

Can alternate-day Statin regimen minimize its adverse effects on muscle and tendon? A systematic review

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Abstract

Objective: To review evidence-based data with respect to safety and efficacy of alternate-day statin therapy in dyslipidaemia compared to the standard daily dose.

Methods: The literature review was conducted at Aga Khan University Hospital, Karachi from July, 2016 to August, 2017. Electronic database search was carried out to compile available literature using PubMed, Excerpta Medica database and Google Scholar. The most relevant evidence-based research articles published over 10 years were selected. The latest search was dated August 03, 2017.

Results: A total of 2,074 articles were initially located. Alternate day statin regimen was reported in 53% of articles. Adverse effects on muscle and tendon were reported in 69% of articles. After scrutiny, 19(0.9%) studies covering alternate-day statin-mediated muscle and tendon disorders and 9(0.4%) studies encompassing the potential pathophysiological mechanisms of statin-associated muscle and tendon injury were selected. Except pravastatin and lovastatin, alternate-day statin therapy was almost as effective in lowering total cholesterol, low-density lipoprotein cholesterol and triglycerides as the daily dosing with low incidence of muscle toxicity and tendinopathy.

Conclusion: Alternate-day statin regimen was found to be very well tolerated and might be an effective and safe remedy in clinical practice.

Keywords: Statin, Alternate-day regimen, Muscle disorders, Tendon disorders, Adverse effects. Cancer. (JPMA 69: 1006 2019)

Introduction

Statins are lipid-lowering drugs by competitively inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase enzyme (HMGCR) and thus limiting cholesterol biosynthesis.¹ Statins are administered daily as standard therapy for primary and secondary prevention of coronary heart disease (CHD), stroke and peripheral arterial disease (PAD).² Commonly used statins are rosuvastatin, atorvastatin, fluvastatin, lovastatin, simvastatin, pravastatin and pitavastatin. Despite their clinical benefits, several patients discontinue these drugs due to intolerance, increasing the risk of cardiovascular morbidity and mortality. Most common side effects of statin are myopathy, tendinopathy, hepatotoxicity, type 2 diabetes, cataract, polyneuropathy, memory loss, behavioural changes and, rarely, headache, gastrointestinal disturbance, rash etc.³

In 1987, lovastatin, the first statin drug, was approved by the Food and Drug Administration (FDA) and was released for marketing. Later, except with the least potent fluvastatin, it was identified that statin, in combination with gemfibrosil, produced severe myopathy and rhabdomyolysis.

Statins can lead to myalgia (muscle pain), myopathy, elevated creatinine kinase (myonecrosis) and rhabdomyolysis.^{4,5} Studies have reported that muscle and tendon related side effects were most commonly noticed in patients treated with rosuvastatin while pravastatin and lovastatin have the lowest rate of side effects.⁶

Onset of myalgia varies from patient to patient and starts after a few weeks to years of statin therapy.⁷ Myalgia could be generalised or localised, and persists for more than 3 months after discontinuation of statin therapy with average duration of six-and-a-half months.⁸ While on statins, up to 10% of the patients, specifically older

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patients and females, experienced muscle pain.⁹ Risk factors for statin-induced myopathy include concomitant drugs, diabetes, old age, female gender, hepatic and renal insufficiency, hypertension and hypothyroidism.¹⁰ Statin-mediated myopathy with more than 10 times elevation of creatinine kinase level is a serious side effect and, according to one study, one per 1,000 patients to one per 10,000 patients may be effected each year depending on statin dose administered.¹¹ Therefore, FDA recommends lowest effective dose of statins to reduce statin-associated myopathies.¹² In most of the statin treated patients, anti-HMGCR antibodies are not detected and their myopathy resolve after statin dose adjustment or discontinuation. However, it is recently identified that statin may induce such antibodies and cause immune-mediated myopathy. Antibody-positive patients are most likely having an autoimmune myopathy that is progressive and persists after drug withdrawal. These patients require immunosuppressive drugs, preferably oral prednisolone (1 mg/kg/day) and sometimes other immunosuppressants like azathioprine, methotrexate, intravenous (IV) immunoglobulin (Ig) after confirmation.¹³

Statins can also lead to rhabdomyolysis, and release of muscle intracellular constituents due to muscle injury could lead to renal failure. After several reports of cerivastatin-associated rhabdomyolysis and deaths, the drug was withdrawn from the market.¹⁴ According to new safety updates; FDA does not recommend simvastatin administration at the starting dose of 80mg due to serious myopathies and rhabdomyolysis.¹⁵ Tendinopathy is another side effect related to statin treatment and is frequent in patients with diabetes, hyperuricaemia, history of tendon disorders, and in persons involved in active sports.^{6,16}

Tendinopathy was first reported in four patients in 2001. Two patients were on simvastatin. One patient was at a dose of 10 mg/d (co-administered with enalapril and nifedipine-atenolol) and one patient at a dose of 20 mg/d. Two patients were treated with atorvastatin. One patient was at a dose of 20 mg/d and one patient at a dose of 40 mg/d initially which increased to 80 mg/d respectively. Out of four patients, one developed extensor tenosynovitis at the hands, one developed tenosynovitis of the tibialis anterior tendon and two had

Achilles tendinopathy. The tendinopathy developed 1 to 2 months after treatment initiation.

Tendons mostly involved in statin therapy are Achilles, rotator cuff, biceps brachii, extensor carpi radialis brevis, gluteus medius, quadriceps, patellar tendon, tibialis anterior and finger extensor and flexor tendons.^{17,18}

Tendinitis or inflammation of a tendon was reported in patients on statin therapy particularly involving tendons like Achilles, quadriceps, deltoid etc.^{17,19}

According to FDA-based eHealthMe report, 0.01% patients on statin therapy have enthesopathy, a disorder involving the attachment of a tendon or ligament to a bone.²⁰

Several animal studies have been conducted to elucidate the mechanism of myotoxicity and tendon injury, and multiple mechanisms have been shown to be involved.^{4,18}

In clinical practice, statin dose is adjusted from 5mg to 40mg once daily according to blood lipid profile and statin type. FDA recommends discontinuation of the drug if patient experiences statin-associated muscle or tendon adverse effects.⁶

To overcome statin-induced muscle toxicity and tendinopathy and to determine efficacy and safety, several studies administered alternate-day statins compared to standard daily regimen. It was evaluated that except pravastatin and lovastatin, alternate-day therapy was as effective in lowering total cholesterol (TC), low density lipoprotein (LDL) cholesterol and triglycerides (TG) as the standard daily dosing. Overall incidence of adverse drug reactions were lower in alternate-day regimen, particularly rosuvastatin and atorvastatin were very well tolerated in patients who were intolerant to these statins on a daily dose.²¹ Grounded on all ascertained statin-related adverse reactions, statin compliance is a major concern for treating physicians. Alternate-day statin regimen has been proposed by studies to reduce adverse effects from statin therapy compared to the daily dose. The current study was planned to focus on statin-mediated muscle and tendon disorders, mechanism of tissue injury and safety and effectiveness of alternate-day statin regimen reported to date.

Materials and Methods

The literature review was conducted by the research team from Aga Khan University Hospital, Karachi. Initial scoping review was conducted in July-August, 2016 and comprehensive focussed literature search was undertaken till August, 2017. Electronic database search was carried out to compile available literature using PubMed, Excerpta Medica database (EMBASE) and Google Scholar. The most relevant evidence-based research articles published over 10 years were selected. Except for one research article published post-submission and was added in the revised manuscript, the latest search was dated August 03, 2017.

Keywords and phrases used for the search were 'alternate-day statin', 'statin-associated myopathy', 'statin-associated tendinopathy', 'statin-related adverse effects', 'statin-associated enthesopathy', 'statin-related mechanism of tendon injury', 'statin-related mechanism of muscle injury', and 'alternate-day statin efficacy and safety'. Research articles in which alternate-day or daily statin regimens were used but contained no information on muscle or tendon disorders were excluded. Referenced citations from relevant publications were also considered. Findings of research studies involving human subjects with study designs such as randomised double- or single-blind trials, randomised open label trials, non-randomised before-after comparison trials, randomised crossover trials and prospective or retrospective studies comparing the safety and efficacy of alternate-day statin regimen were primarily included for analysis. Research studies explaining statin-induced key pathophysiological mechanisms were also included.

Results

A total of 2,074 articles were initially located. Alternate day statin regimen was reported in 1,110 (53%) articles. Adverse effects on muscle and tendon were reported in 1,430 (69%) articles. After scrutiny, 19(0.9%) studies covering alternate-day statin-mediated muscle and tendon disorders and 9(0.4%) studies encompassing the potential pathophysiological mechanisms of statin-associated muscle and tendon injury were selected. Drugs analysed included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin (Table).

The review found several studies that were conducted to assess the safety and efficacy of alternate-day atorvastatin

administration. Most of these studies compared safety of alternate-day statin regimen to daily regimen. In different research studies, mixed results for efficacy of alternate-day atorvastatin regimen were observed.

Few studies reported that in dyslipidaemia with coronary artery disease, 6-12 week alternate-day regimen treatment significantly increased LDL cholesterol and TC levels. About 10-20mg alternate-day atorvastatin regimen non-significantly decreased TG level after 3 months of treatment. Alternate-day regimen was not as effective as the daily regimen.²²⁻²⁶

Contrary to above studies, in some studies, when patients with dyslipidaemia, with or without type 2 diabetes, were treated with 10-20 mg alternate-day atorvastatin regimen there was significant decrease in LDL cholesterol, TC and TG levels with non-significant increase in high density lipoprotein (HDL) level after 6-12 weeks treatment.²⁷⁻³⁰

Alternate-day atorvastatin regimen was well tolerated in all studies with few side effects like flu-like symptoms, somnolence, increase in serum transaminases and muscle enzymes, myalgia, headache, dyspepsia, dizziness and paresthesia compared to daily regimen.

In terms of fluvastatin, in one crossover study, patients with hypercholesterolaemia who were on diet restriction therapy were first treated with fluvastatin 40 mg daily or 20 mg alternate-day for 6 weeks. Both groups of patients were then switched to other regimen for further 6 weeks. LDL cholesterol and TC decreased significantly in both regimens. There was non-significant decrease in TG and increase in HDL cholesterol while few adverse effects were observed.³¹ The limiting factor for this study was that there was no drug washout period in between the drug regimen switchover.

Regarding lovastatin, in two studies, patients with dyslipidaemia were treated with 20 mg lovastatin for 6 weeks to 4 months. There was significant decrease in TC and LDL cholesterol, while non-significant decrease in TC and increase in HDL cholesterol were observed.^{32,33} On alternate-day lovastatin regimen, angioedema and muscle cramping were observed in two patients only. Daily regimen was not administered in these studies, therefore, alternate-regimen could not be compared for safety.

On the basis of results, although this drug seems to be effective, there are some limitations in these studies like the selection of male participants only, small number of patients, retrospective in nature, lack of external validity

Table: Research studies on alternate-day statin regimen - precise details.

	Studies	N	Alternate day dose	Daily dose	Change from baseline level by Alternate day dose				Treatment Duration	Adverse effect
					LDL-C	TG	HDL	TC		
Atorvastatin	Matalka et al (double-blind, placebo controlled study) ²⁶	35	10 mg-(dose doubled in 79% pts. at 6 weeks)	10 mg-(dose doubled in 17% pts at 6 weeks)	↓	↓	↓ at 12 weeks	↓	12 weeks	DD: Muscle weakness, severe depression, uncontrolled diabetes, mildly elevated CPK and GIT disturbances AD: Flu like symptoms
	Jafari et al (randomized, prospective, non-blinded, controlled trial)	54	10 mg (gp 2) and 20 mg (gp 3)	10 mg (gp 1)	↓	↓	↑ NS	↓	6 weeks	Well tolerated
	Piamsomboon et al (prospective study) ²⁹	60	10 mg	-	↓	↓	↑ NS	↓	8 weeks	Somnolence, increased serum transaminase and increased serum muscle enzyme.
	Ferrer-Garcia et al (prospective study) ³⁰	44	10 mg (DD doubled 6 weekly till LDL-C goal achieved. Dose shifted to AD)	-	↓	↓	↔	↓	12 weeks (After achieving LDL-C goal)	AD: Well tolerated. Only 02 patients has elevated liver enzyme level
	Aghasadeghi et al (randomized, blinded, controlled trial) ²⁸	66	20 mg (gp 3)	10 mg (gp 1) & 20 mg (gp 2)	↓	↓ NS	↑ NS	↓	6 weeks	Well tolerated
	Keles et al (prospective randomized trial) ²⁵	61	20 mg	20 mg	↓	↓ NS	↑	↓	3 months	-
	Pattanaik et al (randomized open label trial) ²²	300	Previous dose	Previous dose	↑	↑	↔	↑	12 weeks	Myalgia
	Rifaie et al (randomized single-blinded two armed trial) ²³	60	10 mg	10 mg	↑	↔	↔	↑	6 weeks	Well tolerated
	Ghia CJ et al (comparative, randomized, parallel group, non-blinded study) ²⁴	100	10 mg	10 mg	↓	↓ NS	↑ NS	↓	3 months	DD: Headache, asthenia, dyspepsia, myalgia, elevated liver enzymes, depression, dizziness and parasthesia AD: Headache, Dyspepsia, Dizziness and Parasthesia
Fluvastatin	Rindone et al (Randomized, non-blinded, crossover study) ³¹	23	40 mg (after A-drug, 20 mg daily for 6 weeks)	20 mg (after D-drug, 40 mg A-drug for 6 weeks)	↓	↓ NS	↑ NS	↓	12 weeks	GIT problems and urinary retention
Lovastatin	Rindone et al (pilot study) ³²	21	20 mg	-	↓	↓ NS	↑ NS	↓	6 weeks	Angioedema and muscle cramping
	Dennis et al (retrospective study) ³³	20	20 mg	-	↓	↔	↑ NS	↓	4 months	Not described
Pravastatin	Graham et al (prospective, randomized, open-label study) ³⁴	104	Adjusted dose	Half of adjusted dose	↑	↑ NS	↔	↑	4 months	Nausea, diarrhea, anorexia, night sweats, heartburn and myalgia
Rosuvastatin	Wongwiwatthanakut et al (randomized, open-label, parallel trial) ³⁵	80	10 mg	10 mg	↓	↓	↑ NS	↓	8 weeks	DD: Elevated liver enzyme levels, malaise and myalgia AD: Headache, liver enzyme levels not increased >3 times UL of normal
	Backes et al (retrospective study) ²¹	51	2.5 to 10 mg	-	↓	↓	↔	↓	4 ± 2.9 months	AD: Tolerated in 37 (out of 51 patients). myalgias, GIT problems, memory impairment, rash and fatigue.
	Li JJ et al (randomized, open-label trial) ³⁶	37	10 mg	10 mg	↓	↓	↑	↓	6 weeks	Well tolerated
	Dulay et al (prospective, crossover study) ³⁷	45	20 mg (washout-4 weeks) 10 mg	10 mg (washout-4 weeks) 20 mg	↓	↓	↑	↓	1 st and 2 nd regimen 6 weeks each (4 weeks washout)	GIT disturbances
Simvastatin	Kayikcioglu et al (randomized, prospective clinical study) ³⁸	74	10 mg (+ fenofibrate 250 mg)	10 mg (+ fenofibrate 250 mg)	↓	↓	↑	↓	6 months	DD: CK level increased less than 3 times the UL of normal, GIT disturbances AD: Well tolerated
	Copher et al (non-randomized, before-after comparison trial) ³⁹	15	Double the previous dose	-	↓	↓	↑	↓	8 weeks	Well tolerated

LDL-C: Low density lipoprotein cholesterol, HDL: High density lipoprotein, TC: Total cholesterol, TG: Triglyceride), N: Number of patients, NS: Not significant, AD: Alternate-day drug dose, DD: Daily drug dose, Pt: Patient, UL: Upper limit, gp: Group, ↓ = decrease, ↑ = increase, ↔ = no change

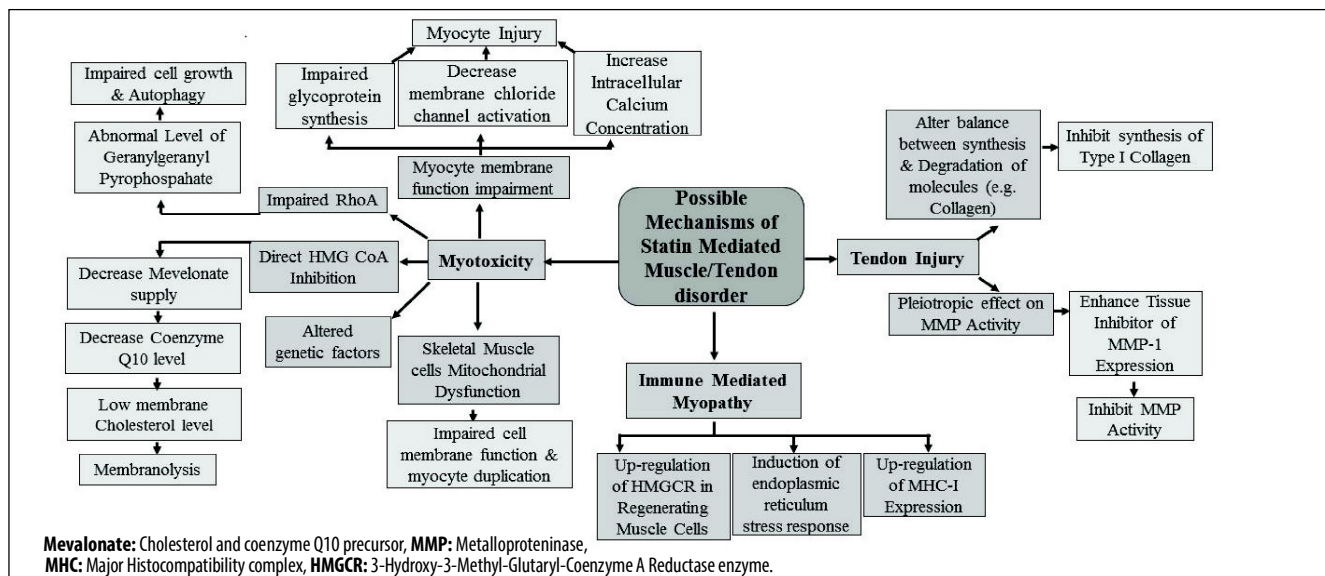


Figure: Possible mechanisms of statin mediated muscle and tendon disorders.

etc.

In terms of pravastatin, step-down treatment either every other day or half of the adjusted dose significantly increased TC and LDL cholesterol levels while TG and HDL cholesterol increased non-significantly, thus, was ineffective.³⁴ Adverse events, like nausea, heart burn, myalgia, diarrhoea, night sweats were recorded in alternate-day regimen group.

Regarding rosuvastatin, in some studies when patients with dyslipidaemia were treated with 2.5-20 mg alternate-day regimen, there was significant decrease in LDL cholesterol, TG and TC compared to the baseline values. In most studies, HDL cholesterol was non-significantly increased.^{21,35-37}

Discussion

In the light of these studies, it seems that alternate-day administration of rosuvastatin is almost as effective as the daily regimen. Alternate-day rosuvastatin regimen was well tolerated in all studies with few side effects like headache, increase in liver enzymes which did not exceed more than three times the normal upper limit, myalgia, fatigue, rash, gastrointestinal tract (GIT) disturbances and some memory impairment.

Regarding simvastatin, in few studies, simvastatin, with or without fenofibrate, was administered in alternate days at dose of 10-80 mg in dyslipidaemia patients. There was significant decrease in LDL cholesterol, TG and TC and increase in HDL cholesterol compared to baseline

values.^{38,39} Alternate-day regimen of simvastatin was well tolerated. In one study, simvastatin was co-administered with fenofibrate, therefore lipid-lowering effect and incidences of adverse effects were inconclusive for simvastatin.

Speculated mechanisms involved in statin-induced myotoxicity and tendon injury.

- Actual mechanism involved in statin-associated myotoxicity is still unclear. Several studies, mainly on rat models, were conducted to explore this phenomenon (Figure). It seems that several pathological events are involved in muscle injury including direct HMGCR,^{40,41} decrease in muscle ubiquinone level,⁴² mitochondrial dysfunction in skeletal muscle cells leading to impaired cell membrane functions as well as defect in myocyte duplication, impaired cell membrane glycoprotein synthesis, decreased muscle membrane chloride channel activation and increase in intracellular calcium concentrations leading to membrane function impairment resulting in myocyte injury,^{4,43} impaired function of Ras homolog gene family member A due to lipid synthesis problem with geranylgeranyl pyrophosphate which is an intermediate in HMGCR pathway and is involved in the mechanisms of statin-induced skeletal muscle toxicity⁴⁴
- Genetic factors are also reported to be responsible for muscle toxicity.⁴⁵

Likewise, exact mechanism of immune-mediated myopathy is unclear, but it is suggested that it could be due to induction of endoplasmic reticulum stress response, up-regulation of major histocompatibility complex-I expression with antigen presentation by muscle fibres, and up-regulation of HMGCR in regenerating muscle cells and autoimmune response generation leading to immune-mediated necrotising myopathy.^{13,46} Several statin-induced mechanisms are deliberated upon to produce tendon injury. Severity of tendon injury depends on the dose and type of statin used.

Pleiotropic effect of statins on metalloproteinase activity leads to tendon pathology. Statins enhance tissue inhibitor of metalloproteinase-1 expression in macrophages and thus inhibit metalloproteinase activity resulting in tendinopathy.^{16,47}

Statin-associated tendon micro damage is caused by extracellular matrix components derangement, particularly in Achilles tendon. These evidences indicate that statins alter balance between the synthesis and degradation of several molecules, particularly involving collagen I which is the main constituent in tendon extracellular matrix.¹⁸

Statin induce muscular and tendon side effects could be life-threatening and devastating leading to non-compliance of the daily statin regimen. Although several mechanisms at molecular level are detected in animal models that seem to be involved in myotoxicity, tendon injury and immune-mediated myopathy but still definite pathophysiological mechanism of these side effects is still unclear. This suggests that multifactorial causes are involved in these adverse effects. To overcome these side effects and for better adherence to the drug compliance, studies were conducted in which daily statin regimen was switched to alternate-day regimen.

Although several studies have been published with the aim of investigating safety and efficacy of alternate-day statin regimen, results cannot be generalised for different patient populations as the studies stated above are mainly conducted on specific set of patients.

Studies conducted on alternate-day atorvastatin showed mixed results in drug efficacy to treat dyslipidaemia and thus results were inconclusive for drug efficacy although it was well tolerated. Alternate-day dose of pravastatin was ineffective in treating dyslipidaemia. The most favourable results were obtained in studies with alternate-

day rosuvastatin regimen with study design of randomised and crossover clinical trials. Alternate-day rosuvastatin was almost as effective as daily regimen and was also well tolerated. Simvastatin was effective in treating dyslipidaemia and was also well tolerated by the patients but either co-administered with other lipid-lowering drug or was not compared with daily statin dose.

A cross-sectional study was conducted in Pakistan on 400 patients between 40 and 70 years of age. There was significant difference in the frequency of myalgia in patients on alternate-day statin that was 4% compared to every-day statin regimen that was 10%. Lipid-lowering effect was not evaluated in this study which was one limiting factor to infer alternate-day drug regimen results.⁴⁸

Based on all these facts, the studies cited above were limited due to study design and patient selection bias as in the case of alternate-day lovastatin, pravastatin and simvastatin treatment studies. Therefore, pooled analysis was not acquiescent. Retrospective studies conducted have the potential for bias, therefore results are inconclusive. Further, small sample size, short study duration, dose adjustments according to lipid level goals and lack of washout period in some studies did weaken the findings. As in the above-mentioned studies, no cardiovascular outcome has been evaluated so far. For external validity of results, appropriately designed studies to reach scientifically sound conclusions are required to be conducted before implementation of alternate-day regimen in routine practice. Nevertheless, foremost strength of these studies is that the research was directly conducted on human subjects with dyslipidaemia. Patients were generally randomised in identically constituted groups for comparison. Consequently, the results can propose new direction for future larger clinical trials.

On the basis of this review it appears that alternate-day dose may be better due to fewer side effects, but a systematic review and meta-analysis are required to clearly define the risk versus benefit.

Conclusion

Weighing statin benefits against statin toxicity, alternate-day regimen may be a suitable option for those patients who cannot tolerate statins daily. Clinical trials will help physicians to consider evidence-based clinical efficacy of drugs when making safety and resource-allocation decision while prescribing drugs. It is recommended that

physicians supervise patients on statin therapy by considering risks associated with statins, particularly autoimmune myopathy and rhabdomyolysis.

Disclaimer: A poster of the initial literature review done between July and August 2016 focussing on safety and general adverse effects of statins was presented at the 10th Health Sciences Research Assembly, Aga Khan University, Karachi, on August 23-24, 2016. The current manuscript differs from that poster as it contains focussed review on muscle and tendon side effects conducted thereafter until August 2017.

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