Atorvastatin-Induced Myalgia in Iranian Patients: A Hospital-Based Study to Determine the Prevalence and Associated Risk Factors

Farzaneh Dastan[1,2], Jamshid Salamzadeh[1], Ali Saffaei[3], Yasaman Nabavi[1], Mohammad Abbasinazari[1*]

[1]Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[2]Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[3]Student Research Committee, Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

ARTICLE INFO

ABSTRACT

Background: Statins are associated with several muscle complaints, such as: myositis, myalgia, muscle weakness, muscle spasms and rhabdomyolysis. Age, race, gender, dose of statin, concomitant medications, concomitant disorders and genetics have been reported as the most important risk factor for statin-induced myalgia. The aim of this study was to determine the prevalence and associated risk factors of atorvastatin-induced myalgia in hospitalized patients in Tehran, Iran.

Methods: In this cross sectional study, a questionnaire was developed by expert panel opinions. The questionnaire was included various items regarding demographic data and myalgia evaluation factors. Seven hundred patients were included in the study and necessary data were gathered. Finally, the data were analyzed and a statistical model was designed to predict the myalgia risk factors.

Results: The rate of myalgia was 44.3% among studied patients. By developing a multivariate logistic model, female gender (OR= 0.47, P-value<0.001) was one of the most important factors in myalgia occurrence.

Conclusion: The results of this study suggest that gender, age, atorvastatin dose, duration of atorvastatin usage and presence of myotoxic disease are the main predictors of myalgia in Iranian population. Hence, the findings of this study can be considered to predict the myalgia incidence risk in Iranian population.

J Pharm Care 2020; 8(4): 176-179.

► Please cite this paper as:

Dastan F, Salamzadeh J, Saffaei A, Nabavi Y, Abbasinazari M. Atorvastatin-Induced Myalgia in Iranian Patients: A Hospital-Based Study to Determine the Prevalence and Associated Risk Factors. J Pharm Care 2020; 8(4): 176-179.

Introduction

Statins are associated with several muscle complaints, such as: myositis, myalgia, muscle weakness, muscle spasm and rhabdomyolysis. These adverse effects may occur concurrently with serum creatine kinase (CK) elevations (1). Statins significantly decrease the cholesterol levels and the morbidity and mortality associated with heart disease (2). Myalgia is the most prevalent statin complication, and defined as muscle pain. It can impair the patient's quality of life. Also, it has a negative effect on patient's adherence to their medication (3). Interruption of the HMG-CoA (5-hydroxy-3-methylglutaryl-coenzyme A) reductase pathway and depletion of downstream intermediate metabolites and end products, are the probable mechanisms of statin-induced myotoxicity (4). Risk and severity of myalgia increase in presence of certain risk factors such as: age, race, gender, dose of statin, concomitant medications and concurrent disorders (5). In addition, genetic and genome polymorphism have undeniable roles in the occurrence of myalgia by altering the metabolism of statins (6, 7). Some studies suggested that individualized risk assessment for statin-induced myalgia should be determined by population-based studies (5). Atorvastatin is the most used statin in Iranian hospitals (2). On the other hand, there is lack of evidences regarding the true frequency of statin-induced myalgia (8).

Corresponding Author: Dr Mohammad Abbasinazari
Address: Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Niayesh Highway, Valiasr Ave., Tehran, Iran.
Telefax: +982188200118. Zip code: 1991953381.
Email: m_abbasi@sbmu.ac.ir

The aim of this study was to evaluate the prevalence and associated risk factors of atorvastatin-induced myalgia in Iranian patients. The primary outcome was to determine incidence of myalgia rate in evaluated patients. The secondary outcome was to determine related risk factors of atorvastatin-induced myalgia as well.

Methods

This cross sectional study was done in Masih-Daneshvari and Taleghani hospitals, two main referral centers, between January 2018 and September 2019. This study was approved by the ethics committee of Shahid Beheshti University of medical Sciences (Approval Number: R. SBMU.PHNM.1395.548). Convenience sampling approach has been used for patient selection in the present study.

The inclusion criteria were defined as all patients who were receiving atorvastatin during past three months. Patients with any known fibromyalgia, diabetic neuropathy or connective tissue diseases were excluded from the study. An expert panel, consisting of five expert clinical pharmacists developed a valid and reliable tool. This tool was developed based on the Rosenson et al., study that designed an algorithm for the evaluation of patients with statin-induced myalgia (9). In addition, this tool was improved by the comments of the expert panel to be more feasible in Iranian population. The tool has two sections regarding demographic characteristics including age, gender, ward, smoking status, atorvastatin dose, duration of atorvastatin consumption, concurrent medications, and concurrent diseases. Second section was consisted of some items to evaluate the myalgia including presence of myalgia, pattern of myalgia and the onset of myalgia occurrence.

The interviewer of this study referred to the hospitals regularly. All patients who were taking atorvastatin were identified by using hospital information system. The interviewer visited the patients and the required items based on the developed tool, were filled by a face-to-face interview. The data collector was a trained student of pharmacy.

Finally, the gathered information imported into SPSS version 23.0 software (SPSS Inc., II, USA). The descriptive statistics presented and Kolmogorov-Smirnov test was used to determine the normality distribution. Consequently, the differences of myalgia characteristics were compared between different demographic variables by chi-square test. Also, a statistical model was computed to predict the effects of demographic variables on the final outcomes. The significant level considered as P value less than 0.05 and the results were reported as Mean ± Standard Division (SD). Sample size has been determined by using Gpower software (Clincalc.com). As statin induced myopathy has been reported up to 51% in previous study (10) by considering incidence of at least 45% incidence of this adverse reaction in present study, alpha equal to 0.05 and beta equal to 80%, sample size has been estimated at least 543. So we have evaluated 700 patients (more than estimated amount).

Results

In this cross sectional study, 700 patients were visited and the required items were gathered. The mean age of studied patients was 61.32 ± 12.51 years. Three hundred and forty (48.6%) of patients were male and 360 (51.4%) of patients were female. From 700 patients, 310 patients (44.3%) reported myalgia. Distributions of demographic and related parameters regarding statin usage have been shown in Table 1.

Table 1. The baseline characteristic of patients who screened in this study.

Variables		Patients with Myalgia	Patients without Myalgia	*P*-value
Number		310	390	-
Age (Mean±SD)		67.08 ± 11.33	56.74 ± 11.48	<0.001
Gender N(%)	Male/Female	133 (19%) / 177 (25.28%)	207 (29.57%) / 183 (26.14%)	0.007
Ward N(%)	Cardiovascular care unit	121 (17.28%)	171 (24.42%)	0.21
	Endocrinology	83 (11.85%)	88 (12.57%)	
	Pulmonary disease	45 (6.42%)	57 (8.14%)	
	Nephrology	34 (4.85%)	28 (4%)	
	Internal medicine	27 (3.85%)	46 (6.57%)	
Smoking N(%)	Yes/No	34 (4.85%) / 276 (39.42%)	41 (5.85%) / 349 (49.85%)	0.85
Atorvastatin dose (Mean±SD)		25.68 ± 10.24	22.41 ± 8.01	<0.001
Duration of atorvastatin consumption N(%)	Less than one month	13 (1.85%)	108 (15.42%)	<0.001
	Less than three months	8 (1.14%)	74 (10.57%)	
	More than three months	289 (41.28%)	208 (29.71%)	
Consumption of Susceptible myotoxic Drugs N(%)	Yes/No	145 (20.71%) / 165 (23.57%)	122 (17.42%) / 268 (28.28%)	<0.001
Presence of myotoxic associated diseases N(%)	Yes/No	269 (38.42%) / 41 (5.85%)	199 (28.42%) / 191 (27.28%)	<0.001

The second section of the developed tool was regarded to the characteristics of myalgia pain. The pattern of myalgia pain is summarized in Table 2.

Table 2. The pattern of myalgia pain in this study.

Pattern	Incidence N (%)
Non-specific pain	6 (1.93%)
Symmetric calf aches or symmetric upper proximal aches	98 (31.61%)
Symmetric hip flexor/thigh aches	15 (4.83%)
Symmetric calf aches and symmetric upper proximal aches	17 (5.48%)
Symmetric calf aches or symmetric upper proximal aches and symmetric hip flexor/thigh aches	59 (19.03%)
Symmetric calf aches and symmetric upper proximal aches and symmetric hip flexor/thigh aches	115 (37.09%)

Based on the results, 115 patients (37.1%) experienced symmetric calf aches and symmetric upper proximal aches and symmetric hip flexor/thigh aches. On the other hand, non-specific pain pattern was the less probable one, which was reported in the study. The onset time of myalgia showed that 41 patients (13.22%) manifested myalgia less than four months. Twenty-two patients (7.09%) showed myalgia for less than four months ago, and 247 patients (79.67%) suffered from myalgia for less than 12 months ago. Finally, based on the gathered data, a statistical model was developed by multivariate logistic regression. This model showed that female gender (Odds Ratio= 0.47, P-value<0.001), high doses of atorvastatin (Odds Ratio= 1.07, P-value<0.001), longer duration of atorvastatin consumption at older ages (Odds Ratio= 1.02, P-value<0.001), and presences of associated myotoxic diseases at older ages (Odds Ratio= 1.024, P-value<0.001) are the most prevalent risk factors for developing myalgia (Figure 1).
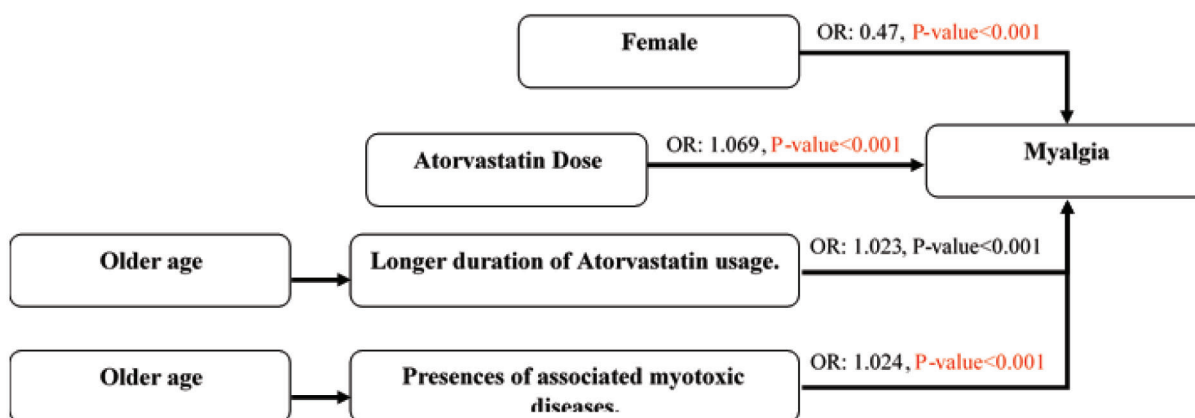
Figure 1. The statistical model of associated risk factors involving in atorvastatin-induced myalgia.

Discussion

In this cross sectional study, the prevalence of atorvastatin-induced myalgia and its associated risk factors were studied in two main educational hospitals of Tehran, Iran. The prevalence of atorvastatin-induced myalgia was 44.3% in this study.

Atorvastatin-induced myalgia prevalence was reported 4% in the previous studies, which is much lower than the numbers reported by our study (10). Conversely, the prevalence of muscle related symptoms with statins have been reported over 42% in some trials (11). In a cross-sectional study which was done by Sadeeqa et al., in Pakistan, the prevalence of statin-induced myopathy have been reported as high as 51% (12), which was similar to our study; however, these results contradict much lower rates reported by previous authors (9). Sadeeqa et al., results also suggest that the patients with older age may develop myalgia more than younger patients. This result is similar to other published studies in which reported the association of age and statin-induced muscular symptoms

(13). In the older adults, lipophilic statins can be deposit in their tissues more than younger people (14). Another finding of this study showed that the female patients reported myalgia more than male patients. Generally, adverse drug reactions are more prevalent among females (15). Females tend to have more of body fat, which alters the volume of distribution of some medications and can meaningfully increase the half-life of statins, particularly lipophilic statins (16, 17).

In 2017, Manoj et al., studied the prevalence and risk factors of statin-induced myopathy in Indian population. They found that the statin-induced myopathy is more prevalent in the female gender compared to the male gender. The results also showed that smoking is not a significant predictor of atorvastatin-induced myalgia. Other previous studies also found the smoking as a non-significant predictor of myalgia (18). In contrast, Bruckert et al., in 2005, revealed that smoker patients experience myalgia lower than non-smoker ones (19). Atorvastatin dose and duration of therapy are the other important predictors of myalgia. This finding is similar to the

previous published studies in which myalgia is introduced as a dose-dependent adverse effect of statins. In addition, to manage the statin-induced myalgia, it is recommended to switch to low-dose, non-daily doses of long-acting statins (8). Parker et al., in 2013, found that taking atorvastatin at high doses for 6 months did not lead to myalgia in healthy, previously untreated subjects (20).

Concurrent medications and diseases are also important predictors of myalgia. Interactions between atorvastatin and other medications, such as Colchicine and lipid lowering agents, lead to accumulation of statins in the body. Also, there are some underlying diseases such as hypothyroidism, renal or liver disease, diabetes mellitus and trauma in which the statins induced-myalgia is increased (21). The final model of this study suggests that gender, age, atorvastatin dose, duration of atorvastatin usage and presence of myotoxic disease maybe the main predictors of myalgia in Iranian population. Hence, the finding of this study can be considered as a model to predict the myalgia incidence risk. By using the results of this study, the myalgia may prevent effectively and the patients' compliance to their medication can be improved.

References

1. Tobert JA. Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors. Nat Rev Drug Discov 2003;2(7):517-26.

2. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol 2006;48(3):438-45.

3. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA 2003; 289(13):1681-90.

4. Chatzizisis YS, Koskinas KC, Misirli G, Vaklavas C, Hatzitolios A, Giannoglou GD. Risk factors and drug interactions predisposing to statin-induced myopathy: implications for risk assessment, prevention and treatment. Drug Saf 2010;33(3):171-87.

5. Feng Q, Wilke RA, Baye TM. Individualized risk for statin-induced myopathy: Current knowledge, emerging challenges, and potential solutions. Pharmacogenomics 2012;13(5):579-94.

6. Frudakis TN, Thomas MJ, Ginjupalli SN, Handelin B, Gabriel R, Gomez HJ. CYP2D6*4 polymorphism is associated with statin-induced muscle effects. Pharmacogenetics Genomics 2007;17(9):695-707.

7. Arrigoni E, Del Re M, Fidilio L, Fogli S, Danesi R, Di Paolo A. Pharmacogenetic Foundations of Therapeutic Efficacy and Adverse Events of Statins. Int J Mol Sci 2017;18(1):104.

8. Abd TT, Jacobson TA. Statin-induced myopathy: a review and update. Expert Opin Drug Saf 2011;10(3):373-87.

9. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel. An assessment by the Statin Muscle Safety Task Force: 2014 update. J Clin Lipidol 2014;8(3 Suppl):S58-71.

10. Mashayekhi SO, Ghandforoush Sattari M, Baghdadchi ME, Kheyri M. Patients' report of statins use and side-effects in a sample of hospitalized cardiac patients in the Islamic Republic of Iran. Eastern MediterraneanHealth Journal 2011;7(5):460-464.

11. Riaz H, Khan AR, Khan MS, et al. Meta-analysis of Placebo-Controlled Randomized Controlled Trials on the Prevalence of Statin Intolerance. Am J Cardiol 2017;120(5):774-81.

12. Sadeeqa S, Maqsood M, Ahmad M. Prevalence of statin induced myopathy in Lahore, Pakistan. Pak J Pharm Sci 2018;31(2(Suppl.)):617-22.

13. Iwere RB, Hewitt J. Myopathy in older people receiving statin therapy: a systematic review and meta-analysis. Br J Clin Pharmacol 2015;80(3):363-71

14. Bitzur R, Cohen H, Kamari Y, Harats D. Intolerance to statins: mechanisms and management. Diabetes Care 2013;36 Suppl 2:S325-30.

15. Tran C, Knowles SR, Liu BA, Shear NH. Gender differences in adverse drug reactions. J Clin Pharmacol 1998;38(11):1003-9.

16. Anderson GD. Gender differences in pharmacological response. Int Rev Neurobiol 2008;83:1-10.

17. Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol 2001;2(6):349-51.

18. Manoj K, Jain N, Madhu SV. Myopathy in Patients Taking Atorvastatin: A Pilot Study. Indian J Endocrinol Metab 2017;21(4):504-9.

19. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. Cardiovasc Drugs Ther 2005;19(6):403-14.

20. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. Circulation 2013;127(1):96-103.

21. Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. Circulation 2004;109(23 Suppl 1):III50-7.