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FREQUENCY OF ADVERSE EVENTS ASSOCIATED WITH STATIN USE IN ROUTINE CLINICAL PRACTICE IN PAKISTANI POPULATION

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Contribution

MNM, SAZ helped in literature review, research design and finalizing the manuscript. TA AMB helped in data collection and data analysis.MNM helped in final draft. All authors contributed significantly to the submitted manuscript

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ABSTRACT

Objective: To evaluate the frequency of adverse events associated with statins use in routine clinical practice in Pakistani population.

Methodology: This cross sectional study was conducted at PNS SHIFA a tertiary care hospital in Karachi, Pakistan from January 2015 to December 2015. Male and female patients aged between 20-80 years who were taking statin for more than 3 months and were willing to participate in the study were included. Demographic data like age, gender, medical morbidities e.g. diabetes mellitus , hypertension, ischemic heart disease, cerebrovasculr accident , type and dose of statin and outcome variables like hepatitis, myalgia, myositis and rhabdomyolysis were recorded in a performa. Sample size was calculated using open Epi software. Data was entered and analyzed using SPSS version 21.0. $P < 0.05$ was taken as significant.

Results: A total of 1350 patients aged between 20-80 years of age(Mean age 55.7 ± 10.2 years) were included in the study. There were 53.1 % male patients. Majority of patients (56.9%) were between 41-60 years of age group. About 58.2 % patients had diabetes mellitus ,41.9 % had hypertension,26 % patients had dyslipidimia, 88 % patients were with ischemic heart disease and 9.41 % patients had CVA. Rosuvastatin were prescribed to 56.3% patients, atorvastatin to 33% and simvastatin to 10.7% patients. Regarding the adverse effects, myalgias were most frequently reported in 6.7 % patients; myositis was noted in 0.8 % patients, while rhabdomyolysis was not reported in any patient. Statin induced hepatitis was noted in 2.9%.

Conclusion: There is overall a low frequency of adverse events associated with the use of commonly prescribed statins in routine clinical practice. Further large scale studies are needed to validate our findings.

Key Words: Cerebrovascular accident, Ischemic heart disease, Hepatitis, Myositis, Myalgia, Rhabdomyolysis, Statin.

INTRODUCTION

Cardiovascular disease is the leading cause of premature death and a major cause of morbidity worldwide and about 25 million people use lipid-lowering drugs (statins) on a regular basis because of their beneficial effects in coronary artery disease. [1,2] Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA-reductase) inhibitors are the most important lipid-lowering drugs and have been proven to be effective in the primary and secondary prevention of atherosclerotic vascular events. [2-3] Appropriate use of statins in carefully selected patients can markedly reduce vascular and coronary events in high-risk patients. [4,5]

Results of various clinical trials regarding safety and efficacy of statins has led to the formation of guidelines by the National Cholesterol Education Program and Adult Treatment Panel among high risk patients. [5] Statins vary in their pharmacokinetic and pharmacological properties leading to difference in their safety profile. In 2001, the first statin, cerivastatin was withdrawn from market worldwide after confirmed reports of serious myopathy/rhabdomyolysis. [6] The most common side effects associated with statins were asymptomatic increase in liver enzymes and musculoskeletal disorders including myalgia, myositis, and rhabdomyolysis. Reported frequency of myalgia with statin use is about 5%, myositis has been noted in 0.1 to 0.2% patients, and rhabdomyolysis in about 0.01% patients. Asymptomatic elevations of liver enzymes have been noted in about 0.5 to 2% of patients using statins. [7] Since then a number of clinical trials have evaluated the safety and efficacy of statins in reduction of cardiovascular risks. Most trials concluded statins effective and safe pharmacological agents having considerable benefits with only mild and transient adverse effects which are dose dependent. [8] Overall, statins have a good safety record andserious and life threatening side effects likerhabdomyolysis is rarity. [9]

There is lack of data regarding statin use and safety profile from our Pakistani population therefore the aim of our study was to evaluate the frequency and side effects of commonly used statins in our routine clinical practice.

METHODOLOGY

This cross sectional study was conducted at Pakistan Navel hospital PNS SHIFA over a period of 12 months from January 2015 to December 2015. Patients of either gender aged between 20-80 years who were taking statin for more than 3 months and were willing to participate in the study were enrolled. This study excluded pregnant women, patients on other concurrent lipid lowering agents such as fenofibrate, ezetimibe or niacin as well as patients who are seriously ill and patients with history/ confirmed reports of viral hepatitis or CLD. Demographic data like gender, age, medical morbidity like DM, HTN, IHD and CVA, statin type, dose and duration of use and any adverse effects like myalgia, myositis, rhabdomyolysis and hepatitis were recorded in a preformed performa. Myalgias were defined as any muscle weakness, soreness, tenderness, cramping or aching without any elevation of Creatine Kinase (CK).Myositis was defined as any muscle weakness, soreness, tenderness, cramping or aching with a raised Creatine Kinase (CK) level of equal to or more than 10 times of upper limit of normal (CK $=/>$ 10 xULN). Rhabdomyolysis was defined as elevation of Creatine Kinase to more than 50 times of Upper Limit of Normal (CK $=/>$ 50 x ULN). Hepatitis was defined as elevation in Alanine amino transferaselevel (ALT) of equal to or more than 3 times of upper limit of normal (ALT $=/>$ 3 x ULN).

Sample size was calculated using open Epi software. Sample size based on frequency in population was calculated with 95% of Confidence Interval, considering 2% risk prevalence ratio of atherosclerotic cardiovascular disease in local Pakistani population. Study was approved by the PNS-Ethical review committee

Data was entered and analyzed using SPSS version 21.0.Qualitative data like gender, medical morbidities like DM, HTN, IHD and CVA and type of statin were presented by frequencies and percentages. Mean and SD was calculated for quantitative variable. Chi-square test was applied and p-value < 0.05 was taken as significant.

RESULTS

A total of 1350 patients aged between 20-80 years (Mean age 55.7 $\pm$ 10.2) were included in the study. Majority of patients 768 (56.9%) were between 41-60 years of age group. There were 717 (53.1 %) male patients. Regarding the frequency of co morbidities 786 (58.2 %) had diabetes mellitus (DM), 566 (41.9 %) had hypertension (HTN), 351 (26 %) of the patients had dyslipidimia, 1186 (87.9 %) of patients had ischemic heart disease (IHD, and 127(9.41 %) of the patients had CVA. Commonly prescribed statins were rosuvastatin, atorvastatin and simvastatin. Rosuvastatin (10-20mg) was prescribed to 760 (956.3%) patients, atorvastatin (20-40 mg) to 445 (33%) and simvastatin (20-40 mg) to 145 (10.7%) patients. (Table.1)

The most common side effect noted was myalgia, 91 (6.7%) patients. Second most common side effect was hepatitis, noted in 39 (2.9%) patients. Myositis was less common and was reported in 11 (0.8%) patients. All adverse effects i.e. myalgias, hepatitis and myositis were significantly more common at Atorvastatin and simvastatin 40 mg and also in female gender ($p \leqslant 0.05$).Rhabdomyolysis (CK $\geqslant$50 ULN) was not reported in any patient. (Table.2)

Table 1: Demographic Characteristics of the study population. (n=1350)

Variables	n (%)
Total no of patients	1350(100)
Mean Age	55.7±10.2
Age groups:	
20-40 yrs.	118 (8.7)
41-60 yrs.	768 (56.9)
61-80 yrs.	464 (34.4)
Gender	
Male	717 (53.1)
Female	633 (46.9)
DM	786 (58.2)
HTN	566 (41 .9)
Dyslipidimia	351 (26)
Ischemic heart disease	1186 (88)
CVA	127 (9.4)
Statins :	
Rosuvastatin :	
10 mg	496 (36.7)
20 mg	264 (19.6)
Atorvastatin :	
20 mg	255 (19
40 mg	190 (14)
Simvastatin :	
20 mg	76 (5.6)
40 mg	69 (5)

DISCUSSION

Like all other medicines statins have adverse side effects. On the basis of our study, the frequency of adverse events associated with currently available, FDA approved statins is low. Musculoskeletal system, liver and renal functions are known to be affected by statin treatment.[10]

One of the most frequently reported side effects of statinsis myalgia. According to studies the incidence ofmyalgia with currently prescribed statins ranges from 1.1% to5.0 %.[11,12] In our study the reported frequency was 6.7% which is a bit higher than reported in the literature. Of these who developed myalgias (n=91) majority were taking atorvastatin (n = 31) and simvastatin (n = 49). No special intervention was done other than prescription of common pain killer acetaminophen. Although occurrence of myalgia is universally acknowledged with the use of statins, the potential to cause myalgiasvaries among different statins. However various other factors may be responsible for this presentation such as damage of muscle fibers without elevated CK levels.[11]

Myositis is generally accompanied by the presence of pain, tenderness, weakness secondary to pain and restriction in mobility with elevation of CK. In an analysis of different randomized, placebo-controlled trials of FDA-approved statins, there was a non-significant reported frequency of

Table.2. Adverse effects of the statins of study population (n=1350)

Variables	Myalgia	Myositis	Rhabdomyolysis	Hepatitis
	n (%)	n (%)	n (%)	n (%)
Age groups				
20-40 yrs.	07 (.06)	00 ()	0	04 (10)
41-60 yrs.	45 (.058)	05 (45)	0	19 (48)
61-80 yrs.	39 (.084)	06 (55)	0	16 (42)
Gender;				
Male	46 (.064)	02 (18)	0	19 (48)
Female	45 (.071)	09 (82)	0	20 (52)
DM yes	56 (.071)	10 (91)	0	30 (77)
no	35 (.062)	01 (09)	0	09 (23)
HTN yes	42 (.04)	05 (45)	0	23 (59)
no	49 (.06)	06 (55)	0	16 (41)
Dyslip yes	23 (.065)	03 (27)	0	09 (23)
no	68 (.068)	08 (77)	0	30 (77)
CAD yes	83 (.07)	11 (100)	0	36 (92)
no	08 (.05)	00 (00)	0	03 (08)
CVA yes	10 (.08)	00 (00)	0	06 (15)
no	81 (.06)	11 (100)	0	33 (85)
Statins:				
Rosuvastatin				
10 mg	01 (.002)	00 ()	0	00
20 mg	05 (.02)	00 ()	0	01 (2.5)
Atorvastatin				
20 mg	01 (.004)	00 ()	0	01 (2.5)
40 mg	31 (.16)	05 (45)	0	14 (36)
Simvastatin				
20 mg	04(.05)	00 ()	0	07 (18)
40 mg	49 (.7)	06 (55)	0	16 (41)

myalgia in statin-treated patients compared with placebo-treated patients. This is consistent with recent reports suggesting relatively low rates of myalgia in patients enrolled in clinical trials.[12,13] Furthermore myositis (defined as elevations greater than 10 times upper limit of normal) occurred in only 0.9% of patients treated with any of the approved statins, which was not statistically significant compared with the incidence of CK elevations in patients receiving placebo therapy. In the present study statins were tolerated very well by all the participants; none of them withdrew because of any disabling adverse event. Body aches, pains and muscle tenderness were observed but only11 (0.8%) of these patients had laboratory evidence of myositis. Of these five patients were taking atorvastatin and six patients were taking simvastatin. In these patients we reduced the dose of statin. Upon reduction of the dose both symptoms and CK level improved.

Rhabdomyolysis is a rare but serious side effect of statin use secondary to muscle damage. It is characterized by marked elevation of CK activity usually greater than 50-fold, plus myoglobinemia leading to myoglobinemia, and ultimately myoglobin-induced acute renal failure.[15] Rhabdomyolysis is more aggressive and severe form of statin-induced myopathy, resulting in severe skeletal muscle injury, and excretion of dark brown urine. We did not find a single case of this serious side effect secondary to statin use in our study population. The result of present study is consistent with previous studies and supports the rare incidence of rhabdomyolysis with currently available statins.[13,14]

Elevations in hepatic transaminases occurred significantly more frequently with statins than with placebo but progression to liver failure is exceedingly rare. Overall statin-induced hepatotoxicity is rare and may present with asymptomatic elevation of serum transaminases. Elevated transaminase levels are usually not significant and reverse back to normal with dose modification. In the present study 39 (2.9%) developed statin induced hepatitis of which 14 were on atorvastatin 40mg and 16 were on simvastatin 40mg. ALT levels improved upon dose reduction/ switch over to other statin. We did not find any significant signs and symptoms suggestive of serious liver disease. This finding isconsistent with previous published reports.[16,17] However, statin induced hepatotoxicity may lead to hepatitis, cholestasis, and acute liver failure (ALF). Statin-induced ALF is usually dose and duration dependent therefore FDA now recommend that liver enzyme tests should be performed before starting statin therapy and when clinically indicated .

Most of the adverse findings were with recommended doses of atorvastatin and simvastatin i.e. 40 mg each. It is possible that at higher doses like 80 mg, atorvastatin or simvastatin be with more side effects. Female gender symptoms were also significant.

Due to presence of various co-morbid conditions, it has been suggested that lowest possible dose of statins should be used in elderly patients.The current guidelines state that statins may be used safely in patients with chronic renal diseases if the dose is appropriately adjusted. None of patients in our study were with any chronic liver or chronic renal disease.

The low incidence of adverse events seen in our study supports the current American College of Cardiology/ American Heart Association/National Heart, Lung, and Blood Institute guidelines and recommendations regarding performing laboratory tests only after patients present with symptoms.

LIMITATIONS

In the present study patients self reported symptoms and signs were evaluated therefore recall biased could not be avoided. We had no data to perform subgroup analyses based on higher doses i.e. rosuvastatin 40 mg, atorvastatin/ simvastatin 80 mg and thus no inferences canbe made with respect to very high doses of individual statins. None of our patients were with chronic renal disease. Liver function tests and serum creatine kinase levels were not routinely checked in all patients because of limited resources before the starting of the drug. Therefore the findings of our study must be interpreted from the perspective of the limitations of the study.

CONCLUSION

There is a low frequency of adverse events associated with the use of commonly prescribed statins in routine clinical practice. Further large scale studies are needed to validate our findings especially on higher doses and in patients with chronic co morbidities. The knowledge of common statin-associated adverse effects will enable health care professionals regarding appropriate use of statins for their patients as the benefits of statins greatly outweigh its risks.

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