



Original Article

Statins everyday versus alternate days: Is there a difference in myalgia rates?☆



Ramsha Riaz, Aleena Zehra Merchant, Muhammad Salman Ul Haq, Syed Ali Raza Nasir, Yusra Rizvi*, Jehanzeb Ahmed Khan, Sara Mohiuddin Zakaria, Hassaan Jawed, Khizar Hamid, Noor-ul-ain Zehra, Madiha Ahmed, Hussain Asif Ali, Kaneez Fatima

Dow Medical College, Dow university of Health Sciences, Karachi, Pakistan

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ABSTRACT

Objective: Statins are widely used drugs, known to cause myalgia, leading to high discontinuation rates. The objective of our study was to determine the frequency of myalgia in patients on everyday-dose (EDD) regimen with those on alternate-day dose (ADD) regimen.

Methods: This cross sectional study was conducted in a tertiary care hospital of Pakistan. A sample size of 400 patients between the age of 40–70 years, taking simvastatin 40 mg for at least 6 months or more were selected. Patients with prior musculoskeletal or neuromuscular complains, and family history of muscular disorders were excluded. Subjects were evaluated for myalgia via a self-administered questionnaire, and those complaining of myalgia were then evaluated for serum vitamin D levels. Data was analyzed through SPSS 16.0 and compared using chi square test.

Results: The overall prevalence of myalgia was 7% (28/400). Frequency of myalgia in patients taking simvastatin everyday (n = 20, 10%) was significantly higher compared to those taking it every alternate day (n = 8, 4%) (p = 0.02). There was no significant difference between the time of onset, nature, severity, type, or location of myalgia between the 2 groups. The most common cited triggering factor for pain was physical exercise. Of the patients experiencing myalgia, 13 (6.5%) from the EDD group and 6 (3%) from the ADD group had low levels of vitamin D.

Conclusions: ADD regime was better tolerated by the patients than EDD regime. Alternate day therapy, with or without vitamin D supplementation, may be used by the physicians for troublesome muscular complains.

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1. Introduction

Statins are the most widely used lipid lowering drugs in the world with approximately 25 million people currently on statin

☆ Considering the heavy burden of cardiovascular disease, statins are commonly administered drugs. In our study, we tried to assess if alternate-day dose (ADD) could help improve compliance by decreasing the incidence of myalgia compared to everyday-dose (EDD). In our cross sectional study, we took 400 patients taking simvastatin for at least past 6 months, and those who were complaining of Myalgia were further investigated for vitamin D levels. Frequency of myalgia in patients taking simvastatin everyday (n = 20, 10%) was significantly higher compared to those taking it every alternate day (n = 8, 4%) (p = 0.02). Based on our findings, we conclude that ADD was better tolerated by patients than EDD. Hence, to achieve better patient compliance and reduce the incidence of myalgia physicians should consider ADD.

* Corresponding author at: A-110, Main Khayaban-e-Muhafiz, Phase 6 DHA, 75500, Karachi, Pakistan.

E-mail address: yusrarizvi9910@gmail.com (Y. Rizvi).

therapy.¹ Statins are highly effective for primary and secondary prevention of cardiovascular diseases (CVD).^{2,3} Although statins are usually well tolerated, skeletal muscle related side effects are commonly reported leading to high discontinuation rates.⁴

Statin associated myopathies (SAM) encompass a number of diseases ranging from simple myalgia to life threatening rhabdomyolysis.^{1,5} The term myalgia represents a heterogeneous group of muscular complains including muscle ache, stiffness, heaviness, and cramping muscle sensation.⁶ These symptoms may interfere with everyday activities and in some cases they may be severe enough to confine the patient to the bed.⁷ The incidence of myalgia in patients on statins can lie between 1 and 5% in clinical trials; but it can be as high as 15–25% in everyday clinical practice.^{5,7}

The prevalence of CVD is especially high in South Asian countries as compared to the rest of the world.^{8,9} The South Asian population has been reported to have elevated lipoprotein A which is associated with higher incidence of atherosclerosis, thrombogenesis, and other adverse clinical events.¹⁰ Moreover, the

dietary habits and growing propensity towards refined diet and fast food are all leading factors attributing to an increased risk of cardiovascular diseases.¹¹ Although extensive research has been done to understand specific lipid abnormalities, less study has been done to assess statin intolerance amongst patients in our part of the world. One proposed mechanism of improving statin tolerance is alternate day statin therapy;^{12–14} but so far no specific management goals and treatment plans exist for South Asians because of lack of data.¹⁵ The primary objective of our study was to compare the frequency of myalgia in patients who take statins every day versus every alternate day.

2. Methods

A descriptive, cross-sectional study was conducted in a tertiary care hospital of Pakistan, after approval from the hospital institutional review board. We assessed patients taking statin therapy for at least 6 months for any symptoms of myalgia.

Our sample population was divided into two groups, one group was taking simvastatin 40 mg daily, while the other group was taking simvastatin 40 mg every alternate day. These dosage levels were taken because higher doses of simvastatin are associated with an increased risk of myopathy.¹⁶ Both the groups had been on statin treatment for a similar duration of time. Purposive sampling was used to select 200 patients between the age of 40 and 70 years in each group. We did not include patients above 70 years of age because of age associated pain complaints.¹⁷ We also excluded patients with muscle complaints before the start of therapy, prior musculoskeletal or neuromuscular symptoms, or a positive family history of muscular disorders.

A self-administered questionnaire was designed that was filled by the participants. The questionnaire evaluated the duration for which the patients had been on statin therapy, the drug that they were using, its dose, and whether they were taking the dose daily or on alternate days. Other factors assessed were the patient's compliance, duration of the daily physical activity of the patient,¹ the time of onset of symptoms after the initiation of therapy, the nature, severity, location, and type of pain, and the triggering factors according to the patient. The questionnaire was translated in Urdu and interviewers were used to fill out questionnaires for patients who could not read or write. The patients who complained of myalgia were evaluated for serum vitamin D levels, since vitamin D deficiency is linked to statin-induced myalgia.¹⁸

Initially, a pilot study was performed by distributing the questionnaire amongst 15 patients who fulfilled our inclusion criteria. This was done to ensure that there were no ambiguities in any of the questions in the questionnaire.

The data were entered into Statistical Package for the Social Sciences (SPSS) 16.0 and analyzed. Chi-square test was used to assess for significance between discrete variables. An alpha value of 0.05 with a 95% confidence interval was used to measure significance for all statistical tests.

3. Results

Table 1 shows the baseline characteristics of both the groups. There was no significant difference between the groups in terms of age, gender and other variables. The difference in co-morbidities between the two groups was also insignificant apart from those caused by cardiovascular conditions ($p=0.03$).

The incidence of myalgia in patients taking simvastatin every day was significantly higher as compared to those taking it every alternate day ($p=0.02$). Twenty (10%) patients who were on a daily dosage developed myalgia, compared to 8 patients on alternate day therapy. A total of 28 (7%) patients from the entire study group complained of myalgia, amongst which more than half of the patients began experiencing symptoms in the first month. The most frequently reported nature of symptoms was cramps and weakness. Out of the 28 patients, only a few patients ($n=3$, 10.7%) described the intensity of their symptoms as being severe.

Physical exercise was the most common cited triggering factor for the symptoms in both the groups. Almost 6 times more people had intermittent pain compared to continuous pain in both the groups. Vitamin D levels among those complaining of myalgia were low in 13 (6.5%) patients from the everyday-dosage group and in 6 (3%) patients from the alternate-day therapy group. There were no significant differences between the time of onset, nature, severity, type, location or triggering factors of pain among the two groups (Table 2).

Among the drugs being taken by patients in addition to simvastatin, the most common ones were RAS acting agents, beta blockers, diuretics, anti-diabetics and anti-platelets (Table 3).

4. Discussion

Our study reveals that the overall incidence of myalgia in patients taking simvastatin 40 mg was 7% with the majority of these patients belonging to the everyday-dose (EDD) group. In randomized controlled trials, the prevalence of statin induced musculoskeletal symptoms has been found to be 1–5%,¹⁶ while cross-sectional studies have reported a much wider range, being as high as 44%.²⁰ Reasons for this wide discrepancy are the exclusion of high risk population groups in randomized controlled trials with most trials only reporting the most severe form of myopathy and

Table 1
Patient characteristics and co-morbidities. *P-value calculated using the chi-square test.

Patient Characteristics	Everyday statin n (% of 200)	Alternate day statin n (% of 200)	*P-value
Elderly patients (>65years)	78(39)	86(43)	0.42
Sex (Female)	92(46)	108(54)	0.11
Intensive laborer/athlete	10(5)	16(8)	0.22
Alcohol abuse(Yes)	10(5)	8(4)	0.63
Smoking (Yes)	42(21)	58(29)	0.06
Drugs of abuse (Yes)	12 (6)	6(3)	0.15
Co-morbidities (Total)	194(97)	196(98)	0.52
Cardiovascular	176(88)	188(94)	0.03
Metabolic and Endocrinological	166(83)	162(81)	0.60
Diabetes	141(71)	135(68)	0.52
Hypothyroidism	20(10)	15(8)	0.38
Gastrointestinal	68(34)	74(37)	0.53
Hepatic	98(49)	106(53)	0.42
Renal	62(31)	72(36)	0.29
Respiratory	38(19)	48(24)	0.22
Psychiatric and Neurological	10(5)	14(7)	0.40

Table 2
Number of patients that experienced myalgia and details of their symptoms. *P-value calculated using the chi-square test.

	Everyday statin n (% of 200)	Alternate day statin n (% of 200)	*P-value
Myalgia	20 (10)	8 (4)	0.02
<i>Onset of symptoms</i>			
<1 month	11 (5.5)	5 (2.5)	0.72
<3 months	5 (2.5)	2 (1)	>0.99
<6 months	4 (2)	1 (0.5)	0.64
<i>Nature of pain</i>			
Cramps	8 (4)	3 (1.5)	0.90
Heaviness	1 (0.5)	0 (0)	0.52
Soreness	2 (1)	1 (0.5)	0.85
Stiffness	3 (1.5)	0 (0)	0.25
Weakness	6 (3)	4 (2)	0.32
<i>Severity of pain</i>			
Mild	8 (4)	5 (2.5)	0.28
Moderate	9 (4.5)	3 (1.5)	0.72
Severe	3 (1.5)	0 (0)	0.25
<i>Type of pain</i>			
Intermittent	17 (8.5)	7 (3.5)	0.86
Continuous	3 (1.5)	1 (0.5)	0.86
<i>Location of pain</i>			
Generalized	9 (4.5)	6 (3)	0.15
Localized	11 (5.5)	2 (1)	0.15
<i>Triggering factors</i>			
Physical exercise	12 (6)	5 (2.5)	0.90
Resting or lying down	5 (2.5)	2 (1)	>0.99
Cold/flu	3 (1.5)	1 (0.5)	0.86
Low Vitamin D	13 (6.5)	6 (3)	0.61

Table 3
Drugs taken by participants along with simvastatin. NSAIDs: nonsteroidal anti-inflammatory drugs, RAS: renin-angiotensin system.

Drug	Everyday statin (% of 200)	Alternate day statin (% of 200)
RAS acting agents	75%	72%
Beta Blockers	59%	63%
Diuretics	62%	65%
Calcium channel blockers	33%	27%
Digoxin	12%	9%
Antiarrhythmic	6%	4%
Antidiabetics	63%	61%
Antiplatelet	54%	48%
Anticoagulants	21%	19%
Immunosuppressive agents	6%	8%
Antimicrobials	17%	16%
NSAIDs	25%	22%
Steroids	15%	11%
Fibrates	5%	7%
Proton pump inhibitors	27%	22%

overlooking the much more common myalgia; and failure of the enrolled participants in trials to recognize and report symptoms of myalgia, leading to underestimation of the enormity of the situation.^{7,21}

Most of the previously conducted researches comparing the efficacy of altering drug regimen involve patients on either rosuvastatin^{22,23} or atorvastatin,^{2,24} since these statins have longer half-lives.²⁵ Hence, there's a paucity of data concerning the effectiveness of simvastatin in this regard. Results of our study are similar to previously conducted researches employing either of these 2 long-acting statins. In a study conducted by Backes et al²² on previously statin intolerant patients, it was found that >70% of them were able to tolerate the drugs when shifted to an every other day rosuvastatin regimen. Similarly, another study demonstrated that in individuals experiencing previous statin adverse effects, a once per week dosage of rosuvastatin was tolerated by 74% of the 50 participants.²³

A link between lipid lowering efficacy of the 2 drug regimens was not investigated in our study, but various researchers have found no significant difference in the lipid lowering efficacy of EDD and an alternate-day dose (ADD) regimen of statins in participants

taking simvastatin,²⁶ rosuvastatin²⁷ or atorvastatin.^{2,24} This indicates that an ADD may prove to be an effective option not only in reducing the frequency of myalgia, but also in terms of comparable lipid lowering capacity. On the contrary, a review article has emphasized on the cautious use of ADD, since this regimen provides 10–15% lower LDL-C reduction compared to the everyday regimen, and has not been proven to reduce cardiovascular events.²⁵ Therefore, addition of non-statin drugs may be essential for treatment of high risk patients who develop myalgia with daily dose regimens, and need to shift to an alternate day regimen.

Although the exact mechanism of statin induced muscle symptoms is poorly defined and remains largely misunderstood,²⁵ one of the reasons why subjects on ADD may have had lower frequency of myalgia could be the lower overall plasma and muscle concentration of drug and a positive psychological factor of receiving less than required drugs.^{22,25} Another factor to be taken into account is the fact that the risk of myopathy is amplified with more lipophilic statins such as simvastatin²⁸ and hence it may have accounted for a greater overall prevalence of myalgia in our study.

We observed that physical exercise was the most common triggering factor for myalgia. Several studies support the hypothesis that statin-associated musculoskeletal side effects can be exacerbated by physical activity.^{29–31} This effect might be because physically active individuals are more inclined to receive low level muscle injury, which then becomes more pronounced by statin treatment,³¹ manifesting more often as myalgia. Conversely in another study, myalgia was reported to occur most often during rest and the lying position.³² Since exercise is a commonly advised component of lifestyle modification for patients with CVD,³³ it is imperative to carry out further research to find out the level and type of exercise which patients on statins can safely undertake.

The findings of this study have important future implications in clinical practice for both physicians and patients. Studies report that myalgia often poses a limitation to statin use by patients, and is one of the leading reason patients are either non-compliant to therapy or discontinue the use of statins.¹⁹ Improved compliance to statin therapy and subsequent decreased risk of cardiovascular events would help lower the economic burden of this disease, and save the overall costs of medical bills. Moreover, alternate day therapy can provide some financial relief by bringing down medical expenses, and contribute in reducing the grave consequences of inadequate compliance.

Our study also reports that majority of subjects complaining of myalgia (65% EDD, 75% ADD) were found to have concurrent low Vitamin D levels. Previous literature studying the relationship between statins and vitamin D has been rather inconsistent and inconclusive. This finding of our study is supported by a number of researches that have found a vitamin D deficit in patients on statin therapy.^{18,34} Furthermore, a meta-analysis involving 2420 statin-treated patients from 7 studies provided substantial evidence of a link between plasma vitamin D levels and statin-associated myalgia.³⁵ On the other hand, some studies have failed to find any link between low plasma levels of vitamin D and associated statin-induced myalgia,^{36,37} further supported by a recent randomized controlled trial that did not find any significant effect on vitamin D levels with short-term simvastatin (40 mg/day) use.³⁸ Since we did not measure our subject's vitamin D levels prior to statin therapy, we cannot conclude whether the deficiency was a result of statin use or prior deficiency led to the development of myalgia in these patients.

Several studies have reported that when patients with low serum vitamin D levels are supplemented with vitamin D, resolution of muscle symptoms occur in 92% patients,¹⁸ with subsequent reversal of statin intolerance.³⁹ Keeping these findings in mind, the physician could consider trying supplement therapy in statin intolerant patients.

There are a number of limitations in our study which need to be considered. Firstly, the sample size was small and subjects were selected from only one tertiary care hospital of the city. Even though it is one the largest hospitals of Pakistan, with a daily influx of patients from all over the country, including subjects from various other health care units and taking a much larger sample size would have allowed us to generalize our results to a wider population. Secondly, our study was based on a self-reporting tool to assess symptoms and severity of myalgia. This approach is not only subjective and arbitrary, but also includes the element of recall bias, since subjects may have had difficulty giving an account of events occurring over the last 6 month period. Thirdly, our study lacked randomization and the use of a control group in the form of either subjects receiving placebo, or age and gender matched subjects not diagnosed with hyperlipidemia and not receiving any lipid lowering therapy. Similarly, myopathy as a result of the use of lipid-lowering drugs has been reported to occur more often in subjects with conditions such as impaired renal function.⁴⁰ Since greater than 30% subjects from

each group had concurrent renal disease there's a possibility that myalgia may have been over exaggerated in these subjects. Lastly, our study did not measure, compare, or contrast the plasma lipid levels between both the groups, and did not follow up the patients for a period of time, hence we cannot assess whether the benefits of ADD in reducing myalgia outweigh the risk of ineffective lipid lowering efficacy.

5. Conclusion

The results of our study indicate that an ADD regimen was better tolerated than an EDD regimen. Hence the physician may consider choosing an alternate day therapy, and vitamin D supplementation for patients with troublesome muscular complaints affecting their compliance. However, large scale randomized controlled trials are required to fully assess the effectiveness of ADD regimen.

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Conflict of interest

None.

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