Pharmacological Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

The effect of lipophilicity and dose on the frequency of statin-associated muscle symptoms: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 28 July 2017
Received in revised form
19 September 2017
Accepted 20 September 2017
Available online xxx

Keywords:
Statin-associated muscle symptoms
Dose
Lipophilicity
Meta-analysis
Randomised controlled trial

ABSTRACT

Addressing the factors which lead to the development of statin-associated muscle symptoms (SAMS) is vital for maintaining patient compliance with these pharmaceuticals, and thus improving patient outcomes. This study aimed to clarify the relationship between statin lipophilicity, or dose, and the frequency of adverse muscle symptoms using a systematic review of randomised controlled trials (RCTs). RCTs, including statin monotherapy and placebo groups, which reported data on muscle adverse events were identified through the PubMed and Scopus databases. Risk ratios (RRs) and 95% confidence intervals (CI) were pooled using a random-effects meta-analysis. A total of 135 RCTs were included in this review. Statin therapy was associated with a significant, but modest, increase in the risk of adverse muscle symptoms compared to placebo (RR = 1.050; 95% CI = 1.014–1.089; $P = 0.007$; $I^2 = 3.291\%$). This significant association was primarily due to the inclusion of RCTs recruiting participants with a history of statin intolerance. Lipophilic statins had no appreciable impact on the development of SAMS compared to hydrophilic formulations. A univariate meta-regression of dose (standardised to atorvastatin dose equivalents) and the risk of musculoskeletal complaints also showed no significant association. The results obtained from this meta-analysis indicate that there is a slight increase in the risk of SAMS, especially in individuals with a history of statin intolerance. There is limited evidence to suggest that the risk of SAMS would differ between the use of lipophilic and hydrophilic statins, or high- and low-dose therapy.

Contents

Abbreviations: BMI, body mass index; CI, confidence intervals; CK, creatine kinase; LDL-C, low-density lipoprotein cholesterol; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register for Systematic Reviews; RCTs, randomised controlled trials; RR, risk ratios; SAMS, statin-associated muscle symptoms; ULN, upper limit of normal.

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http://dx.doi.org/10.1016/j.phrs.2017.09.013
1043-6618/

1. Introduction

Statins are the most effective pharmaceuticals for the treatment of hypercholesterolemia and are currently used by an estimated 25 million people worldwide [1–4]. While these medications are safe and well-tolerated, they can cause adverse statin-associated muscle symptoms (SAMS) in some individuals, which in turn, leads to poor patient compliance [5,6]. Statin discontinuation has been shown to cause a near three-fold increase in cardiac event risk, as well as higher rates of all-cause mortality [7,8]. Hence, addressing the factors which lead to the development of SAMS, and maintaining adequate compliance with these pharmaceuticals, is critical for improving patient health outcomes.

SAMS range in severity from mild-to-moderate muscle pain, weakness or fatigue (with or without creatine kinase elevation) to potentially life-threatening rhabdomyolysis [4,9,10]. The exact mechanisms which underlie the pathogenesis of SAMS remain unclear, though there are several identifiable factors that appear to increase the likelihood of its onset, such as female gender, old age, hypothyroidism, lower body mass index (BMI), strenuous exercise, physical disability and low vitamin D levels [11–14]. Pharmacological characteristics of statins themselves, namely lipophilicity and dose, are also postulated to affect the frequency of SAMS; however, data from RCTs regarding these associations is inconsistent [5,15–20].

Several meta-analyses and reviews have investigated the overall effect of statins on the development of adverse muscle symptoms in RCTs [18,21–24]. Unlike these previous studies, however, the present meta-analysis includes results from RCTs which have recruited individuals with a statin intolerance. Indeed, in comparison to past meta-analyses, the inclusion criteria of this investigation is broader with no restrictions placed on sample size, study duration/follow-up period or study quality. Having a broader inclusion criteria allows for a wider demographic of study participants so that unbiased and representative outcomes may be obtained [25]. Furthermore, while previous meta-analyses have considered the effect of lipophilicity and/or dose on the development of SAMS [22,23], the present study has sought to provide a more in-depth analysis of these factors. Namely, statin doses have been standardised in order to account for differences in potency between these medications and the effect this may have on the pathogenesis of SAMS [26,27]. Ultimately, the present systematic review and meta-analysis aimed to update and further the findings of previous meta-analyses by assessing the impact of statin lipophilicity and dose on the frequency of adverse skeletal muscle events across a broader range of participants in order to clarify the relationship between these pharmacological factors and the onset of SAMS.

2. Methods

2.1. Search strategy

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the study protocol was registered with International Prospective Register for Systematic Reviews (PROSPERO - CRD42016048342) [28]. PubMed and Scopus databases were searched from inception to 1 June 2017 using a combination of the terms, 'lovastatin', 'fluvastatin', 'pitavastatin', 'simvastatin', 'atorvastatin', 'rosuvastatin', 'pravastatin', 'cerivastatin', 'myalgia', 'statin-induced myopathy' and 'myopathy' (**Supplementary Table S1**). Reference lists of selected articles were also searched to identify further sources.

2.2. Eligibility criteria

All publications included in the review were screened according to selection criteria constructed *a priori*. RCTs (parallel or cross-over design) with at least one group randomised to statin monotherapy as treatment, and a placebo/usual care group as comparator, were included. If RCTs also included a group which had been given statins in combination with other lipid-lowering pharmaceuticals, only the data from the statin monotherapy and control groups were collected. Studies were required to be written in English, include participants $\geq$ 18 years and to have explicitly reported the frequency of at least one type of adverse skeletal muscle event amongst participants. For RCTs with a cross-over design, only events unique to each group (i.e. adverse muscle symptoms with statin but not placebo, or vice versa) were counted. There was no minimum follow-up period, or sample size specifications, however, RCTs were excluded if patients were required to take medications associated with an increased risk of myotoxicity when used in combination with statins (e.g. cyclosporine). Trials which administered vitamin D/coenzyme Q10 supplements to participants were not excluded, but both statin monotherapy and control groups must have received the supplement. Studies were removed if they included participants with other conditions known to cause adverse muscle-related effects (e.g. dengue fever). Duplicate publications and case-control studies were also omitted from the review.

2.3. Data extraction

Titles, abstracts and full articles (if applicable) were screened according to predefined selection criteria. Information pertaining to study type, randomisation methods, blinding, patient characteristics, sample size, interventions, trial duration, low-density lipoprotein cholesterol (LDL-C) entry criteria, primary outcomes, creatine kinase (CK) levels and adverse muscle symptoms was collected. Screening and coding of data was performed independently by two authors. Any discrepancies were resolved through discussion or by the inclusion of a third author.

2.4. Quality of study design and risk of bias assessment

The quality of study design was assessed using the Jadad Quality Scale [29]. Studies were not excluded if they were identified as low quality (Jadad score $\leq$2), but a sensitivity analysis to establish the effect of including these trials was conducted. Publication bias was evaluated for the main analysis using a funnel plot graph and Egger regression asymmetry test [30].

Please cite this article in press as: J.C. Irwin, et al., The effect of lipophilicity and dose on the frequency of statin-associated muscle symptoms: A systematic review and meta-analysis, Pharmacol Res (2017), http://dx.doi.org/10.1016/j.phrs.2017.09.013