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Statins Everyday Versus Alternate days: Is There a Difference in Myalgia rates?☆

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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.

1. Introduction

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

☆ 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.

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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 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 overlooking

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

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