

COMPARATIVE EFFICACY AND SAFETY PROFILE OF 5 MG ROSUVASTATIN VERSUS 10 MG ROSUVASTATIN IN PATIENTS WITH ISCHEMIC HEART DISEASE

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ABSTRACT

Objectives: To compare the efficacy and clinical profile of 5 mg rosuvastatin versus 10 mg rosuvastatin in improving the management of patients with IHD.

Material and Methods: This study was jointly conducted by Department of Pharmacology, Khyber Medical College, and Cardiology Department of Khyber Teaching Hospital from January 2011 to August 2011. The patients presenting to coronary care unit and cardiology OPD were randomized into a two groups; Group A and Group B each comprising 50 patients. Group A received 5 mg of rosuvastatin and Group B received 10 mg of rosuvastatin for three months. National cholesterol Education programme adult treatment panel III (NCEP ATP III) guideline for LDL-C was chosen as the primary objective while assessing the safety profile and toxicity was considered the secondary end point. A rise in HDL-C was also anticipated.

Results: Thirty-four (68%) patients in group A and 41 (82%) patients in group B were male. All the patients were resident of Peshawar. Their mean ages were 51.4 ± 7.6 and 49.35 ± 5.65 years respectively in group A and B. The LDL-C dropped to NCEP ATP III value of < 100 mg/dL in 3 (26%) patients in group A compared to 4 (8%) in group B $P < 0.0004$. LDL-C levels after the 3 month treatment showed a mean reduction of 66.2 ± 3.8 and 84.1 ± 4.3 in group A and B respectively implying 39.02% and 48.38 % reduction with a P value < 0.0001 . The reduction to total cholesterol (TLC) was 31.69% (mean 83.2 ± 7.5) and 41.28% (mean 107.0 ± 3.3) in the respective groups with a P value of < 0.0001 . The significant value for triglycerides was a $P < 0.04$ for group B while the HDL-C improvement was 0.0006 in group B (receiving 10 mg rosuvastatin). The reported increase in the incidence of myalgia and muscle weakness was statistically insignificant $P < 0.06$.

Conclusion: Rosuvastatin; clinically proven antilipidemic agent for the management of IHD has a better efficacy with almost identical adverse effects in 10 mg doses as compared with 5 mg doses and this satisfies the NCEPATP III guidelines.

Keywords: Ischemic heart disease, low density lipoprotein, high density lipoprotein, high density lipoprotein efficacy, safety profile, rosuvastatin.

INTRODUCTION

Hypercholesterolemia is a major risk factor for atherosclerosis along with hypertension, diabetes mellitus, smoking, male gender and age¹. This atherosclerosis is then the pathophysiology for the target organ damage like coronary artery disease (CAD) clinically presenting with ischemic heart disease (IHD)². Among the subset of cholesterol, low density lipoprotein cholesterol (LDL-C) are associated with greater morbidity and mortality while high density lipoprotein cholesterol (HDL-C) have a protective effect³. Subsequently guidelines aiming at low LDL-C

have been devised to limit the incidence of IHD⁴. National cholesterol education program Adult Treatment panel III (NCEP ATP III) is the latest in the series⁵ which advocates six steps for the dietary and pharmacological management of hypercholesterolemia. The set targets for LDL-C are values less than 100 mg/dL; total cholesterol less than 200 mg/dL and HDL-C more than 60 mg/dL⁶. Statins are the antilipidemic agents used extensively in the primary and secondary prevention trial aimed at reducing the mortality from new coronary events and in all cause mortality⁶. Statins are the competitive and reversible inhibitors of the enzyme HMG CoA reductase the rate limiting enzyme in the synthesis of cholesterol⁷. But their major protective role lies in mitigating the inflammatory activity of macrophages and is evident after 2-3 months therapy⁸ manifest in decreased formation of isoprenoid intermediates like geranyl pyrophosphate⁹. Atorvastatin was initially

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shown to be more beneficial than simvastatin, pravastatin and lovastatin; all of both being hydrophobic¹⁰. Rosuvastatin is novel statin; being hydrophilic¹¹ which has been shown to be effective in 10 mg dose comparable with the 40 mg of Atorvastatin¹². The hydrophilicity of rosuvastatin allows for its higher diffusion into the non hepatic cells¹³. This proved a better role of rosuvastatin among the statin; was approved by FDA in August 2003 for dyslipidemia, hypercholesterolemia and hypertriglyceridemia. Ultimately in February; 2010 it got the FDA approval for primary prevention of cardiovascular events. Unfortunately other than the comparative studies of rosuvastatin with other studies, scant international data is available on its efficacy in the different doses, there being none on the national level. We therefore decided to conduct this study based on the effects of rosuvastatin in 5 mg and 10 mg doses also outlining its safety profile. This study will help rationalize the use of this useful drug on a more practical outline keeping our low national affordability status.

MATERIALS AND METHODS

This study was conducted as joint venture of Department of Pharmacology, Khyber Medical College, and Department of Cardiology, Khyber Teaching Hospital, from January 2011 to August 2011. A total of 100 patients aged 35 to 75 years who were clinically obese and presented to coronary care unit and out patient departments of cardiology unit Khyber Teaching Hospital with incipient coronary event or a history of ischemic heart diseases (IHD) were included in this study. Patients were randomized into two groups; group A comprised 50 patients who received 5 mg rosuvastatin while group B comprised 50 patients who received 10 mg rosuvastatin. A baseline total cholesterol (TLC) LDL- (Low Density Lipoprotein) cholesterol; HDL-C (High Density Lipoprotein-Cholesterol) and TG (Triglyceride) values were noted for both the groups. Patients presenting with IHD for the first time and those with a history of IHD who did not receive any statin therapy for the last 6 months were included in the study. The study group included non diabetic; moderately controlled diabetic irrespective of history of hypertension and smoking. Patients with history of statins (anyone) in the last 6 months, poorly controlled diabetes, those with congestive heart failure, cirrhosis liver, end stage renal disease, nephrotic syndrome, history of use of thiazide diuretic,azole antifungals, long term macrolides and oral contraceptives (in females) and warfarin were excluded from the study.

We also excluded those patients with unstable angina, surgical vascular emergencies, stroke myositis, malignancy and hypothyroidism for clarity and brevity of objectives. A printed proforma was used to record the demographic and study variables; after taking a written informed consent.

After the patients had received the designated doses of rosuvastatin for 3 months; the lipid profile was repeated. Both the baseline and 3 month values were obtained by autoanalyzer using enzymatic methods after 8-10 hour fasting. For justifying the inclusion and exclusion criteria appropriate tests like blood sugar, ECG, echocardiography, ALT, CPK and TFTs were rationally advised on both the start and end of study. Subjective adverse effects like myalgia, muscle weakness, abdominal pain, anorexia, debility and inability to perform daily activities were noted on the proforma after taking the drugs for 3 months. A two fold rise in ALT and 10 fold rise CPK from the baseline was regarded as significant biochemical marker of toxicity.

NCEP ATP III guidelines for the reduction and improvement in the LDL-C was the primary end point. Associated TLC, HDL-C and TG values were also analyzed for improvement. The secondary end point was the objective and biochemical evidence of adverse effects after the use of two sets of dosage regimens of rosuvastatin. The retrieved data was analysed on SPSS 16 software computer window. P values were obtained for the significant variables. Mean values were used for analysis and chi-square and student 't' test were appropriately used. A P value of <0.05 was considered statistically significant. Patients who expired didn't follow up were promptly replaced so that a final sample of 100 patients; 50 in each group was secured for analysis.

RESULTS

Out of the 50 patients in group A and group B each; 34 (68%) in group A were male, and 16 (32%) females while 41 (82%) in group B were male and 9 (18%) were female. Overall in both the groups 75 (75%) were male and 25 (25%) were female in a M:F ratio of 3: 1 (Table 1). All the patients belonged to Peshawar. This ensured their proper documentation and follow up. The mean age of the patients in group A was 51.4 ± 7.6 and in group B was 49.35 ± 5.65 . The mean age of the males in group A was 48.5 ± 3.5 years and that of the females was 56.2 ± 0.1 years; in group B it was 45.9 ± 2.7 and 52.38 ± 1.9 years respectively.

The risk factors in etiology of IHD included diabetes mellitus along in 18 (36%) patients in group A and 32 (64%) patients in group B. Hypertension alone was noted in 17 (34%) patients in group A and 18 (36%) patients in group B. 7 (14%) patients in group A and 12 (24%) patients in group B had both diabetes and hypertension. 14 (28%) patients in group A and 23 (46%) were smokers. Thirty-seven (74%) patients in group A and 40 (80%) patients in group B were obese with a BMI 31 – 40; while 9 (18%) in group A and 4

(8%) in group B were overweight with BMI 26-30. Only 4 (8%) in group A and 6 (12%) in group B had a normal BMI of less than 25.

A gender wise breakup of the etiology in both the groups revealed 6 (33.3%) males and 12 (66.6%) females with diabetes along in group A and 27 (84.37%) males and 5 (15.62%) females in group B. For hypertension alone category 15 (88.23) were male and 2 (11.76%) were females in group A and 13 (17.23%) were male and 5 (27.77%) were females in group B. In the category of both hypertension and diabetes 4 (57.14%) were male and 3 (42.86%) were female in group A and 10 (83.34%) were male and 2 (16.66%) were females in group B. Out of the total 14 patients in group A who smoked only one (7.14%) was female,

Table 1: Gender of the patients in two groups

Gender	Group A n = 50	Group B n = 50	Both Groups n = 100
Male	34 (68%)	41 (82%)	75 (75%)
Female	16 (32%)	9 (18%)	25 (25%)

Table 2: Clinical presentation in the study groups

Clinical Pre-sentation	Group A n = 50	Group B n = 50
Angina Pecton	29 (58%)	37 (74%)
Myocardial Infarction	11 (22%)	9 (18%)
CABG/PCI	10(20%)	4(81%)

Abbreviations

CABG = Coronary Artery Bypass grafting
PCI = Percutaneous Coronary Intervention

13 (92.86%) were male; for 23 patients in group B who smoked 3 (13.04%) were female and 20 (86.96%) were male. Clinical presentation in both groups are shown in Table 2. The lipid profile analysis of the study group is shown in Table 3. The incidence of adverse affect after treatment shown in Table 4.

DISCUSSION

Statins have assumed a cardinal role in the management of ischemic heart disease (IHD). This is true not only for the obese patients with IHD but also the non obese individuals⁹. We evaluated the demographic and biochemical parameters in our study with 5mg and 10mg Rosuvastatin respectively to two groups after its uninterrupted treatment for 3 months. The major yield was the affirmation of the proven role of Rosuvastatin based on NCEP AT+P III guidelines. We demonstrated a very significant role for both the groups in terms of total cholesterol, LDL-C, HDL-C and triglycerides. Even more significant was demonstration of the better efficacy and comparable safety profile in 10 mg group as compared to 5mg group; with P value of < 0.0001 for LDL-C the major therapeutic target of NCEP ATP III.

In our study the mean LDL-C showed 39.02% reduction with 5mg as compared to 48-38% with 10mg dose (P < 0.0001). This was even more significant then the mean 26% reduction in the study by Gardala M et al¹⁴. We also demonstrated significant improvement in HDL-C; mean 26.22% improvement (P<0.0006), while Gardala Metal did not report any HDL-C improvement our study results were comparable to COMET study¹⁵. Which demonstrated 46% reduction in LDL-C on 10mg dose, there are however no 5mg dose results for comparison. AURORA trial¹⁶ in patients with advanced renal failure and CORONA trial¹⁷ with congestive cardiac failure did not approve of the role of Rosuvastatin in those setting. This reinforced our

Table 3: Lipid profile at baseline and after 3 months treatment

Lipid Profile	Group An = 50			Group Bn = 50			P-value
	Mean Values		% change	Means Values		% change	
	Baseline	3 months		Baseline	3 months		
LDL-C mg/dl	169.74 ± 17.3	103.5 ± 11.4	39.02%	173.4 ± 8.3	89.5 ±12.7	48.38%	<0.0001
Total cholesterol	262.5 ±13.6	179.3 ±15.1	31.69%	259.4 ±17.3	152.3 ±16.5	41.28%	<0.0001
HDL-C mg/dl	36.13 ±3.9	38.27 ±4.7	5.59%	31.5 ±4.2	42.7 ±7.1	26.22%	<0.0006
Trigly cerides	337.4 ±28.7	229.1 ±18.3	32.09%	350.7 ±25.7	211.6 ±11.7	39.63%	<0.04

Abbreviations

LDL – C = Low density lipoprotein cholesterol
HDL-C = high density lipoprotein cholesterol

Table 4: Incidence of persistent adverse effects after treatment

Adverse Effects	Group A n = 50	Group B n = 50
Myalgia	3 (6%)	4 (8%)
Abdominal pain	1 (2%)	1 (2%)
Muscle Weakness	4 (8%)	7 (14%)
Anorexia	2 (4%)	6 (12%)
Debility	1 (2%)	1 (2%)
Inability to performance work	1 (2%)	1 (2%)

exclusion criteria for patient with renal failure and congestive cardiac failure; where factors other than hypercholesterolemia determine the outcome. It was JUPITER trial (2008); which served as the basis for FDA approval of Rosuvastatin in primary cardiovascular events. It showed a 44% reduction in first vascular events when using Rosuvastatin 20mg versus placebo in 17802 patients. Our study is one such step on national levels which on metatrial will corroborate with JUPITER trial. The JUPITER trial also formed the basis for cardiac risk specification¹⁸ and demonstrated a decrease in the incidence of ischemic stroke even in those patients who had low LDL-C but high sensitive CRP. JUPITER study eligibility for the use of rosvastatin has extrapolated the need for its use in NHANES²⁰ (National Health and Nutrition Examination study), where an estimated 6.5 million additional adults could be potential candidate for statin therapy. Our study is the first such step in right direction which will lay the real foundation of primary prevention in our set up. Although the MERCURY trial²¹ compared rosuvastatin with Atrovastatin and simvastatin our results in terms of LDL-C reduction constasted sharply with the Rosuvastatin subset of MERCURY; i.e. 80.82% reduction in LDL-C versus 48.38% in our 10mg group.

Dedanzrine²² also demonstrated the superiority of Rosuvastatin versus other statins with more than 50% reduction in LDL-C; comparable to our study. A meta analysis using 26 trials has shown 6-25% improvement in LDL-C between 5-10 mg rosuvastatin which is significantly less²³ than our study. The HDL-C were comparably raised in the meta analysis; 10-20% versus 26.22% in our study.

The other components of lipid profile also showed statistically significant improvement. Total cholesterol in our study showed 41.28% and 31.69% reduction in 10 mg and 5 mg dose of Rosuvastatin; the total triglyceride showed 39.63% and 32.09% reduction in respective groups. Together the reduction in LDL-C, total cholesterol and TG conferred better out come to the patients with IHD decreasing the morbidity and mortality.

The improvement in HDL-C in our study with 10 mg Rosuvastatin; mean 42.7 mg was less than that reported by RADAR (Rosuvastatin and Atorvastatin in Different Dosage and reverse cholesterol transport) study; 60 mg. The result of our study 26.22% was however significant compared to 0.66% improvement in HDL-C with Rosuvastatin in Discovery beta trail²⁵.

The finding of increased incidence of myalgia and muscle weakness in 10mg group 8% and 14% was however proven statistically insignificant; $P = <0.7$; this however corroborated with Thompson PD et al²⁶ which also reported myalgia; rhabdomyolysis this myopathy usually does not necessitate the stoppage of treatment; a dose reduction is however advisable²⁷. To summarize the side effects of 5 mg and 10 mg of rosuvastatin are comparable²⁸.

Our study comprised a majority of males and a relatively 75% younger age among the males 48.5 and 45.9 years respectively among 5 mg and 10 mg age group, speaking volumes of the susceptibility of sedentary life style with bad social habits. There was however no racial difference comparable to findings of Albert MA et al²⁹.

CONCLUSION

Rosuvastatin, The novel hydrophilic statin is more efficacious in 10 mg doses as compared to 5mg doses with comparable a toxicity profile. This justifies the use of 10 mg rosuvastatin in patients with IHD for improving the clinical outcome. The 10mg dose helps achieve the NCEP ATP III goals.

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