

Comparative Evaluation of the Efficacy and Safety of Rosuvastatin vs Atorvastatin in patients of Dyslipidemia with Coronary Heart Disease in Indian Scenario.

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Abstract : The majority of clinical trials investigating the efficacy and safety profile of rosuvastatin and atorvastatin have focused on North American or western and northern European populations. Therefore, it is timely to confirm the effects of these agents in Indian patient populations in routine clinical practice. Objectives of the study was to compare the effect of rosuvastatin vs atorvastatin on LDL, total cholesterol, HDL and triglycerides and to compare the safety profile of these two drugs. This randomized, open study was conducted on 100 patients of CHD (coronary heart disease) having dyslipidemia attending the OPD/Wards of Department of Medicine, Pt. B.D.Sharma PGIMS Rohtak. Chronic patients of coronary heart disease having serum LDL-cholesterol >100 mg/dl and aged e" 18 years were included in the study. The patients were randomly divided into 2 groups of 50 each, group A and B. Group A was put on Rosuvastatin 10 mg and Group B was put on Atorvastatin 20 mg. The patients were followed at 3 and 6 months and their efficacy and safety profile was compared. The mean percentage fall in LDL in group A was significantly more than group B both at 3 and 6 months (33.78% and 37.66% vs 29.59% and 33.76%). The mean percentage fall in total cholesterol in group A was significantly more than group B both at 3 and 6 months (22.30% and 25.07% vs 20.18% and 22.95%). The mean percentage increase in HDL in group A was significantly more than group B at both 3 and 6 months (8.08% and 9.92% vs 4.99% and 6.12%). The mean percentage fall in triglycerides in group A was comparable to group B at both 3 and 6 months (14.74% and 19.32% vs 15.52% and 19.66%). In group A 45(90%) patients achieved the ATP-III serum LDL goal of 100 mg/dl and in group B, 37(74%) patients achieved ATP-III serum LDL goal of 100 mg/dl at the end of 6 months ($p < 0.05$). Prevalence of side effect in general was low. In group A, 2(4%) patients complained of nausea and similar number of patients complained of myalgia in form of mild muscle ache and tiredness. No patient showed significant increase in serum transaminase levels. In group B, 2(4%) patients complained of nausea and 1(2%) patient complained of myalgia. No patient showed significant increase in transaminase levels. There was no significant difference between the two groups ($p > 0.05$). **Conclusion:** The study concluded that both the drugs had significant effect on the lowering serum LDL cholesterol, total cholesterol, triglycerides and on increasing serum HDL levels. Rosuvastatin 10 mg was significantly more effective than atorvastatin 20 mg in lowering LDL, total cholesterol and increasing HDL levels. Significantly more patients achieved ATP III LDL goal of 100 mg/dl with rosuvastatin than with atorvastatin. Both the drugs were tolerated and incidence of side effects was low.

INTRODUCTION

Dyslipidemia is a heterogeneous group of disorders of lipid metabolism that results from accelerated or retarded degradation of lipoproteins that transport cholesterol and triglycerides through plasma and consists of excessive accumulation or lowered levels of one or more of major lipids transported in plasma and is a manifestation of one or more abnormalities of metabolism of transport¹. Dyslipidemia is inseparably associated with atherosclerosis and both have a close relation right from initiation to the final stages leading to clinical events. The World Health Organization estimates that dyslipidemia is associated with more than half of global cases of ischemic heart disease and more than 4 million deaths per year². Atherosclerosis remains the major cause of death and premature disability in industrialized countries and emerging as one of the most concerned public health problems in developing countries like India. With rapid industrialization and urbanization, sedentary life style, the problem is heading towards epidemic proportions. Coronary artery

disease accounts for 12 million deaths annually over the globe³. In United States only, 13.5 million individuals have documented coronary artery disease and each year 1.5 million individuals suffer a myocardial infarction with approx. 0.5 million deaths⁴. Among conventional risk factors in atherosclerosis, dyslipidemia is the most important modifiable risk factor. Derangement of any one or more than one of various lipid and lipoprotein constituents (e.g. total cholesterol, LDL-C, HDL-C, VLDL-C, or triglycerides) has their relative contribution to atherogenesis⁵. The relationship of dyslipidemia with atherosclerosis has been established by various observational studies⁶⁻⁹. Serum LDL-C as a CAD risk meets most of the criteria established by Koch in 19th century to inculcate as an aetiological agent of disease¹⁰. Several committees including U.S. National Cholesterol Education Program (ATP-III guidelines), European Atherosclerosis Society (EAS) and British Hyperlipidemia Association hold LDL-C as primary target for lipid lowering therapy. The HMG-CoA reductase inhibitors represent the major advances in prevention of coronary artery disease. In landmark Primary & Secondary Prevention trials, treatment with these agents have been associated with 24-37% decrease in coronary mortality and morbidity¹¹. They are the most widely used hypolipidemic drugs

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worldwide. A large number of trials have affirmed their efficacy and a large number of studies are underway to know about the specific potency of different statins. The two most commonly used statins i.e. Rosuvastatin and Atorvastatin differ markedly with respect to dyslipidemia. The data is very scarce on comparison of these two drugs in this part of the world. So we planned this study we to compared the efficacy and safety of two statins rosuvastatin and atorvastatin in context to the Indian patients of coronary artery disease with dyslipidemia.

MATERIAL AND METHODS

This study was conducted on 100 patients of CHD (coronary heart disease) having dyslipidemia attending the OPD/Wards of Department of Medicine, Pt. B.D. Sharma PGIMS Rohtak. Patients aged ≥ 18 years having Serum LDL-cholesterol >100 mg/dl were included. Patients having Hypersensitivity to statins, Pregnancy/nursing mothers, Diabetes mellitus, Active liver disease, Acute or chronic renal failure, Nephrotic syndrome, Uncontrolled hypothyroidism, isolated hypertriglyceridemia, muscle disorder, known gastric acid disease/peptic ulcer disease, having concurrent intake of drugs affecting plasma lipid concentration or known to interact with study medication (OCP's, digoxin, erythromycin, azole antifungal) were excluded from the study. The study was conducted on 100 patients. The patients were randomly divided into 2 groups of 50 each, group A and B. Group A was put on Rosuvastatin 10 mg and Group B was be put on Atorvastatin 20 mg per day. All the patients were advised standardized therapeutic lifestyle changes (TLC) / life style modification in the form of Smoking cessation, Weight reduction in overweight individuals and to maintain weight in normal weight individuals, to avoid the saturated fats and take polyunsaturated fats instead. Patients were encouraged to eat complex carbohydrates and soluble dietary fiber, physical activity of at least 30 minutes walking 5 days a week, moderate alcohol consumption for those who drink alcohol (up to two pegs per day for men and one peg per day for women).

This study began by recording lipid profiles in every patient at start and was followed at 3 and 6 months and their serum lipid profile, blood urea, serum creatinine, SGOT and SGPT levels were done. The percentage fall in LDL levels in both the groups was calculated. Percentage of patients meeting the NCEP ATP-III LDL goal of 100 mg/dl was calculated. Also the effect on total cholesterol, triglycerides and HDL were compared. The patients were looked for the toxicity of the drugs if any and the safety profiles of the two drugs were compared.

RESULTS

Out of total 100 patients, 78 were males and 22 were females. In group A, 41(82%) were males and 9(18%) were females. In group B, 37(74%) were males and 13(26%) were females. In group A, mean age of males was 51.9 years and mean age of females was 58.66 years while in group B, mean age of males was 52.45 years and mean age of females was 58.84 years.

The mean percentage fall in LDL was 33.78% vs 29.59 in the two groups at 3 months and 37.66% vs 33.76% at 6 months. In both group A and B, at the end of 3 and 6 months the decrease was highly significant ($p<0.001$).In group A, the percentage decrease was more than group B and was highly significant ($p<0.001$) both at end of 3 and 6 months (table 1).

Table 1: Mean Percentage Decrease in Serum Ldl at 3 and 6 Months

GROUP	0 vs 3 Months	0 vs 6 months
A	33.78	37.66
B	29.59	33.76

The mean percentage fall in total cholesterol was 22.30% vs 20.18% at 3 months and 25.07 vs 22.95 at 6 months in the two groups. In both group A and B, at the end of 3 and 6 months the decrease was highly significant ($p<0.001$).In group A, the percentage decrease was more than group B and was significant ($p<0.05$) both at end of 3 and 6 months (table 2).

Table 2: Mean percentage decrease in serum total cholesterol at 3 and 6 months

GROUP	0 vs 3 Months	0 vs 6 months
A	22.30	25.07
B	20.18	22.95

The mean percentage increase in HDL were 8.08 vs 4.99 at 3 months and 9.92 vs 6.12 at 6 months in the two groups. In both group A and B, at the end of 3 and 6 months the increase in HDL was highly significant ($p<0.001$).In group A, the percentage increase was more than group B and was highly significant ($p<0.001$) both at end of 3 and 6 months (table 3).

Table 3: Mean percentage increase in serum Hdl at 3 and 6 Months

GROUP	0 vs 3 Months	0 vs 6 months
A	8.08	9.92
B	4.99	6.12

The mean percentage fall in serum triglycerides were 14.74% vs 15.52% at 3 months and 19.32% vs 19.66% at 6 months in the two groups. In both group A and B, at the end of 3 and 6 months the decrease was highly significant ($p<0.001$).In group A, the percentage decrease was comparable to group B and the difference between the two groups was not significant ($p>0.05$) both at end of 3 and 6 months (table 4).

Table 4: Mean percentage decrease in Serum Triglycerides at 3 and 6 months

GROUP	0 vs 3 Months	0 vs 6 months
A	14.74	19.32
B	15.52	19.66

In the present study, in group A 45(90%) patients achieved the ATP-III serum LDL goal and in group B, 37(74%) patients achieved ATP-III serum LDL goal 100 mg/dl at the end of 6 months. This difference is statistically significant ($p<0.05$) in the favor of group A.

Prevalence of side effect in general was low. In group A, 2(4%) patients complained of nausea and similar number of patients complained of myalgia in form of mild muscle ache and tiredness. No patient showed significant increase in transaminase levels. In group B, 2(4%) patients complained of nausea and 1(2%) patient complained of myalgia. No patient showed significant increase in transaminase levels. There was no mortality and no patient was dropped from the study due to any side effect.

DISCUSSION

The mean percentage fall in LDL in group A in present study were 33.78% at 3 months and 37.66% at 6 months. In group B the percentage fall were 29.59% and 33.76% at 3 and 6 months respectively. In both group A and B, at the end of 3 and 6 months the decrease was highly significant ($p < 0.001$). In group A, the percentage decrease was more than group B and was highly significant ($p < 0.001$) both at end of 3 and 6 months. This was in accordance with MERCURY 1¹² trial which observed 47.0% reduction with rosuvastatin 10 mg and 43.7% reduction with atorvastatin ($p < 0.001$), PULSAR¹³ study which observed 44.6% reduction with rosuvastatin 10 mg and 42.7% with atorvastatin 20 mg ($p < 0.05$). Similarly STELLAR¹⁴ trial observed 45.8% reduction with rosuvastatin 10 mg and 42.6% reduction with atorvastatin 20 mg ($p < 0.001$). In contrast ARIES¹⁵ study observed 37.1% reductions with rosuvastatin 10 mg and 38.5% with atorvastatin 20 mg (p - not significant).

The mean percentage fall in total cholesterol in group A in present study were 22.30% at 3 months and 25.07% at 6 months. In group B the percentage fall were 20.18% and 22.95% at 3 and 6 months respectively. In both group A and B, at the end of 3 and 6 months the decrease was highly significant ($p < 0.001$). In group A, the percentage decrease was more than group B and was significant ($p < 0.05$) both at end of 3 and 6 months. This was in accordance with MERCURY 1 trial which observed 32.5% reduction with rosuvastatin 10 mg and 30.9% reduction with atorvastatin ($p < 0.001$), PULSAR study which observed 30.8% reduction with rosuvastatin 10 mg and 30.7% with atorvastatin 20 mg (p - not significant). Similarly STELLAR trial observed 32.9% reduction with rosuvastatin 10 mg and 31.8% reduction with atorvastatin 20 mg (p - not significant). In contrast ARIES study observed 26.6% reductions with rosuvastatin 10 mg and 28.7% with atorvastatin 20 mg (p - not significant).

The mean percentage rise in HDL in group A in present study were 8.08% at 3 months and 9.92% at 6 months. In group B the percentage rise were 4.99% and 6.12% at 3 and 6 months respectively. In both group A and B, at the end of 3 and 6 months the percentage increase was highly significant ($p < 0.001$). In group A, the percentage increase was more than group B and was highly significant ($p < 0.05$) both at end of 3 and 6 months. This was in accordance with MERCURY 1 trial which observed 9.2% increase with rosuvastatin 10 mg and 5.7% increase with atorvastatin ($p < 0.001$), PULSAR study which observed 6.4% rise with rosuvastatin 10 mg and 3.1% with atorvastatin 20 mg ($p < 0.001$). Similarly STELLAR trial observed 7.7% increase with rosuvastatin 10 mg and 4.8% increase with atorvastatin 20 mg ($p < 0.002$). ARIES study also observed 7.0% rise in serum HDL with rosuvastatin 10 mg and 3.7% with atorvastatin 20 mg ($p < 0.05$).

The mean percentage fall in triglycerides in group A in present study were 14.74% at 3 months and 19.32% at 6 months. In group B the percentage fall were 15.52% and 19.66% at 3 and 6 months respectively. In both group A and B, at the end of 3 and 6 months the decrease was highly significant ($p < 0.001$). In group A, the percentage decrease was comparable to group B and the difference between the two groups was not significant ($p > 0.05$) both at end of 3 and 6 months. MERCURY 1 trial observed 18.9% reduction with rosuvastatin 10 mg and 18.3% reduction with atorvastatin ($p < 0.01$), PULSAR study observed 17.9% reduction with rosuvastatin 10 mg and 19.1% with atorvastatin 20 mg (p - not significant), STELLAR trial observed 19.8% reduction with rosuvastatin 10 mg and 22.6% reduction with atorvastatin 20 mg (p - not significant). ARIES study observed 16.0% reductions with rosuvastatin 10 mg and 19.6% with atorvastatin 20 mg (p - not significant).

The present study has shown that both rosuvastatin and atorvastatin have their effect on all lipid parameters. Both reduce serum LDL, total cholesterol, serum triglycerides and raise serum HDL level. Rosuvastatin 10 mg was more effective than atorvastatin 20 on all these parameters except on serum triglycerides on which effect was comparable in two groups.

In the present study, in group A 45(90%) patients achieved the ATP-III serum LDL goal and in group B, 37(74%) patients achieved ATP-III serum LDL goal of 100 mg/dl at the end of 6 months. This difference is statistically significant ($p < 0.05$) in the favor of group A and is in accordance with landmark trials¹²⁻¹⁴.

Prevalence of side effect in general was low and both the drugs were well tolerated. There was no serious side effect. In group A, 2(4%) patients complained of nausea and similar number of patients complained of myalgia in form of mild muscle ache and tiredness. No patient showed significant increase in transaminase levels. In group B, 2(4%) patients complained of nausea and 1(2%) patient complained of myalgia. No patient showed significant increase in transaminase levels. Comparing the overall incidence of side effects, between group A and group B, there was no significant difference between the two groups ($p > 0.05$).

CONCLUSION

In this randomized open study on 100 patients of coronary artery disease having dyslipidemia, we compared two most widely used statins; rosuvastatin and atorvastatin. The study concluded that both the drugs had significant effect on lowering serum LDL cholesterol, total cholesterol, triglycerides and on increasing serum HDL levels. Rosuvastatin 10 mg was significantly more effective than atorvastatin 20 mg in lowering LDL, total cholesterol and increasing HDL levels. Significantly more patients achieved ATP III LDL goal of 100 mg/dl with rosuvastatin than with atorvastatin. Both the drugs were tolerated and incidence of side effects was low.

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