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Review

Statin impact on disease activity and C-reactive protein concentrations in systemic lupus erythematosus patients: A systematic review and meta-analysis of controlled trials

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ABSTRACT

Background and purpose: Efficacy and safety of statin therapy in patients with systemic lupus erythematosus (SLE) is controversial. The aim of this meta-analysis was to evaluate whether statin therapy affects SLE disease activity and systemic inflammation (C-reactive protein, CRP) according to the evidence from controlled clinical trials.

Experimental approach: A systematic review followed by a bibliographic search in Medline and SCOPUS (up to March 2015) was performed. Quantitative data synthesis was performed using a random-effects model and the generic inverse variance weighting method. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI).

Key results: Meta-analysis of five controlled trials reporting statin impact on SLE disease activity did not suggest any significant effect of statin therapy on SLEDAI. Evaluation of seven controlled trials with reported effects on CRP levels suggested a significant reduction of plasma CRP concentrations in patients with SLE independent of the treatment duration. The effect size on plasma CRP concentrations was significant with lipophilic (atorvastatin) but not hydrophilic (pravastatin and rosuvastatin) statins.

Conclusion and implications: The present results suggest that statin therapy is likely to be safe in patients with SLE. In addition, statin-treated SLE patients may benefit from CRP reduction in terms of managing severe cardiovascular complications associated with the disease.

Contents

Abbreviations: ACR, American College of Rheumatology; ALT, Alanine aminotransferase; BILAG, British Isles Lupus Assessment Group; BMI, Body mass index; CI, Confidence interval; CPK, Creatine phosphokinase; CRP, C-reactive protein; HMG-CoA, 3-hydroxy-3-methyl-glutaryl coenzyme A; hs-CRP, High sensitivity C-reactive protein; SLAM, Systemic lupus activity measure; SLE, Systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; RCT, Randomized controlled trials; WMD, Weighted mean difference.

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1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with pathogenesis still being poorly understood [1]. The main features of the disease involve accumulation of anti-nuclear autoantibodies, hyperactivation of immune cells and multiple organ damages triggered by immune complexes deposition [2–5]. In terms of immune cell responses, defective elimination of autoreactive lymphocytes, loss of self-tolerance and immune responses against autoantigens, and particularly, altered immune cell apoptosis are the major contributing factors in disease susceptibility [6]. Among several complications arising from the impairment of immune responses, severe cardiovascular complications (specifically atherosclerosis) are the main cause of morbidity and mortality in SLE patients [7–9].

Being eight-fold more common than in the normal population after correction for the traditional Framingham risk factors [10], the increased incidence of coronary artery disease cannot be explained by traditional cardiovascular risk factors [11]. Supporting the higher risk compared to non-SLE patients, about one-third of SLE patients were evidenced to have subclinical atherosclerosis at carotid or coronary arteries [12,13], and more than half of the subjects to have endothelial dysfunction, even independently on the presence of conventional risk factors for atherosclerotic disease [14,15]. These so called "SLE-associated risk factors for atherosclerosis" include chronic inflammation and oxidative stress, anti-phospholipid antibodies [16], chronic use of glucocorticosteroids, inflammatory cytokines, high homocysteine levels or anti-oxidized LDL antibodies [17,18]. Accordingly, the key strategy to reduce the risk of cardiovascular events in patients with SLE aims for the alleviation of vascular endothelium activation and prevention of atherosclerosis in these subjects.

After more than three decades of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors existence, it is clear that statins are no more just hypolipidemic drugs. By acting on the enzyme converting HMG-CoA to mevalonic acid, statins reduce cholesterol synthesis and increase LDL uptake. The efficacy of statins in both primary and secondary prevention of coronary artery disease has been demonstrated in several large-scale trials [19,20], however the extent of the protection can be hardly explained by a simple lowering effect on plasma cholesterol and other lipids [21]. Statins possess several pleiotropic effects including anti-inflammatory, immune modulatory, anti-thrombotic, and endothelial function-improving properties [22–27]

Aside from their established role in reducing cardiovascular morbidity and mortality [28], statins have been also considered for the treatment of autoimmune diseases. Indeed, statins demonstrated to be beneficial in several autoimmune diseases like rheumatoid arthritis or multiple sclerosis [29,30]. Statins were also proved to prevent endothelial cell activation induced by anti-phospholipid antibodies [31], reduce autoreactive B-cell activation [32], minimize Th1-driven autoimmunity [33], and decrease serum homocysteine levels [34]. Several trials have also pointed to a beneficial effect of statins on high sensitivity C-reactive protein (hs-CRP) reduction [35,36].

In patients with SLE, hs-CRP was not associated with cardiovascular damage in the Hopkins lupus cohort, but it was associated with damage to various organs, particularly those of the pulmonary and musculoskeletal systems [37]. Despite the favorable vessel-protective effects, there has been little evidence for the effectiveness of statins in cardiovascular symptom-free SLE patients. Moreover, there have been some relatively rare reports of lupus-like syndrome induced by statins [38–40]. On the other hand, since the statin-induced adverse effects often appear late after the beginning of the treatment and the autoantibodies do not drop off immediately after the discontinuation of the treatment, the causal relation between statins and autoimmune response is still controversial and hard to prove [34]. Even more, statins are still widely recommended for patients with SLE, suggesting their benefits tend to exceed their risk [41–43].

Taken together, despite some evidence that a higher percentage of patients with SLE could benefit from such intervention, data for statin use safety in SLE remain inconsistent. Therefore, the aim of this meta-analysis was to evaluate whether statin therapy affects SLE disease activity and progression, especially with respect to safety of statin treatment in SLE patients.

2. Methods

2.1. Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [44]. SCOPUS (http://www.scopus.com) and Medline (http://www.ncbi.nlm.nih.gov/pubmed) databases were searched using the following search terms in titles and abstracts (also in combination with MESH terms): (atorvastatin OR simvastatin OR rosuvastatin OR fluvastatin OR pravastatin OR pitavastatin OR lovastatin OR cerivastatin OR "statin therapy" OR statins OR statin) AND (lupus OR "systemic lupus" OR "systemic lupus erythematosus" OR SLE). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in human. The literature was searched from inception to March 21, 2015.

2.2. Study selection

Original studies were included if they met the following inclusion criteria: (i) being a controlled trial with either parallel or cross-over design, (ii) recruiting patients with a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) criteria [45], (iii) investigating the impact of statin therapy on a valid disease activity index including Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [46] and British Isles Lupus Assessment Group (BILAG) [47], or reporting the impact of statin therapy on plasma/serum concentrations of CRP, (iv) treatment duration of at least two weeks, and (v) presentation of sufficient information on disease activity score or CRP concentrations at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were (i) non-interventional studies, (ii) lack of a control group in the study design, (iii) case reports or observational studies with case–control, cross-sectional or cohort design, and (iv) lack of sufficient information on baseline, follow-up or change values for disease activity score or CRP concentrations. For the latter reason, attempts were made to obtain data from the author(s).