4   |
| % reduction in 24 weeks  | 29.72       | 34.5     | 26.3       | 1.4       |
| p value                  | <0.0001     | <0.0001   | <0.0001    | 0.59      |

Results are expressed as mean±SD (n=198); p<0.05 taken as significant. LDL: Low-density lipoprotein, TG: Triglycerides, HDL: High-density lipoprotein, SD: Standard deviation

Table 3c: Effects on the lipid profile and serum transaminase of atorvastatin 40 mg after 24 weeks.

| Atorvastatin 40 (n=140) | Cholesterol | LDL | TG | HDL |
|-------------------------|-------------|-----|----|-----|
| Baseline                | 224.5±11.9  | 166.2±5.16 | 193.7±8.3 | 42.5±7.3 |
| 24 weeks                | 146.8±7.4   | 101.2±7.27 | 137.2±11.1 | 40.9±8.1 |
| Mean reduction          | 67.7±6.7    | 65.6±5.9  | 56.5±5.9   | 1.6±0.4   |
| % reduction in 24 weeks | 30.15       | 39.1     | 29.2       | 3.7       |
| p value                 | <0.0001     | <0.0001   | <0.0001    | 0.59      |

Results are expressed as mean±SD (n=140); p<0.05 taken as significant. LDL: Low-density lipoprotein, TG: Triglycerides, HDL: High-density lipoprotein, SD: Standard deviation
within the target normal range in the majority of patients, the significant decrease in HDL-C level pointing toward further dose reduction to 5 mg atorvastatin on daily basis, in this population.\(^5\) In the present study, though there was a marginal increase in HDL-C with ATR 10 mg/day, there was progressive reduction of the same with further increase in dose to 20/40/80 mg/day to the extent 5.4% in ATR 80 group. Considering the lipid profile of Indian population this should be considered as a potential caveat for increasing the dose of ATR over 20 mg/day as monotherapy. This should be either treated through a different statin with no such effect on HDL-C reduction or (e.g. rosuvastatin) or through a combination of other lipid-modifying agents that do not affect HDL-C adversely.

Adverse events associated with statins include headache, altered liver function, paraesthesia and gastrointestinal effects (including abdominal pain, flatulence, diarrhoea, nausea, and vomiting). Rash and hypersensitivity reactions have been reported, but are rare. Muscle effects (myalgia, myositis and myopathy) have also been reported with the use of statins. Severe muscle damage (rhabdomyolysis) is a very rare, but significant side-effect.\(^5\) It was observed that with escalation of doses, the incidences of adverse events also increased to the extent of discontinuation in therapy. In ATR 80 group eight out seventy-eight patients were compelled to discontinue therapy due to myalgia and two of them have developed myopathy. This finding corroborates with the study of Pedersen where they observed that patients treated with atorvastatin 80 mg were more likely to discontinue therapy due to adverse effects than with moderate doses of the drug (p<0.05).\(^5\)

In the Indian perspective where the LDL values are not very high, and HDL-C values are strikingly low, therapeutic measures, which untowardly reduces HDL-C can pose as an independent risk factor that predicts an adverse cardiovascular outcome. Escalating dose of atorvastatin does not give additional clinical benefit. On the contrary, there is reduction of HDL, which itself predicts an adverse cardiovascular outcome. There are also increased adverse events and the burden of cost must also be taken into account, while prescribing atorvastatin. Considering the lipid profile of Indian population this should be considered as a potential caveat for increasing the dose of ATR over 20 mg/day as monotherapy. This should be either treated through a different statin with no such effect on HDL-C reduction or (e.g. rosuvastatin) or through a combination of other lipid-modifying agents that do not affect HDL-C adversely.

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