Autoimmunity Reviews xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

The anti-inflammatory effects of statins on patients with rheumatoid arthritis: A systemic review and meta-analysis of 15 randomized controlled trials

Guo-min Li [1], Jie Zhao [1], Bing Li, Xiao-fei Zhang, Jian-xiong Ma, Xin-long Ma, Jun Liu *

Tianjin Hospital, No. 406 Jiefang South Rd, Hexi District, Tianjin 300211, China

ARTICLE INFO

Article history:
Received 11 October 2017
Accepted 17 October 2017
Available online xxxx

Keywords:
Rheumatoid arthritis (RA)
Statins
Atorvastatin
Randomized controlled trial (RCT)
Meta-analysis

ABSTRACT

Background: Over the past several years, numerous studies investigated the anti-inflammatory effects of statin on patients with RA. However, the findings of the individual studies were often inconsistent or conflicting.
Materials and methods: The Pubmed, Web of Science, Embase, Cochrane Library and CNKI literature databases were searched in order to identify randomized controlled clinical trials where the association between the anti-inflammatory effect of statin and RA was investigated. Two researchers performed data extraction from eligible independently. Quality parameters and risk of bias in the included studies were assessed according to Cochrane's guidelines. The pooled Standardized Mean Difference (SMD) with a 95%CI was used to assess the anti-inflammatory effect of statin in patients with RA.
Results: Fifteen randomized controlled clinical, classified as "high quality" and with a relatively low risk of selection bias, were included in the meta-analysis. Of these, eight reported that there was no difference in the level of serum total lipids between the atorvastatin-treated and the conventional treatment group. However, the pooled analysis showed that atorvastatin could increase the level of serum amount of high-density lipoprotein (HDL) in RA patients by approximately $x \pm SD95\%$ [HDL: SMD = 0.807, 95%CI = (0.187, 1.426), p = .011]. Meanwhile atorvastatin could reduce the level of serum low-density lipoprotein (LDL), total cholesterol (TC), and triglyceride (TG) in RA patient by $x \pm SD95\%$ [LDL: SMD = −4.015, 95%CI = (−5.848, −2.183), p = .000; TC: SMD = −4.497, 95%CI = (−6.457, −2.537), p = .000; TG: SMD = −1.475, 95%CI = (−2.352, −0.599), p = .001]. Nine studies reported a change in C-Reactive Protein (CRP) after atorvastatin treatment, and the pooled analysis showed that atorvastatin decreased CRP in RA patients by $x \pm SD95\%$ [SMD = −3.033, 95%CI = (−4.460, −1.606), p = .000]. Seven studies investigated the change of Erythrocyte Sedimentation Rate (ESR), and the pooled analysis showed that atorvastatin decreased ESR by $x \pm SD95\%$ [SMD = −2.097, 95%CI = (−3.408, −0.786), p = .002]. Nine studies reported the improvement of disease activity score in RA patients after taking atorvastatin for 12 weeks, and the pooled analysis showed atorvastatin could decrease the DAS28 score in RA patients by $x \pm SD95\%$ [SMD = −2.001, 95%CI = (−3.191, −0.811), p = .001].
Conclusions: Statins have a significant anti-inflammatory effect in RA patients. However, atorvastatin was superior to simvastatin both in terms of its anti-inflammatory and lipid-lowering activities.

Contents

Abbreviations: RA, rheumatoid arthritis; RCT, randomized controlled trial; DMARDs, Non-biologic Disease-Modifying Anti-Rheumatic Drugs; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TG, triglyceride; TC, total cholesterol; DAS28, disease activity score-28; SMD, standardized mean difference; CI, confidence interval; MTX, methotrexate.

* Corresponding author.
E-mail address: liujun570@163.com (J. Liu).
[1] These two authors contribute equally to this work.

https://doi.org/10.1016/j.autrev.2017.10.013
1568-9972/

1. Introduction

Rheumatoid arthritis (RA), occurring in approximately 1% of the general population, is a chronic progressive inflammatory disease causing articular inflammation and damage, functional decline and expedited mortality, mainly due to cardiovascular events, whose etiology is yet unknown [1–3]. The morbidity of rheumatoid arthritis is 2.5 times higher in females than in males, and the prevalence increases with age in adults [4, 5]. The major objectives of RA treatment are to relieve pain, reduce inflammation, preserve joint function, prevent systemic involvement, and reduce morbidity. Conventional treatments include non-biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs), biologic DMARDs, glucocorticoids, and rehabilitation, which are known to be effective in RA treatments, including in management of symptoms and disease progression [6]. Limitations of the conventional treatments include drug intolerance, variation in drug's response duration and magnitude, and side effects [7].

Statin, a lipid-lowering agent, prevents the production of cholesterol in the liver by inhibiting HMG-CoA reductase [8]. This agent reduces total cholesterol and low-density lipoprotein (LDL) levels, decreasing cardiovascular morbidity and mortality [9, 10]. However, increasing evidence shows the beneficial effect of statin cannot be merely attributed to its beneficial effect on the level of lipids [11]; statin has also been reported to have an anti-inflammatory effect [12–16]. Additionally, atorvastatin, which is a statin-based medication, has been attributed anti-inflammatory functions [17]. The anti-inflammatory properties of statin, and of atorvastatin, in particular, have attracted attention to its probable benefits in routine therapy of RA [18–20], further desirable due to this drug's low-risk safety profile [21].

To date, numerous studies investigated the anti-inflammatory effects of statin on patients with RA, but the results are still conflicting. In this meta-analysis study, we aimed to summarize quantitative evidence from a systematic review of good quality randomized controlled clinical trials in order to clarify the anti-inflammatory effect of statin on RA patients.

2. Materials and methods

2.1. Search strategy

The Pubmed, Web of Science, Embase, Cochrane Library and CNKI literature databases were searched in order to identify randomized controlled clinical trials which investigated the association between the anti-inflammatory effect of statin and rheumatoid arthritis. The search includes studies published by September 20, 2017, and no restrictions on publication date or country of publication were included. The search terms were “Hydroxymethylglutaryl CoA Reductase Inhibitors” OR “Inhibitors, Hydroxymethylglutaryl-CoA Reductase” OR “Reductase Inhibitors, Hydroxymethylglutaryl-CoA” OR “Inhibitors, HMG-CoA Reductase” OR “Reductase Inhibitors, HMG-CoA” OR “HMG-CoA Reductase Inhibitors” OR “Statins, HMG-CoA” OR “HMG-CoA Statin” OR “Inhibitors, Hydroxymethylglutaryl-CoA” OR “Hydroxymethylglutaryl-CoA Inhibitors” OR “Inhibitors, Hydroxymethylglutaryl CoA” OR “Statins” OR “Inhibitors, Hydroxymethylglutaryl-Coenzyme A” OR “Hydroxymethyglutaryl-Coenzyme A Inhibitors” OR “Inhibitors, Hydroxymethylglutaryl Coenzyme A”) and (“Arthritis, Rheumatoid” OR “Rheumatoid arthritis” OR “RA”). We checked in order to find additional studies that could contribute to the general discussion on this topic.

2.2. Selection criteria

All eligible studies met the following selection criteria: (1) Randomized controlled trials; (2) human studies; (3) patients with rheumatoid arthritis; (4) treatment based on statins, such as atorvastatin and simvastatin; (5) the outcome of interest was the anti-inflammatory effect of statin in RA. Case reports, editorials letters, science reviews, and expert opinions were excluded.

2.3. Data extraction

Two researchers independently performed data extraction from the eligible studies. A third researcher resolved any divergence still present after discussion. Data extracted from the selected studies included authors' name, publication year, country of study, trial design, characteristics of participants, treatment of drugs and dose, duration of treatment, results, and length of follow-up period.

2.4. Quality assessment and publication bias

The two authors independently judged the quality of the included studies by assessing the risk of bias according to the Cochrane's risk of bias guidelines [37]. Seven sources of bias were assessed: random sequence generation, allocation concealment, the use of blinded participants and practitioners, the use of blinded of outcome assessors, incomplete outcome data, selective reporting, and other bias.

2.5. Statistical analysis

Meta-analysis was performed using STATA version 14.0. The pooled SMD with 95%CI was used to assess the anti-inflammatory effect of statin in RA patients. Statistical differences between groups were determined by Z-test. $p < .05$ was considered significant. To detect heterogeneity among those eligible studies, data were pooled using random-effects meta-analysis [38]. The I^2 statistic was used to assess the heterogeneity across the included studies as suggested by literature [39–40]. When I^2 was higher than 50%, a meta-regression analysis was carried out to identify potential sources of heterogeneity. Factors

Please cite this article as: Li G, et al, The anti-inflammatory effects of statins on patients with rheumatoid arthritis: A systemic review and meta-analysis of 15 randomiz..., Autoimmun Rev (2018), https://doi.org/10.1016/j.autrev.2017.10.013