Original Article

COMPARING SAFETY PROFILE OF ROSUVASTATIN WITH SIMVASTATIN IN TERMS OF MUSCLE SYMPTOMS

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ABSTRACT

OBJECTIVES: To compare frequency of muscle symptoms among patients taking either simvastatin or rosuvastatin.

METHODS: Patients who were taking either simvastatin or rosuvastatin for at least past 2 months were enrolled in the study. They were divided into two groups: group A and group B receiving Simvastatin and Rosuvastatin respectively. Detailed clinical history was taken in each case. Blood samples were drawn from all the patients for serum LDL cholesterol, triglycerides, creatinine and creatine kinase levels. Primary outcome variables included myalgia, myopathy and rhabdomyolysis.

RESULTS: The two groups were comparable in terms of various baseline characteristics such as mean age (54.12±9.67 vs 55.20±10.11), gender (20/30 vs 15/35), mean BMI (28.46±4.12 vs 29.04±3.87), serum LDL cholesterol (176.60±58.13 vs 183.63±64.37) and serum triglycerides level (198.61±83.31 vs 203.45±88.12). Myalgia was reported in 10(20%) patients in group A whereas 15(30%) patients reported myalgia in group B.

CONCLUSION: Rosuvastatin was equally safe as simvastatin with respect to various musculoskeletal side effects.

KEYWORDS: Myalgia, Statin Induced Myopathy, Rhabdomyolysis

INTRODUCTION:

Statins are one of the most widely used drugs worldwide.[1] They are lipid lowering agents that work by inhibiting the enzyme (3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase ; a key rate limiting step in the cholesterol synthesis pathway.[2] Common uses of statins include management of hypercholesterolemia, primary and secondary prevention of cardiovascular events e.g stroke, myocardial infarction etc. and management of dyslipidemias in diabetic patients.[3]

Currently , seven statins are available for clinical use.These include lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin and most recently pitavastatin.[4] Several adverse effects have been identified over the past years including neurocognitive symptoms, musculoskeletal problems and rarely nephrotoxicity and hepatotoxicity.[5] The commonest of these are the musculoskeletal side effects of statin therapy.They are present in upto 10-15% of the patients. The clinical spectrum of these complaints ranges from mild myalgias to severe symptoms seen in rhabdomyolysis (severe skeletal muscle damage accompanied by acute kidney injury).[6] The constellation of these symptoms is termed as statin induced myopathy. Mechanism is poorly understood however reduction in ubiquinone in skeletal muscle may have a role to play.[7]

Statin user is quite common among Pakistanis owing to the huge burden of diabetes and various cardiovascular diseases. All the statins differ from each other in terms of efficacy and safety profile. The differences observed are due to slight variations in pharmacokinetics and pharmacodynamics of these drugs.[8] There are very few local studies comparing the safety profiles of different statins. Arshad et al[9] compared atorvastatin with low dose rosuvastatin and showed no significant difference in safety profile of the two drugs (p value =0.432). Myalgia was the only adverse effect reported by them present in 5 (7.94%) patients treated with atorvastatin and 8 (12.12%) patients treated with rosuvastatin. Tariq et al[10] while comparing rosuvastatin with atorvastatin reported muscle symptoms

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at much lower dose than that recommended by American Heart Association. JUPITER trial reported muscle symptoms to be present in 16.0% of the patients.[11] Simvastatin is one of the commonest prescribed statins. Riaz et al[12] reported frequency of myalgia in patients taking simvastatin to be 10%. However, literature review yielded no local study comparing simvastatin safety profile with other statins. Consequently, we conducted this study with principal objective of comparing safety profile of simvastatin with rosuvastatin focusing primarily on the musculoskeletal side effects.

MATERIALS AND METHODS:

This comparative cross-sectional study was conducted at Medical unit 01 , Lahore General Hospital from July 2017 to Dec 2017. The sample size was calculated using Openepi calculator with the statistical assumptions of 5% alpha error and 95 % confidence interval taking proportion of myalgia to be 38% in patients taking simvastatin and 67% in those taking rosuvastatin13 and came out to be at least 48 patients in each group for this study. Ethical approval was taken from the institutional review board. Patients who were taking either simvastatin or rosuvastatin for at least past 2 months were offered to be enrolled in the study. Informed consent was taken from each patient. Patients were divided into two groups: group A and group B receiving Simvastatin and Rosuvastatin respectively. Detailed clinical history was taken in each case. Blood samples were drawn from all the patients for serum LDL cholesterol, triglycerides, creatinine and creatine kinase levels. Primary outcome variables included myalgia, myopathy and rhabdomyolysis. Myalgia was defined as muscle pain or soreness, weakness and/or cramps without CK elevations. Myopathy was defined as symptoms of myalgia plus CK > 10 upper limit of normal (ULN). Rhabdomyolysis was defined as CK > 10 x ULN plus an elevation in serum creatinine.

All the data was recorded on a pre-designed proforma and analyzed by SPSS version 23.0. Mean and standard deviation was calculated for all quantitative variables like age, BMI etc.Frequency and percentage was calculated for all qualitative variables like presence of myalgia, myopathy etc. Chi square test was applied to compare the frequency of muscle symptoms amongst the two groups taking p value < 0.05 as statistically significant.

RESULTS:

A total of 100 patients took part in this comparative cross sectional study.There were 35 males and 65 females with an overall mean age of 54.68±9.21 years (Table 1). Myalgia was reported in 10(20%) patients in group A whereas 15(30%) patients reported myalgia in group B. (p value = 0.25) (Table 2).Myopathy was found in only one patient who belonged to group B. No case of rhabdomyolysis was reported in any of the groups.Diabetes was prevalent in 85% of the study population whereas 64% of the patients were found to be hypertensive (Table 1). The two groups were comparable in terms of various baseline characteristics such as mean age (p value = 0.59), gender (p value = 0.29), mean BMI (p value = 0.47), serum LDL cholesterol (p value = 0.57) and serum triglycerides level (p value = 0.78) (Table 1).

Table-1:Baseline characteristics

	Overall (N=100)	Group A (N=50)	Group B (N=50)	p value
Mean age ± SD in years	54.68±9.21	54.12±9.67	55.20 ±10.11	0.59
Male / Females	35 / 65	20(40%) / 30(60%)	15(30%) / 35(70%)	0.29
Mean BMI ± SD in kg/m²	28.81±3.92	28.46±4.12	29.04±3.87	0.47
Serum LDL cholesterol in mg/dl	179.42±60.26	176.60±58.13	183.63±64.37	0.57
Serum triglycerides in mg/dl	200.12±86.46	198.61±83.31	203.45±88.12	0.78
Diabetes mellitus		40 (80%)	45 (90%)	0.16
Hypertension		34 (68%)	30 (60%)	0.40
MI in past		4 (8%)	2 (4%)	0.40
Stroke in past		3 (6%)	5 (10%)	0.46

Table 2: Frequency of muscle symptoms in study population

	Group A (N=50)	Group B (N=50)	p value
Myalgia	10 (20%)	15 (30%)	0.25
Myopathy	0	1	1
Rhabdomyolysis	0	0	NS

DISCUSSION:

An estimated 25 million people are currently on statin therapy.[14] They are used primarily for the primary and secondary prevention of cardiovascular diseases. Musculoskeletal side effects constitute an important subset of statin adverse effects. These are responsible for majority of compliance issues seen with statin use.[15] Therefore, we conducted this study with the objective of comparing frequency of muscle symptoms among patients taking either simvastatin or rosuvastatin.

Our study reported myalgia to be present in 20% of the patients in simvastatin group compared with 30% of the patients in rosuvastatin group. The difference was not significant as noted earlier (p value=0.25). This was in contrast to the findings of Ruaño et al[13] who reported a much higher

frequency of myalgia i.e 38% in simvastatin users and 67% in rosuvastatin users. On the contrary, a local head to head trial comparing atorvastatin with rosuvastatin reported a myalgia prevalence rate of just 12.12% in rosuvastatin group. The possible differences in the myalgia rates observed among these studies are probably due to differences in operational definition of myalgias in each of these studies. We couldn't infer the criteria used for labelling myalgia in these studies probably because their primary objective was not to compare myalgia rates. JUPITER trial, the most comprehensive trial on any statin to date, reported presence of muscle symptoms in 16% of patients taking rosuvastatin.[11]

A great majority of the patients in our study were diabetics(85%) and many other were hypertensive(64%). Similar trend was noted by Arshad et al[9]. The two groups were comparable with regards to various baseline characteristics in our study. This was not entirely the case in Arshad et al[9] study. Mean overall age of patients was 54.68±9.21 in our study. This was similar to findings of Tariq et al[10] who reported a mean age of 57.46 ±10.19 years. Majority of patients were females (65%). Similar trend was noted by Tariq et al.[10] We reported a mean BMI of 28.81±3.92 kg/m^2 which was slightly higher than that reported by Arshad et al.[9]

There were certain key limitations to our study with the most important being the cross-sectional study design. Ideally it should have been a double blind randomized controlled trial with a washout period before starting the medications. This would have minimized various elements of bias that are usually associated with a cross-sectional study design. Moreover, effect modifier and confounders (age, gender, primary diagnosis) were not controlled via stratification thus introducing another element of bias.

CONCLUSION:

We found no significant difference in the frequency of musculoskeletal adverse effects of simvastatin and rosuvastatin. Keeping in view the various discrepancies in myalgia rates among different studies, there is a need of standardizing definitions of these key outcome variables. Further multicenter, double blinded trials are warranted in near future as this was the first local head to head trial comparing these two drugs.

Author's Contribution

SA: Collected the data and conducted the study. KZ & EM: Helped in conducting the study. UA & SA: Helped in data analysis.

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