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Tolerability and effectiveness of every-other-day atorvastatin compared to daily atorvastatin in patients with muscle symptoms: A randomized controlled clinical trial

Nirmala Wijekoon [a, *], Sanjeewa Wijekoon [b, c], Uditha Bulugahapitiya [c], Nethrani Pathirana [b], Malintha Wickramasinghe [b], Shiran Paranavitane [c], Arosha Kottage [c], Supun Wijayawardena [b], Mihipali Karunarathne [b], Madusha Samarasinghe [b], Subodha Sumanadasa [c], Yanushka Herath [c]

[a] Department of Pharmacology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Gangodawila, Nugegoda, Sri Lanka
[b] Department of Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura, Gangodawila, Nugegoda, Sri Lanka
[c] Colombo South Teaching Hospital, Kalubowila, Sri Lanka

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ABSTRACT

Despite limited evidence, non-daily dosing of statins is recommended for managing muscle symptoms associated with statin therapy. We assessed the tolerability and effectiveness of every-other-day atorvastatin compared to daily atorvastatin in patients having muscle symptoms associated with atorvastatin therapy. A parallel-group, outcome-assessment-blinded, randomized controlled clinical trial was conducted at Colombo South Teaching Hospital, Sri Lanka. Patients with muscle pain, tenderness or cramps alone or in combination for ≥2 weeks while on daily atorvastatin for ≥1 month, with no alternative cause, were recruited. Patient's regular atorvastatin dose was given every-other-day to those in intervention group (IG) and daily to those in control group (CG). Primary outcomes were assessed at 24 weeks and included composite of myalgia and myositis, LDL-cholesterol level and percentage reduction of LDL-cholesterol from baseline. Number recruited was 49 to IG (women:79.6%; mean-age:60.6 ± 8.7years) and 52 to CG (women:73.1%; mean-age:61.7 ± 9.8years). Mean atorvastatin dose per day was 8.6 mg (SD = 4 mg) and 17.6 mg (SD = 8.4 mg) in IG and CG, respectively. Composite of myalgia and myositis at 24 weeks was 79.6% in IG and 69.2% in CG (OR = 1.7, 95% CI 0.7–4.3; p = 0.234). IG failed to show noninferiority for mean LDL-cholesterol (difference:0.31 mmol/L; upper limit 97.5% CI:0.61 mmol/L; p for noninferiority = 0.989) and for mean percentage reduction of LDL-cholesterol from baseline (difference:3.13%; upper limit 97.5% CI:15.5%; p for noninferiority = 0.718). At 24 weeks, mean creatine kinase and discomfort due to muscle symptoms (assessed with Visual Analogue Scale) were not different between the two groups. Findings of this study do not favor every-other-day atorvastatin as an option for managing patients with muscle symptoms associated with atorvastatin therapy.

1. Introduction

Based on a large and consistent body of evidence, statins are recommended for primary and secondary prevention of cardiovascular diseases [1,2]. The most commonly reported adverse effect of statin use in clinical practice is muscle symptoms [3–11]. It is likely to be encountered more frequently as the number of patients eligible for statin therapy continue to rise while the LDL-cholesterol targets are becoming stricter.

The spectrum of muscle symptoms associated with statin use ranges from common but relatively benign myalgia to rare and fatal rhabdomyolysis. American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines defines myalgia as muscle symptoms without creatine kinase (CK) elevation, myositis/myopathy as muscle symptoms with CK elevation above the upper limit of normal (ULN) and rhabdomyolysis as CK elevation >10 times ULN with renal injury [1]. Most often the patients who complain of muscle symptoms in clinical practice have normal or slightly elevated CK level [11].

* Corresponding author.
E-mail address: nirmalawijekoon@sjp.ac.lk (N. Wijekoon).

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Muscle problems of any degree are important from the patient's point of view as they could interfere with an individual's activities of daily living and quality of life [6]. Muscle symptoms are identified as a clinically important cause for poor compliance to statin therapy [1,3,4]. Non-adherence is likely to occur even when the muscle symptoms are not serious and life-threatening because patients receive statins not for improving any symptom but for prognostic benefit. Furthermore, these symptoms could potentially interfere with exercise tolerance, depriving the patient of the cardiovascular benefits of regular exercise.

There are no randomized trials that can provide firm evidence to guide clinicians regarding management of muscle symptoms associated with statin use. However, several options have been recommended based on trials with methodological limitations, observational studies and expert opinion. These include discontinuation and re-challenge, dose reduction, non-daily dosing regimens, switching to an alternative statin and combining low-dose statin with non-statin lipid lowering therapy [1,2,11–15]. Data to support any of these options regarding improved tolerability, LDL-cholesterol reduction or clinical endpoints are limited and there is a need for further research, especially pragmatic clinical trials to determine the best treatment option for this problem [13].

Half-lives of atorvastatin and rosuvastatin are long, 15-h and 19-h, respectively making them suitable candidates for non-daily dosing regimens [15,16]. The duration of the cholesterol-lowering effect of atorvastatin is even longer than expected from its half-life because it has active metabolites with longer half-lives [16,17]. There are several studies providing some evidence to support the use of non-daily dosing regimens of rosuvastatin in those with muscle problems [12,18–25]. Even though the tolerability of non-daily dosing of atorvastatin in combination with non-statin lipid lowering drugs has been evaluated in a few studies [23,26,27], to date no evidence is available regarding the tolerability of intermittent dosing of atorvastatin monotherapy.

We conducted a randomized controlled clinical trial to assess the tolerability and effectiveness of every-other-day atorvastatin compared to daily atorvastatin in a Sri Lankan population with muscle symptoms associated with atorvastatin therapy.

2. Methods

2.1. Study design

This was a parallel-group, outcome-assessment-blinded, randomized controlled clinical trial conducted at a single centre in Sri Lanka. Patients fulfilling eligibility criteria were randomized in a 1:1 ratio to receive, their regular dose of atorvastatin every-other-day or daily for a period of 24 weeks.

2.2. Patients

Study population consisted of patients at three outpatient clinics in Colombo South Teaching Hospital, Sri Lanka who experienced muscle symptoms while on atorvastatin daily. Inclusion criteria for the trial were: age ≥18 years, being on atorvastatin for ≥1 month and presence of unexplained, new onset muscle pain, tenderness or cramps alone or in combination involving two or more of the muscle groups in gluteal regions, thighs, calves, upper arms or forearms and persisting for 2 weeks or more. Exclusion criteria were: rhabdomyolysis (CK elevation >10 times ULN with elevation of serum creatinine), CK > 5 times ULN, thyroid dysfunction, rheumatological disorders, ESR ≥40 mm, hypokalemia, hyponatremia, chronic kidney disease with eGFR ≤45 ml/min/1.73 m^2, chronic liver disease, liver transaminases >3 times ULN, epilepsy, excess alcohol consumption, viral infection in the preceding 2 weeks, unaccustomed physical exertion in the preceding 2 weeks, major surgery within 1 month, major trauma within 1 month, being on concomitant therapy with systemic corticosteroids, antipsychotics, antiretroviral drugs, fibrates, ciclosporin, antifungals, macrolide antibiotics, amiodarone, verapamil, diltiazem or warfarin, pregnancy, breast feeding, terminal disease and participation in another clinical trial within 3 months.

2.3. Randomization and blinding

All eligible and consenting participants were assigned to receive every-other-day atorvastatin or daily atorvastatin using simple randomization which was done centrally via telephone. Participants were assigned to interventions using a computer-generated random allocation sequence by an independent investigator who was not involved in patient enrolment and did not have access to participant data. Participants were not blinded. Outcome assessments were done by an independent assessor blinded to treatment allocation.

2.4. Interventions

Each patient's regular atorvastatin dose was given every-other-day at night to those in the intervention group. Patients in the control group continued to receive their regular dose of atorvastatin daily at night. Trial interventions were for a period of 24 weeks. Atorvastatin was issued from the hospital pharmacy (Atorvastatin Tablets I.P 10 mg manufactured by Interpharm Pvt Ltd. which is a licensed manufacturer in Sri Lanka). A medication calendar was issued to all participants in both groups to ensure compliance. Participants received standard medical care with regard to other management aspects based on their co-morbidities. All were advised to adhere to healthy dietary habits and to continue with their regular level of exercise.

2.5. Trial procedure

At study entry, details regarding demographics, atorvastatin therapy, muscle symptoms, co-morbidities and concomitant medications were recorded. Discomfort due to muscle symptoms during preceding 2 weeks was assessed with visual analogue scale ranging from 0 to 10. CK and lipid profile were measured. All participants were reassessed at 12 weeks (±1 week) and 24 weeks (±1 week) regarding the presence of muscle symptoms, discomfort due to muscle symptoms during preceding 2 weeks (if present) using visual analogue scale, CK and lipid profile. In addition, they were routinely reviewed at the outpatient clinic once in 4 weeks. At each visit compliance to trial medications was checked and muscle symptoms were carefully assessed in order to do further evaluation including additional CK measurements if clinically indicated. At all clinic visits concomitant medications, adverse events and serious adverse events were recorded. Indications for withdrawal from trial interventions included development of rhabdomyolysis, CK > 5 times upper limit of normal, hepatitis and new acute cardiovascular events.

Laboratory assays: The following assays were done using Flex reagent cartridges (Dimension® Clinical Chemistry System): CK by the IFCC reference method, total cholesterol by the cholesterol oxidase - Abell Kendall method, triglyceride by the lipase/glycerol dehydrogenase method and HDL-cholesterol by direct HDL clearance method. LDL-cholesterol level was calculated using Friedewald equation when triglyceride was <400 mg/dL (<4.5 mmol/L) and LDL-cholesterol was directly measured by beta quantification reference method using ALDL Flex reagent cartridges (Dimension® Clinical Chemistry System) when triglyceride was ≥400 mg/dL (≥4.5 mmol/L).

2.6. Outcomes

The primary outcome measures were composite of myalgia and myositis, LDL-cholesterol level and percentage reduction of LDL-

cholesterol from baseline, at 24 weeks. Secondary outcome measures were composite of myalgia and myositis at 12 weeks, LDL-cholesterol level at 12 weeks, percentage reduction of LDL-cholesterol from baseline at 12 weeks, CK level at 12 and 24 weeks and visual analogue scale score for discomfort due to muscle symptoms at 12 and 24 weeks. Myalgia was defined as unexplained muscle pain, tenderness or cramps alone or in combination involving two or more of the muscle groups in gluteal regions, thighs, calves, upper arms or forearms, during the preceding 2 weeks with no other identifiable cause and no elevation of CK. Myositis was defined as unexplained muscle pain, tenderness or cramps alone or in combination involving two or more of the muscle groups in gluteal regions, thighs, calves, upper arms or forearms, during the preceding 2 weeks with no other identifiable cause and CK elevated above the upper limit of normal.

2.7. Statistical analysis

With the assumption of an effect size of 20%, a sample size of 96 was needed to achieve a power of 90% and type 1 error rate of 5%. A target of randomising 107 was set to allow for a dropout rate of 10%.

Outcome analyses were done with the intention-to-treat principle as well as with per-protocol principle. Per-protocol analysis was performed for all outcomes after excluding patients who were not compliant to ≥80% of the assigned study treatment.

The null hypothesis regarding the outcomes related to muscle symptoms was that the rate of composite of myalgia and myositis was not different between the patients receiving atorvastatin daily and every-other-day. Composite of myalgia and myositis was compared between treatment groups using $\chi 2$ test and the effect is reported as an odds ratio with 95% confidence interval. Fisher exact test was used to compare proportion of patients with myositis and $\chi 2$ test was used to compare proportion of patients with myalgia. The mean differences between treatment groups with regard to CK level and visual analogue scale score were assessed by the independent sample *t*-test.

Regarding the outcomes related to LDL-cholesterol, non-inferiority analysis was performed. In this analysis the null hypothesis was that mean LDL-cholesterol level would be higher and percentage reduction of LDL-cholesterol from baseline would be lower in patients receiving every-other-day atorvastatin than in patients receiving daily atorvastatin; the alternative hypothesis was that the mean LDL-cholesterol level with every-other-day atorvastatin would not be greater than with daily atorvastatin by more than the noninferiority margin and the percentage reduction of LDL-cholesterol from baseline with every-other-day atorvastatin would not be lower than with daily atorvastatin by more than the noninferiority margin. The noninferiority margin for the mean LDL-cholesterol was set at 0.4 mmol/L, meaning that if the mean LDL-cholesterol level achieved with every-other-day atorvastatin would not exceed the level achieved by daily atorvastatin by greater than 0.4 mmol/L, then this would be considered as evidence of non-inferiority of every-other-day atorvastatin. This difference of 0.4 mmol/L would ensure that the LDL-cholesterol level achieved by patients receiving every-other-day atorvastatin stays within the recommended target of 2.58 mmol/L (100 mg/dL). The noninferiority margin for the percentage reduction of LDL-cholesterol from baseline was set at 5%, meaning that if the percentage reduction of LDL-cholesterol from baseline achieved with every-other-day atorvastatin would not be lower than by a difference of 5% from that achieved by daily atorvastatin, then this would be considered as evidence of non-inferiority of every-other-day atorvastatin. The statistical test used to determine non-inferiority was one sided *t*-test for independent samples.

Standard deviation was calculated for all means and 97.5% confidence intervals were calculated for the mean differences as the measure of variance. Descriptive statistics and the superiority tests were performed using SPSS (V.19.0) and the non-inferiority tests were performed with Stata 16.0.

2.8. Ethics

Written informed consent was obtained from all participants prior to recruitment. The ethical approval for the trial was obtained from Ethics Review Committee of the Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka (Ref. No.: 78/14). The trial is registered with Sri Lanka Clinical Trials Registry (Reg. No.: SLCTR/2015/010).

3. Results

From June 8, 2015 to February 3, 2018, 101 patients were randomized. 49 patients were assigned to every-other-day atorvastatin group and 52 were assigned to daily atorvastatin group. Two patients from every-other-day atorvastatin group withdrew consent to trial interventions two months after randomization (Fig. 1).

The mean age of the overall population was 61.2 ± 9.3 years and 76.2% were women. There was no statistically significant difference in the baseline characteristics of the two treatment groups (Table 1).

At 24 weeks after randomization, mean atorvastatin dose per day was 8.9 mg (SD = 6.2 mg) for every-other-day atorvastatin group and 17.6 mg (SD = 8.4 mg) for daily atorvastatin group. When the two patients who withdrew consent at the end of 2 months were disregarded, all others had satisfactory compliance (>80%) with the allocated intervention. By the end of 24 weeks, mean compliance with intervention was 98.3% (SD = 4.2%) and 98.5% (SD = 3.6%) in every-other-day atorvastatin group and daily atorvastatin group, respectively (p = 0.865).

With intention-to-treat analysis, the composite of myalgia and myositis at 24 weeks was 79.6% in every-other-day atorvastatin group and 69.2% in daily atorvastatin group (OR = 1.73, 95% CI 0.69–4.31; p = 0.234). (Table 2). At 24 weeks, every-other-day atorvastatin failed to show noninferiority for mean LDL-cholesterol (difference: 0.31 mmol/L; upper limit 97.5% CI: 0.61 mmol/L; p for noninferiority = 0.989) and for mean percentage reduction of LDL-cholesterol from baseline (difference: 3.13%; upper limit 97.5% CI: 15.5%; p for noninferiority = 0.718) (Table 3). Per-protocol analysis produced similar results (Appendix A. Supplementary material: Table 4 and 5).

Safety was assessed in all trial participants. Six patients (12.2%) in every-other-day atorvastatin group experienced a total of 9 serious adverse events (SAEs) and none were related to study treatment [8 hospitalizations: acute cholecystitis (2), gastroenteritis (1), cellulitis (1), acute pyelonephritis (1), dengue fever (1), accidental fall (1), cauda equina syndrome (1); 1 resulting in disability due to dementia]. In the daily atorvastatin group, two (3.9%) experienced 2 SAEs and both were not related to study treatment [2 hospitalizations: cellulitis (1), viral fever (1)]. Neither every-other-day atorvastatin group nor daily atorvastatin group had any deaths, new onset cardiovascular events, rhabdomyolysis or liver disease during the intervention period of 24 weeks. Concomitant medications were recorded in both groups throughout the trial, and no patient received medications that interact with statin metabolism or medications causing myopathy.

4. Discussion

In this controlled clinical trial, we assessed whether every-other-day atorvastatin was tolerated better than daily atorvastatin by patients having muscle symptoms associated with atorvastatin therapy and whether every-other-day atorvastatin was non-inferior to daily atorvastatin in controlling LDL-cholesterol. To date there is only one randomized controlled clinical trial which has evaluated tolerability of non-daily dosing of statins in those with muscle symptoms [25]. This trial assessed tolerability of once weekly rosuvastatin. To the best of our knowledge, our study is the first randomized controlled clinical trial

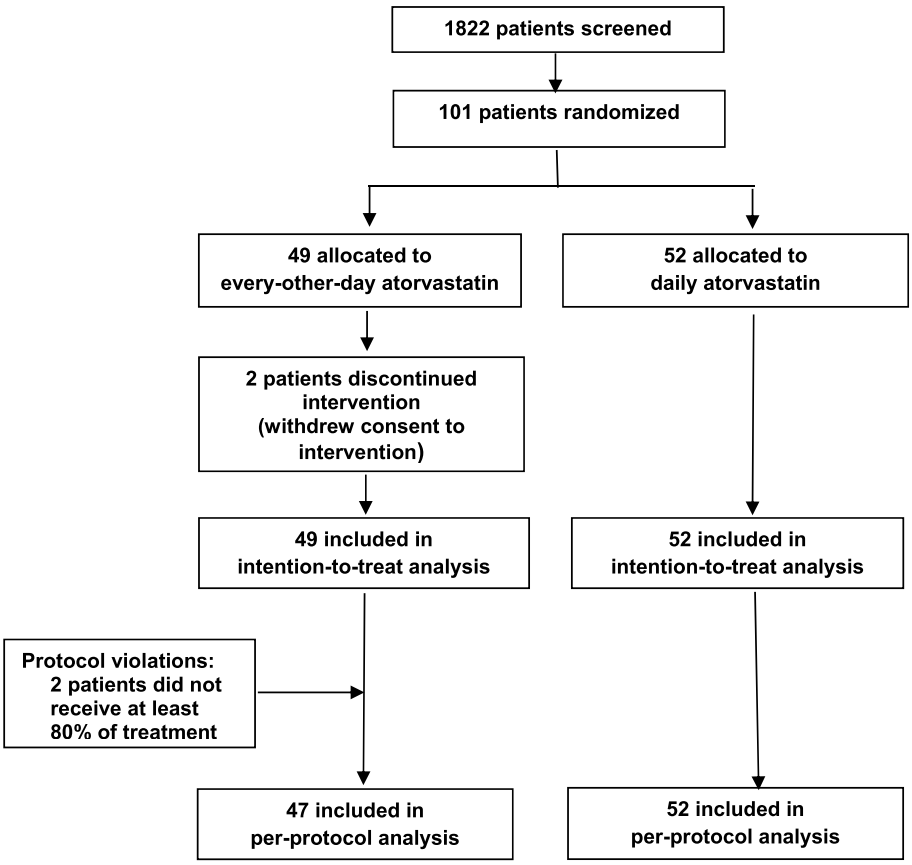

Fig. 1. Study profile.

evaluating the effects of non-daily dosing of atorvastatin in patients with muscle symptoms associated with statin use.

We could not find a significant difference between the two treatment regimens with regard to tolerability. Almost 20% in every-other-day atorvastatin group and 30% in daily atorvastatin group were free of muscle problems by the end of 24 weeks ($p = 0.234$). Though this difference was not statistically significant the observed trend was the opposite of what we expected. When we looked at myositis separately it was less prevalent in every-other-day atorvastatin group. At 24 weeks, only 1 of 49 (2%) had myositis in every-other-day atorvastatin group whereas 5 of 52 (9.6%) in daily atorvastatin group had it. This difference was not statistically significant probably due to the small number of patients experiencing myositis. We consider this as an important finding which needs further exploration as myositis is an objective measure whereas myalgia is subjective. During the 24-week follow up, Visual Analogue Scale Score for discomfort due to muscle symptoms improved in both groups and it was slightly lower in those who received atorvastatin every-other-day (3.2 vs 3.5; $p = 0.537$).

We found that effectiveness of every-other-day atorvastatin was inferior to daily atorvastatin regarding control of cholesterol level. The mean LDL-cholesterol level with every-other-day atorvastatin was greater than with daily atorvastatin by more than the noninferiority margin and the percentage reduction of LDL-cholesterol from baseline with every-other-day atorvastatin was lower than with daily atorvastatin by more than the noninferiority margin at both 12 weeks and 24 weeks.

It is difficult to directly compare our findings regarding tolerability with what is found in literature as the number of studies evaluating the tolerability of non-daily dosing of statins in those with muscle symptoms is limited and they differ from each other with regard to the study design, the type of statin used and the dosing regimen. Tolerability of every-other-day dosing of atorvastatin monotherapy has not been evaluated previously. Two observational studies have assessed the tolerability of non-daily dosing of atorvastatin in combination with non-statin lipid lowering drugs [26,27]. A retrospective study evaluated twice weekly atorvastatin/rosuvastatin combined with twice weekly ezetimibe and twice daily colesevelam in 23 patients who could not tolerate daily rosuvastatin/atorvastatin [26]. In this study, 87% of participants tolerated the non-daily dosing regimen well. The type of statin received by those who could not tolerate the treatment has not been reported. This study is limited by its small sample size (only 9 received atorvastatin out of the total of 23), retrospective design and absence of a control group. Athyros et al. have evaluated the effect of ezetimibe alone twice weekly for 3-months followed by ezetimibe in combination with atorvastatin twice weekly for 3 months in 56 patients who were unable to tolerate once-a-day statin therapy [27]. During the two phases of the study one patient each could not tolerate the treatment due to myalgia. This prospective study with a reasonable number of patients suggested that atorvastatin is well tolerated when administered twice weekly.

Tolerability of non-daily dosing of rosuvastatin in patients with muscle symptoms has been evaluated in several observational studies and case series [12,18–24]. Backes et al. conducted a retrospective study which evaluated every-other-day administration of rosuvastatin in 51 patients who did not tolerate daily statin therapy [18]. In this study majority (72.5%) tolerated every-other-day rosuvastatin well with no recurrence of myalgia. The mean LDL-cholesterol reduction was 34.5% and approximately 50% achieved their LDL-cholesterol goal. Another retrospective study conducted by Ruisinger et al. showed that in 50 patients who were unable to tolerate daily statin therapy, 37 (74%) tolerated once weekly rosuvastatin with a mean LDL-cholesterol reduction of 23% [21]. A higher tolerability rate (80%) has been reported in a different retrospective study ($n = 40$) evaluating twice weekly rosuvastatin [22].

Table 1
Baseline characteristics (n = 101).

	Every-other-day atorvastatin (n = 49)	Daily atorvastatin (n = 52)	P
Age, y, mean (SD)	60.6 (8.7)	61.7 (9.8)	0.540
Women, n (%)	39 (79.6%)	38 (73.1%)	0.442
Muscle pain, n (%)	29 (59.2%)	32 (61.5%)	0.809
Muscle tenderness, n (%)	8 (16.3%)	8 (15.4%)	0.897
Cramps, n (%)	40 (81.6%)	44 (84.6%)	0.689
CKa, IU/L, mean (SD)			
Men	172.5 (104.5)	135.4 (85.1)	0.349
Women	101.1 (49.5)	116 (61.4)	0.244
Myalgia, n (%)	46 (93.9%)	44 (84.6%)	0.135
Myositis, n (%)	3 (6.1%)	8 (15.4%)	0.135
VAS score, mean (SD)	6.6 (2.5)	6.4 (2.4)	0.619
Mean atorvastatin doseb, mg, mean (SD)	16.7 (9.2)	17.6 (8.4)	0.625
Atorvastatin doseb, n (%)			0.372
5 mg	0	1 (1.9%)	
10 mg	26 (53.1%)	20 (38.5%)	
20 mg	18 (36.7%)	26 (50%)	
30 mg	0	1 (1.9%)	
40 mg	5 (10.2%)	4 (4.7%)	
LDL-cholesterol, mmol/L, mean (SD)	3.27 (0.93)	3.02 (0.86)	0.153
AST, IU/L, mean (SD)	26.3 (7.1)	27.1 (8.5)	0.625
ALT, IU/L, mean (SD)	30 (15)	33.7 (17.8)	0.266
Serum creatinine, μmol/L, mean (SD)	77.9 (18.9)	78 (20.1)	0.979
eGFRc, mL/min/1.73 m2, mean (SD)	110.8 (39.5)	109 (39.5)	0.812
Serum sodium, mmol/L, mean (SD)	140.3 (2.8)	140.4 (3.7)	0.861
Serum potassium, mmol/L, mean (SD)	4.6 (0.6)	4.5 (0.5)	0.317
ESR, mm/hour, mean (SD)	23.4 (11)	20.9 (10.7)	0.263
TSH, mIU/L, mean (SD)	2.2 (1.4)	2.0 (1.2)	0.327

CK = creatine kinase; AST = aspartate transaminase; ALT = alanine transaminase; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate, TSH = thyroid stimulating hormone; [a]CK is reported separately for men and women as the normal values are different for men and women; [b]regular daily atorvastatin dose prior to randomization; [c]based on Modification of Diet in Renal Disease (MDRD) Study equation.

Table 2
Primary and secondary outcomes of muscle symptoms by intention-to-treat analysis.

	every-other-day atorvastatin (n = 49)	daily atorvastatin (n = 52)	OR (95% CI)	mean difference (95% CI)	p
Primary Outcomes					
Composite of myalgia and myositis at 24 weeks, n (%)d	39 (79.6)	36 (69.2)	1.73 (0.69–4.31)	–	0.234
Myalgia at 24 weeks, n (%)	38 (77.6)	31 (59.6)	2.34 (0.98–5.59)	–	0.053
Myositis at 24 weeks, n (%)	1 (2)	5 (9.6)	0.19 (0.02–1.74)	–	0.206
Secondary Outcomesd					
Composite of myalgia and myositis at 12 weeks, n (%)	42 (85.7)	41 (78.8)	1.61 (0.57–4.56)	–	0.367
Myalgia at 12 weeks, n (%)	39 (79.6)	36 (69.2)	1.73 (0.69–4.31)	–	0.234
Myositis at 12 weeks, n (%)	3 (6.1)	5 (9.6)	0.62 (0.14–2.72)	–	0.716
CKa at 24 weeks, IU/L, mean (SD)					
Men	175.8 (104.8)	134.2 (50)	–	41.61 (−24.67–107.89)	0.206
Women	96.6 (42)	128.6 (95.3)	–	−31.91 (−65.21–1.37)	0.060
CKa at 12 weeks, IU/L, mean (SD)					
Men	166.5 (95.4)	155.4 (98.7)	–	11.11 (−72.51–94.73)	0.785
Women	107.2 (49.2)	126.8 (79)	–	−19.54 (−49.33–10.26)	0.195
VAS score at 24 weeks, mean (SD)	3.2 (2.3)	3.5 (2.7)	–	−0.31 (−1.30–0.68)	0.537
VAS score at 12 weeks, mean (SD)	4.6 (3)	3.9 (2.7)	–	0.71 (−0.40–1.81)	0.208

CK = creatine kinase; VAS = visual analogue scale; [a]CK is reported separately for men and women as the normal values are different for men and women.

The only previously published randomized controlled clinical trial evaluating tolerability of non-daily dosing of statins in those with muscle symptoms assessed the effect of rosuvastatin 5–10 mg once a week for 8 weeks in 17 men [25]. In this trial with crossover design, recurrent myalgia has been experienced by 3 patients while receiving rosuvastatin and by 2 patients during the placebo treatment phase. Even though LDL-cholesterol reduction achieved with once weekly rosuvastatin (12.2%) was less marked than with previous observational studies it was significantly higher than what was achieved with the placebo (0.04%). However, it is difficult to compare these findings with the findings of our trial for several reasons. Firstly, the two statins are different. It is known that rosuvastatin is better tolerated than atorvastatin due to differences in pharmacokinetics [12,28]. Secondly, the design is different. We started with patients having muscle symptoms and looked at the resolution rate by the end of follow up period and the reported rosuvastatin trial started with patients having previous statin intolerance due to myalgia and looked at the rate of recurrence. Thirdly, our control group received daily atorvastatin whereas the control group in the rosuvastatin trial received placebo. Finally, non-daily dosing regimen of our study was every-other-day and in the rosuvastatin trial it was once-weekly. All these differences could have contributed to the positive results obtained in the rosuvastatin trial conducted by Kennedy et al. Furthermore, it is important to note that utilization of results of this trial is limited because sample size was small, all participants were men, the follow up duration was short and there was potential for crossover effect due to absence of a washout period.

We found that the mean LDL-cholesterol level with every-other-day atorvastatin was greater than with daily atorvastatin by more than the noninferiority margin at both 12 weeks and 24 weeks of treatment. A previous study from Spain done in diabetic patients has shown similar results [29]. Rifaie et al. studied 60 patients who have already achieved cholesterol targets [30]. In this study, the mean percentage increase of LDL-cholesterol from baseline to assessment at 6 weeks was significantly higher in those who were on atorvastatin every-other-day as compared to daily atorvastatin group (32.8% vs 1.5%). However, some other studies have shown that every-other-day dosing of atorvastatin is as effective as daily atorvastatin in controlling LDL-cholesterol [31–33]. Jafari et al. conducted a randomized controlled trial in 54 patients and found that there was no difference in LDL-cholesterol level at 6 weeks between those who received atorvastatin 10 mg daily and 10 mg every-other-day [31]. A clinical trial with crossover design in 40 patients from India, demonstrated that 20 mg of atorvastatin on

Table 3
Primary and secondary outcomes of LDL-cholesterol by intention-to-treat analysis (n = 101).

	every-other-day atorvastatin (n = 49)	daily atorvastatin (n = 52)	Mean Difference (1-Sided 97.5% CI)	noninferiority p value
Primary Outcomes				
LDL-C at 24 weeks, mmol/L, mean (SD)	2.49 (0.63)	2.18 (0.70)	0.31 (0.01, 0.61)a	0.989
Percentage reduction of LDL-C from baseline at 24 weeks, mean (SD)	20.15 (23.45)	23.28 (30.39)	3.13 (−9.21, 15.5)b	0.718
LDL-C at 12 weeks, mmol/L, mean (SD)	2.52 (0.68)	2.17 (0.63)	0.35 (0.05, 0.65)a	0.995
Percentage reduction of LDL-C from baseline at 12 weeks, mean (SD)	19.58 (24.12)	22.44 (32.13)	2.86 (−10.10, 15.79)b	0.692

aevery-other-day atorvastatin value – daily atorvastatin value; bdaily atorvastatin value - every-other-day atorvastatin value; LDL-C = LDL-cholesterol.

every-other-day was as effective as 20 mg of atorvastatin daily with regard to LDL-cholesterol reduction at 6 weeks and 12 weeks [32]. Another randomized clinical trial from Turkey (n = 61) has produced similar results [33]. In this study, by the end of 3 months, LDL-cholesterol level was not different between those who received atorvastatin 20 mg daily and those who received the same dose every-other-day.

We believe that our study makes an important contribution to the evidence base regarding the tolerability and effectiveness of every-other-day administration of atorvastatin. It is a randomized, controlled clinical trial, has a large sample size (n = 101) compared to most of the previous studies and has the longest follow up (24 weeks). This evidence will be particularly useful for low and lower-middle income countries where atorvastatin is the main statin used in clinical practice. Our study has some limitations. Firstly, this was an open label trial. As the outcome measure of myalgia is subjective, absence of blinding could have introduced some bias due to participants' expectations. However, our trial results showed that proportion of patients with myalgia at 6-months was higher in the intervention group in a statistically non-significant manner. This trend was the opposite of what is expected if there had been bias due to participants' expectations. Bias due to assessor's expectations was eliminated by making the outcome assessor an independent individual blinded to treatment allocation. Secondly, the relationship between the muscle symptoms and the statin use was not established by discontinuation and re-challenge. However, this limitation was likely to have affected both groups equally due to random allocation. Third limitation is that our outcomes for effectiveness did not include clinical endpoints such as cardiovascular event rate for which a larger sample size and a longer follow up are needed. Nevertheless, we assessed LDL-cholesterol which is considered as a reasonable surrogate for cardiovascular events.

5. Conclusions

Patients with muscle symptoms did not tolerate every-other-day atorvastatin better than daily atorvastatin. Every-other-day atorvastatin was inferior to daily atorvastatin regarding control of LDL-cholesterol. Therefore, the findings of this study do not favor every-other-day atorvastatin as an option for managing patients with muscle symptoms associated with atorvastatin therapy.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2020.100685.

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