CHALLENGING CLINICAL ISSUE OF MUSCLE SYMPTOMS IN STATIN TREATED PATIENTS: A COMPARISON WITH AHA GUIDELINES

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Abstract -
Objective: To study the frequency of myalgia occurring in Asian population at half or even lower doses of Atorvastatin and Rosuvastatin than latest recommended by American Heart Association.
Methodology: This retrospective cross sectional study included patients undergoing statin therapy with Atorvastatin and Rosuvastatin treated at Rawalpindi Institute of Cardiology, from June to October 2015. Patients were divided into group A receiving 40, 20 and 10mg Atorvastatin and group R receiving20, 10 and 5mg of Rosuvastatin. Interview administered questionnaires were used to collect data regarding their cholesterol profile (mg/dl), statin and its tolerance. For statistical analysis Chi square test was used with $p<0.05$ was taken as significant.
Results: A total of 500 patients were included with 276 patients in group A and 224 in group R. Most patients 99.4% presented with risk factors of atherosclerotic cardiovascular disease: 84.8% had 2 risk factors and 15.2% had <2 risk factors, necessitating use of statins. A majority of patients experienced myalgia, 80.8% in group A and 83.5% in group R ($p<0.05$).
Conclusion: This study provides strong evidence that statin lead to frequent muscle related adverse effects and may be challenging in some patients even at lower doses than the recommendation of American Heart Association.

Key Words - Statins, Myalgia, Asian patients, Statin Intolerance

I. INTRODUCTION

Statins therapy remains the keystone in the prevention of atherosclerotic cardiovascular diseases (ASCVD) and continues to be the mainstay in treating patients with dyslipidemia as well as its secondary causes which constitutes obesity, un-controlled diabetes and alcohol [1]-[3]. Abundant clinical trials and post-marketing experiences with millions of patients treated globally since two decades (when the drug was first available) have presented great forbearance with long term statin therapy. Latest studies demonstrates the pleiotropic properties of statins which involves improving endothelial function, enhancing the stability of atherosclerotic plaques, deterring the thrombogenic response, decreasing oxidative stress and inflammation [4]. However, muscle-related side-effects are becoming more prevalent as the increasing number of patients are treated with statins and a greater number of them are being prescribed high doses of potent statins to achieve low-density lipoprotein targets [5]. As a matter of fact a6 noteworthy amount of patients show non-adherence to statin therapy to statin therapy and statin-related myopathy remains a clinically significant cause of statin intolerance and therapy cessation [1] [8]-[10]. The most recurrent adverse reaction of statin therapy is myalgia accounting for up to 25% of all adverse reactions and the clinical spectrum of statin related myopathy ranges from common but clinically benign myalgia to sporadic but life-threatening rhabdomyolysis [8][10]. Observational studies gives an estimation that 10–15% of statin consumers develop statin-associated muscle adverse effects compassing from mild myalgia to more severe muscle symptoms [11]. The pathophysiology of statin-related myopathy is still incompletely understood. There are multiple risk factors behind statin-induced myopathy that are patient-associated (age, genetics, co-morbidities), dose-dependent, proapoptotic effect, direct effects on mitochondria and drug associated (statin metabolism via the cytochrome (CYP) system, drug–drug interactions and statin drug transport)or combinations thereof, which may be involved [3][6]. Predisposition exists in the patients with impaired hepatic and renal function, hypothyroidism, diabetes and concomitant medications [7].

American guidelines now recommend high intensity statins for people with cardiovascular diseases (CVD). Current guidelines recommended by American Heart Association/ American College of Cardiology for cholesterol treatment are: high-intensity statin therapy (Atorvastatin 40-80 mg and Rosuvastatin 20-40 mg) should be initiated for adults ≤75 years of age with clinical ASCVD who are not receiving statin therapy or the intensity should be increased in those receiving a low- or moderate-intensity statin, unless they have a history of intolerance to high-intensity statin therapy or other characteristics that may influence safety.3 All patients (≥21 years of age) with any form of CVD (not only CHD), or LDL-C ≥ 190 mg/dl:-Treat with high dose statins: Atorvastatin 40-80 mg and Rosuvastatin

20-40mg with the aim to reduce LDL-C by >50% [3]. Previous studies and clinical experiences have shown that Asian patients frequently have amplified response to therapeutic doses due to differences in ethnic origin and genetically based variances in metabolism of statins at the level of hepatic enzymes and drug transporters [5]. Most side effects of the statins are dose related and myotoxic events are more recurrent at higher doses [23][25]. Pharmacokinetic investigations have highlighted increased systemic exposure and greater plasma levels in Asians than in Caucasians. However, it is postulated that high dosage recommendations of statins are not pertinent on Asian population and lower doses of statins tend to attain lipid improvement than those acquired with advanced doses in Caucasians [25]. Consequently the recommended doses are often lower in Asian countries than in western countries and this practice extends to the use of cardiovascular drugs including statins [5]. This study has been conducted to emphasize on the problem of myalgia occurring in the Asian population and myotoxic events which are increasingly reported even at lower dose than the latest recommendations by American Heart Association.

II. METHODOLOGY

A retrospective cross sectional analysis of patients undergoing statin therapy with Atorvastatin and Rosuvastatin from past 2 to 120 months at Rawalpindi Institute of Cardiology was done from June 2015 to October 2015 after approval from Ethical Review Board. Interview administered questionnaires were used to collect data from in patients and out patients who met our inclusion criteria (taking Atorvastatin and Rosuvastatin orally for past 2 months or more). A formal consent was taken from the patients. Patients were divided into nearly equal two groups: group A and group R receiving Atorvastatin and Rosuvastatin respectively. The questionnaire consisted of 10 closed ended questions in which individual's profile (name, age, gender, address) were asked in the beginning. Diagnosis and co-morbid factors including hypertension and diabetes were assessed in the patients and risk factors including family history of cardiovascular events, obesity, smoking, alcohol, old age were noted. Data related to cholesterol profile including low density lipoprotein (LDL) and Triglyceride levels were determined and as well as co-administered medicines (including Spironolactone, Diltiazem, Digoxin, Verapamil). The next section comprised of questions related to the statins including the type of statin they had been prescribed, its potency, duration of statin therapy. Further questions were related to experiencing any symptoms of myalgia. If yes, then what was the severity of myalgia: mild, moderate or severe muscular pain? Since when were they suffering from myalgia after statin therapy? Any modification in the statin therapy after presenting their intolerance to statins such as: cessation of the statin therapy, reduction in the prescribed dose and switching to some other medicine belonging statin class or no change in the statin therapy at all. Responses were coded and entered into SPSS for Windows, version 21, for statistical analysis and Chi square test were used to test for significant differences between groups ($p<0.05$). Any missing data were not included for the analysis.

III. RESULTS

The study included 500 patients with age ranging from 29 to 90 years with mean 57.46 ±10.19 years , 70.4% were female (n=352) and 29.6% male (n=148) who were prescribed Atorvastatin and Rosuvastatin for the past 2 to 120 months with serum LDL levels (measured in mg/dl) ranging from minimum value of 68 to maximum 731 and mean value of 175.73 ±56.36 mg/dl, whereas Serum Triglycerides levels (measured in mg/dl) ranging from minimum value of 75 to maximum 778 and mean of 194.97 ± 98.739 mg/dl. A vast number of patients 99.4% (n=597) had risk factors critical to atherosclerotic cardiovascular events, 84.8% had ≥2 risk factors and 15.2% had < 2 risk factors for which statins were being prescribed to them. Approximately 77.8% had ischemic heart disease, 16.8% had non-ischemic heart disease and 5.4% had no CHD but were hyperlipidemic, moreover these patients were hypertensive, diabetic, both or had none of these co-morbid factors, illustrated in Fig 1.

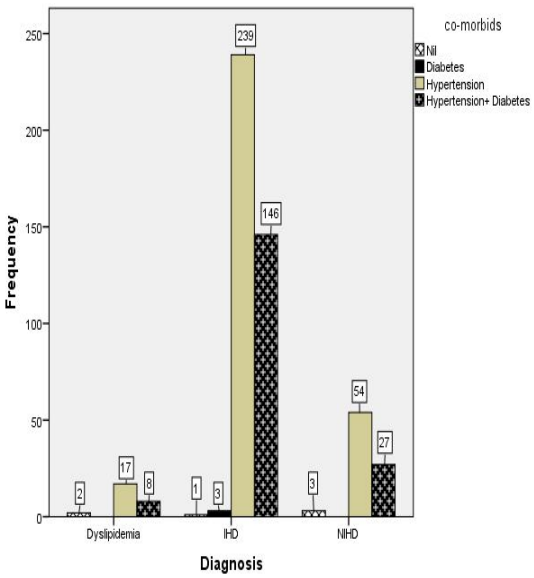


Figure 1: Frequency of Co-Morbid Factors in Study Population (n=500)

Frequency of different doses of Atorvastatin (10mg, 20mg, 40mg) and Rosuvastatin (5mg, 10mg and 20mg) prescribed to Asian patients is given in Fig 2.

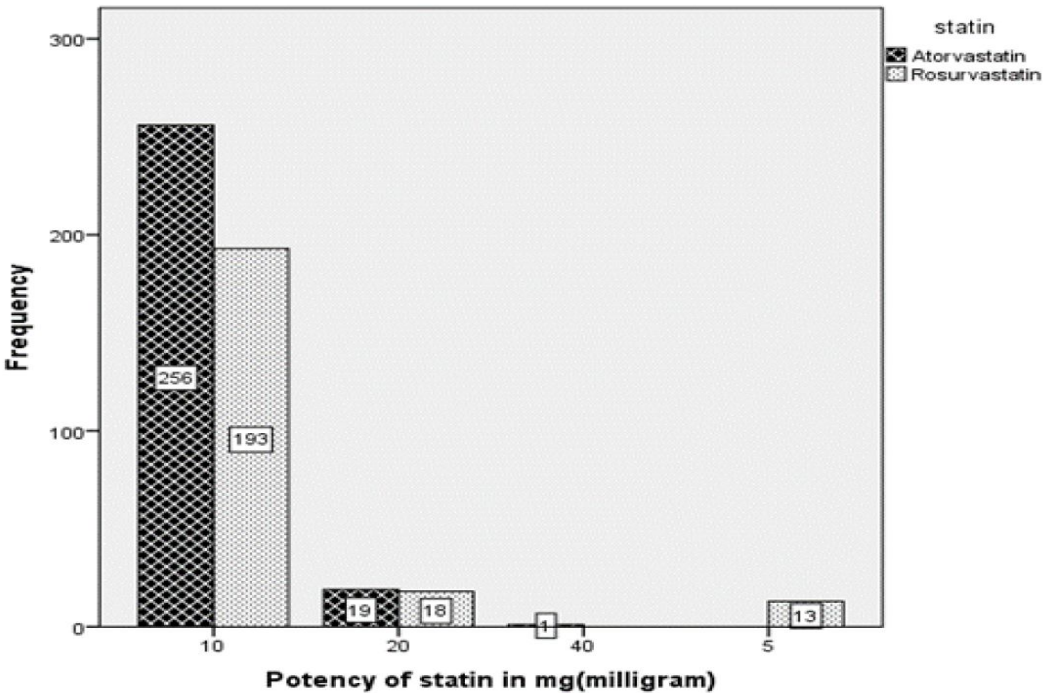


Figure 2: Frequency of Different Doses of Stains Prescribed to Study Population (n=500).

We found that a proptionately larger number of patients 80.8% (n=223) were presented with myalgia in group A and 83.5% (n=187) in group R. Intensity of myalgia occurring in patients is illustrated in Fig 3. Intensity of myalgia and statins are highly associated (x^2 =9.820, DF=3, p<0.05).

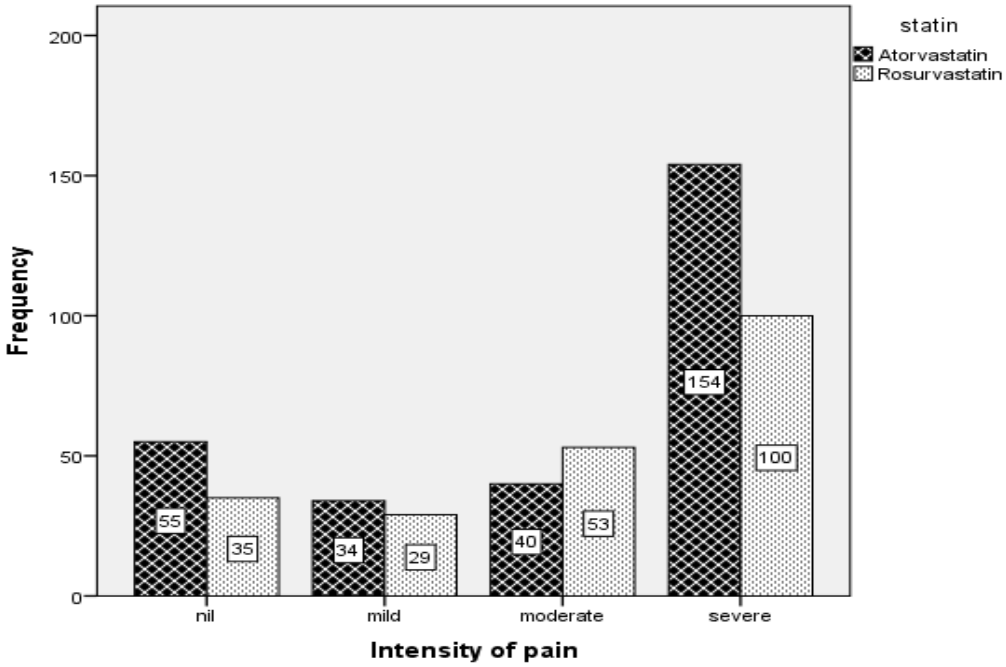


Figure 3: Frequency of Intensity of Myalgia in Study Population (n=500)

Time of onset of myalgia were noted, which ranged from a week to 9 years of statin therapy started , also including those patients whose pain was aggravated as compared to the pain prior to the statin therapy such as pain due to arthritis, anemia, vitamin d deficiency, diabetes, neuropathy, paralysis and old age. Complaints of myalgia and the statins show high correspondence with each other (x2 =53.135, DF=40, p<0.05). We noted that 23.4% patients (n=117) were taking concomitant medications with statins. Concomitant medications and intensity of myalgia are highly correlated to each other (x2 =35.022, DF=18, p<0.05). Dose adjustment pattern and amount of dose reduced in the patients of both groups is given in the

Table 1. Potency of statins and dose adjustment are much linked (x2 =99.984, DF=9, p<0.05) and Intensity of myalgia and quantity of dose adjusted showassociation with each other (x2 =17.711, DF=9, p<0.05).

Table 1: Dose Adjustment Pattern and Frequency of Amounts Reduced in Study Population (n=500).

Quantity of dose reduced	Type of statin		Total
	Atorvastatin	Rosurvastatin	
No reduction	248	212	460
5 mg	0	4	4
10 mg	24	8	32
20 mg	1	0	1
Switched to other Statin	3	0	3
Total	276	224	500

DISCUSSION

South Asians around the world have the greatest occurrence of coronary artery disease (CAD) with an additionally higher risk at younger ages, the rate is 50% to 300% higher among them and prevails about 10 years prior to any other population [21]. Further studies also verify that Asian Indians appear to have at least twice the chances of Coronary Artery Diseases (CAD) than whites [22]. Emerging facts advocate that the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) offer significant advantages and assistance for the enormous population of individuals at elevated risk for CAD [23]. They are widely recommended agents for lowering levels of LDL cholesterol and are beneficial even in patients with normal or low cholesterol levels, indicating pleiotropic mechanisms of therapeutic value thus a corner stone in reducing cardiovascular events in patients with ischemic as well as non-ischemic heart failure [26]. We analyzed the data of hypertensive and diabetic patients with raised cholesterol levels who presented with history of CAD or were at its increased risk being treated with statin. As over the years a remarkable number of randomized trials have repeatedly confirmed the treatment of such patients with statins [17]. A study population with traditional risk factors triggering CAD were taken into account which included obesity, diabetes, old age, hypertension and family history of cardiovascular diseases as previously published studies postulate that such patients are at highest risk for CAD regardless of their lipid profiles and most expectedly receive multiple medications thus being at maximum risk for drug-drug interactions during their statin therapy [23]. Although dose-dependent reductions in levels of atherogenic lipids are observed with all statins however, the influence of increasing their dose has not been fully illuminated [20]. Latest guidelines by American heart association/ American college of cardiology (AHA/ACCP) in 2013 for cholesterol treatment recommend high intensity statins for people with CVD. This study has been conducted to determine the dose of Atorvastatin and Rosuvastatin which is being prescribed to Asian patients and to emphasize the problem of myalgia occurring in Asian population, due to the increasingly observed side effects even at a very lower dose than the latest recommendations by American heart association. It has been proven earlier that East Asians respond to lower doses of statins and focusing on the dissimilarities with respect to pharmacokinetics between East Asians and Caucasians, it might be expected that fall in LDL-C levels would be about 5-6% more in Asians than Caucasians, which is equivalent to doubling of dosing [18], [20]. Our results show that 0.36% of the patients of group A were being prescribed with 40 mg of Atorvastatin which is recommended by AHA/ACCP however 99.64% of the individuals were receiving half or lower doses i.e. 20mg and 10mg. Whereas amongst the patients of group R it was observed that only 8.03% were being prescribed the recommended doses of Rosuvastatin by AHA/ACCP which is 20mg while 91.97% of the patients were receiving half or lower doses i.e. 10mg and 5mg. Our results were comparable to previously published studies among Asian patients which show that statin therapy exhibit better tolerance and remains effective in reducing LDL cholesterol in patients of South-Asian origin (India, Pakistan, Bangladesh, Nepal, and Sri Lanka) with 10mg and 20-mg doses of Rosuvastatin and Atorvastatin respectively facilitating majority of the patients to attain recommended LDL cholesterol goals [24]. As maximum patients (~90%) of Singapore, Korea, Malaysia Taiwan and Thailand tolerate statins at medium or lower equipotency doses [15]. Pharmacokinetic studies show that average systemic exposure of Rosuvastatin in East Asians are approximately double and South Asian patients have intermediate values to those in Caucasians as a result of which regulatory authorities have recommended starting Rosuvastatin with lower doses (5 mg) in Asian patients, particularly those with Japanese and Chinese origin. Plasma exposure to Rosuvastatin and its metabolites was considerably higher in Japan, Chinese, Malay, and Asian-Indian individuals in comparison with the white individuals living in the similar environment. This identifies a safety issue and dosing advice on the basis of ethnicity as recommended by regulatory authorities [18]-[19]. In comparison with the western world where researches suggest solitary doses of as high as 80 mg of

Atorvastatin (once daily) for their population due to its well tolerance among them [16]. High prevalence of elevated response to therapeutic doses was proved by our results showing that 80.08% patients of group A and 85.27% of group R were suffering from myalgia characterized as mild, moderate and severe type. Our study statistically verified that concomitant medications were playing a vital role in increasing the intensity of myalgia occurring in these patients. These medicines included verapamil, diltiazem, digoxin and spironolactone which has proven to increase plasma concentration of statins undergoing degradation via cytochromes (CYP) P450 isoenzymes and carry a particular high risk for interaction with other drugs inhibiting or inducing CYP isoenzymes and other major interaction including inhibition of P-Glycoprotein [12] - [14]. As it is known that the prevalence of myopathy associated with statin therapy is dose related and its risk increases with high serum concentration [23], [25]. A similar pattern was observed in both the groups where majority of the patients were suffering from severe myalgia seen more frequently in individuals starting high-dose statin therapy (55.79% in group A, 44.63% in group R) followed by moderate (14.59% in group A, 22.34% in group R) and then mild type of myalgia (12.40% in group A, 12.94% in group R). They were found to be complaining regarding their symptoms of myalgia with respective to the time of the onset of their statin therapy whereas others reported aggravation of their muscular pain present before their therapy started due to arthritis, anemia, vitamin d deficiency, diabetes, neuropathy, paralysis and old age. So the risk was enhanced in patients who had preexistent risk factors for myopathy. With the expansion of clinical use of statins, muscle related side effects are also predominating in our population as a substantial amount of people were intolerant to statin therapy predominantly those on higher doses. It was seen that therapy was terminated among 25 patients of group A and 12 patients of group R whereas 3 patients were switched to some other statin in group A. Despite of the need of statin therapy their treatment was ceased due to extreme muscular problems, compromising the cholesterol reduction over myopathy presented by the patients. Increased serum concentration of statins makes it impossible to prescribe recommended doses to Asian patients particularly statins.

As clinical trials are chiefly done in Caucasians however these higher doses of statins are inapplicable to our Asian population due intensified response to statins which are related to variances in genetic makeup, drug transporters, body mass and metabolism of statins at the level of hepatic enzymes. We acknowledge the fact that there were certain limitations to our study such as Creatine kinase levels of the patients were not analyzed.

CONCLUSION

Our study has significant implications for both guidelines and regulatory policy because it provides strong evidence of the fact that statin intolerance is real and a challenging clinical issue of muscle symptoms in statin treated Asian patients. Results of this study explicitly show the need for large clinical trials in Asian population with CAD requiring statin therapy regarding appropriate doses and incidence of myalgia.

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