Effect of HMG-CoA Reductase Inhibitor Drugs (Statins) on Systemic Lupus Erythematosus Disease Activity: A Systematic Review and Meta-analysis

Givenchy Maree D. Garcia, M.D.*; Annalyn Q. Urbano, M.D.*; Evelyn O. Salido, M.D.**

Abstract

Introduction: Statins have been shown to have anti-inflammatory and immunomodulatory effects. In vitro studies show that these drugs inhibit inflammatory cells, decrease the expression of major histocompatibility complex (MHC), decrease adhesion molecules and inflammatory cytokines (IL6 and IL10), that are also implicated in SLE pathogenesis. In terms of immunomodulary effects, animal studies demonstrate that statins exacerbate/trigger cellular apoptosis and induce a shift in the Th1/Th2 balance leading to B-cell reactivity and production of pathogenic autoantibodies. Whether statins have clinical effects in SLE have not been widely studied. In terms of disease activity, studies show contradicting results. The researchers aim to determine the effect of statins on the disease activity of SLE based on the best available evidence.

Methods: A systematic literature search of PubMed, Scopus, and Cochrane databases was done with no date and language restrictions. Included studies were on adult SLE patients and randomized controlled trials that used statins as intervention and reported SLE disease activity as an outcome measure. Two reviewers did quality appraisal, risk bias assessment, and data extraction.

Results: Three studies met the eligibility criteria and were included in this review. Quantitative synthesis was done. The pooled analysis of these studies suggests that atorvastatin has no significant effect on disease activity using random effects model with an overall effect of 0.12 (*P*=0.90, 95% CI -1.65, 1.88).

Conclusion: Atorvastatin neither increased nor decreased SLE disease activity. Therefore possibly it can be safely given to SLE patients without the risk of triggering or exacerbating a flare.

Keywords: systematic lupus erythematosus, statins, HMG-CoA reductase inhibtor, systematic review

Introduction

It is widely accepted that immune system alterations result in the generation of autoantibodies and immune complexes and contribute to inflammation, organ damage and to the clinical manifestations of SLE.[1] The reported prevalence of SLE in the Asian population is 30 to 50 cases per 100,000 population.[2]

Statins are drugs that bind to and inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyses the conversion of HMG-CoA to L-mevalonic acid in the first step of cholesterol biosynthesis.[3] Statins have a known effect in reducing the morbidity and mortality due to atherosclerosis in the general population.[4]

Recently, the anti-inflammatory and immunomodulatory effects of statins have been demonstrated.[5] These drugs inhibit monocytes, macrophages and lymphocytes, decrease the expression of major histocompatibility complex (MHC) and decrease adhesion molecules and inflammatory cytokines, IL6 and IL10, that are implicated in SLE pathogenesis.[6] In converse, animal studies demonstrate that statins may trigger cellular apoptosis[7] and induce a shift in the Th1/Th2 balance. This favors B-cell reactivity and production of pathogenic auto-antibodies.[8] Treg cells that are unstable in the periphery may promote autoimmunity.[9] All these may promote the progress of preexisting autoimmune conditions toward clinical disease, such as SLE.

The anti-inflammatory effect of statins may benefit autoimmune diseases like SLE, rheumatoid arthritis and multiple sclerosis.[10,11] The statin studies in patients with lupus primarily look at the endpoint of atherosclerosis, and show conflicting results in terms of lupus disease activity.[12,13,14] Thus, we sought to determine the overall effect of statins on the disease activity of SLE based on the best available evidence.

Methods

Literature search strategy

This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses.[15] Literature search

*Fellow-in-training, Section of Rheumatology, Department of Internal Medicine, University of Philippines-Philippine General Hospital, Manila
**Faculty, Section of Rheumatology, Department of Internal Medicine, University of Philippines-Philippine General Hospital, Manila

Corresponding author: Givenchy Maree Garcia, M.D., University of Philippines-Philippine General Hospital, Manila, Philippines
Email: gdgarcia1@up.edu.ph

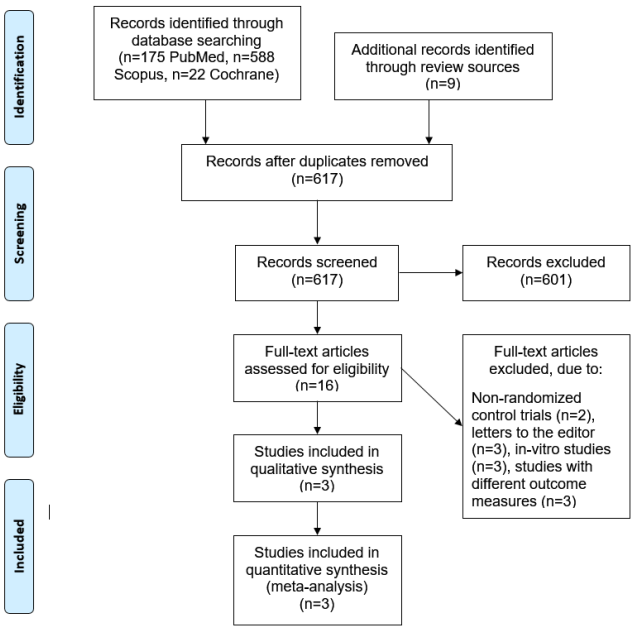

Figure 1. Flow diagram of the selection process of studies

of PubMed, Scopus, and Cochrane databases was done with no date and language restrictions. Queries to identify relevant publications on statins and SLE disease activity were based on Boolean combinations of the following search and MeSH terms: systemic lupus erythematosus, SLE, lupus, hydroxymethylglutaryl-CoA reductase inhibitor, HMG-CoA reductase inhibitor, statins, atorvastatin, simvastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, disease activity, SLE Disease Activity Index (SLEDAI), British Isles Lupus Assessment Group Index (BILAG), Systemic Lupus Activity Measure Index (SLAM). We also identified articles that were cited in review papers.

Study eligibility criteria

This review included studies on adult patients with SLE. The studies were randomized contolled trials using statins asintervention and reporting SLE disease activity as outcome measure. Only randomized controlled trials using statins as intervention and reporting SLE disease activity as outcome measure were included.

Study exclusion criteria

Studies were excluded if it was impossible to extrapolate the necessary data from the published results, or there was considerable overlap between authors, centers, or patient cohorts evaluated in the published literature.

Data extraction

The first author screened the titles and abstracts of all retrieved articles for eligibility. Two authors appraised methodological quality and risk of bias using the Cochrane Collaboration risk of bias tool. Disagreements were discussed until a consensus was reached. Figure 1 describes the study selection process and Table I shows the included studies.

Statistical analysis

The meta-analysis was performed in line with recommendations from the Cochrane Collaboration and Quality of Reporting of Meta-analyses guidelines. The weighted mean difference (WMD) with 95% confidence intervals (CI) of lupus disease activity scores (SLEDAI) was reported. Statistical algorithms were used to calculate means and standard deviations (SDs) for studies that presented data as median and range values, thus standardizing all data for analysis. Analysis was conducted using the Review Manager version 5.3 (The Cochrane Collaboration Software). Sensitivity analysis was then done to explore possible causes of heterogeneity.

Results

Three studies (total of 350 subjects) met the eligibility criteria and were included in this systematic review (see Table I).[16,17,18] The studies were done between year 2010 to 2014, and the duration of the studies ranged from three months to two years. The majority of patients were female and in their forties. In all the studies, atorvastatin was the experimental drug with a dose of 20mg to 40mg per day. There were no eligible studies that investigated the effect of

Table I. Summary of the selected studies on effect of statins on SLE disease activity

Reference	Study design	Study population	Overall mean age (SD)	Mean age (SD)		Intervention		Outcome measures	Mean baseline SLEDAI (SD)	Findings
				Male	Female	Dose	Duration			
Petri et al., 2010	RCT	200 SLE without Cardiovascular Disease	44.7 (11.3)	16	184	Atorvastin 40mg OD	2 years	Coronary Artery Ca, Intima media thickness, Lipids, Markers of endothelial activation SLEDAI	2.0 (4.5)	No evidence that artovastatin reduces subclinical atherosclerossis. Does not appear to reduce biochemical measures of inflammation. No significant change in mean SLEDAI score.
Plazak et al., 2011	RCT	60 SLE	41.8 (13.4)	6	54	Atorvastin 40mg OD	1 year	Myocardial perfusion, Coronary Artery Ca, SLEDAI, Lipids, CRP AST, ALT, CPK	4(4.5)	Calcium deposits increased in placebo, but not in treatment group. Decreased total serum lipids and CRP. No change in mean SLEDAI score.
Fatemi et al. 2014	RCT	90 SLE	38.8 (11)	6	84	Atorvastin 20mg OD	3 months	SLEDAI, Lipids CRP, ESR, Anti dsDNA	3(3.35)	Effect of atorvastatin in lupus activity was inconclusive. Significant decrease in HDL, LDL, and CRP.

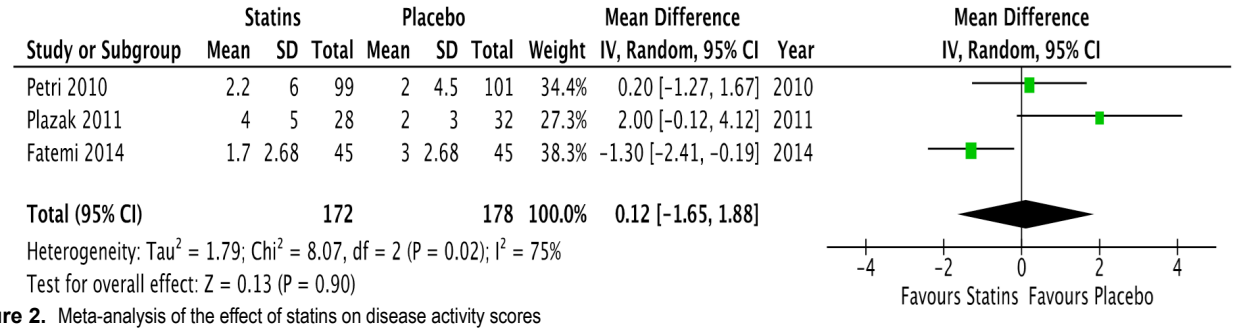

Figure 2. Meta-analysis of the effect of statins on disease activity scores

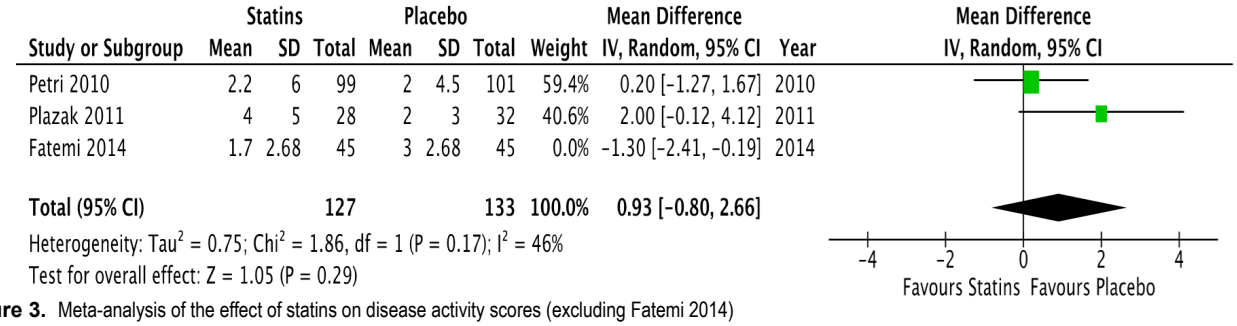

Figure 3. Meta-analysis of the effect of statins on disease activity scores (excluding Fatemi 2014)

other statins on lupus disease activity. Likewise, there were also no studies that used other measures of disease activity such as BILAG and SLAM.

The mean SLEDAI score showed no significant change in two studies[16,17] and was inconclusive in one.[18] The pooled analysis of these studies (Figure 2) suggests that atorvastatin had no significant effect on disease activity on random effects model with an overall effect of 0.12 (*P*=0.90, CI -1.65, 1.88). Pooled studies had high heterogeneity (I^2 of 75%, *p*=0.02). To investigate the source of heterogeneity, a sensitivity analysis was performed. After excluding the trial with a lower atorvastatin dose (Fatemi 2014), this reduced heterogeneity to within acceptable limits (I^2 of 46%, *p*=0.17) but still showed similar results (Figure 3). We also investigated if the baseline SLEDAI score was a source of heterogeneity. However after exclusion of the study by Plazak (2010) with a baseline SLEDAI score of mild to moderate, it did not have a significant impact on the heterogeneity and the pooled estimate.

Discussion

The pleiotropic effects of statins provided the impetus for this review. Given to lupus patients for their lipid-lowering effects, it remains a point of contention whether its pro-inflammatory effects demonstrated in animal studies are translated to clinical correlates. There is paucity of studies to confirm the clinical effects of statins on SLE and many have methodological challenges. Most of the studies are not randomized and have small sample sizes (three to 41 patients). Often, treatment duration is short (eight days to three months), disease activity not measured as an outcome, and the effects of concurrent immune suppressants are not taken into account.[12,13,14] These therefore may have contributed to the contradicting results from these studies. Given the highest strength of cause-effect relation between treatment and outcome derived from randomized controlled trials, these were the only studies included in this review.

The results of this review suggest that statins have no significant effect on SLE disease activity. But it is important to consider four factors that may influence measurement of treatment effect. First, the studies included only used atorvastatin as the experimental drug thus the results may not apply to other statins. Second, in the pooled studies, the SLEDAI was only recorded at two time points (before and after therapy). Knowing that SLEDAI covers signs and symptoms within 10 days prior to assessment, it would have been more valuable if more evaluations were conducted. Third, the duration of treatment (three months to two years) may still be insufficient to show a significant effect. And lastly, baseline disease activity scores were low (<4 points) and may not be as responsive to change as higher scores.

Conclusion

Atorvastatin neither increased nor decreased SLE disease activity; therefore its anticipated clinical benefits must be weighed against the possible but unproven risk of lupus disease flare. There was no data on other statins on SLEDAI score nor data on other measures of lupus disease activity. Further studies on the effects of statins on lupus disease activity are needed.

References

1. **Tsokos GC**. Systemic lupus erythematosus. N Engl J Med 2011;365:2110–21.
2. **Osio-Salido E, Manapat-Reyes H.** Epidemiology of systemic lupus erythematosus in Asia. Lupus 2010;19:1365–73.
3. **Istvan ES, Deisenhofer J.** Structural mechanism for statin inhibition of HMG- CoA reductase. Science 2001;292:1160–4.
4. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial (2002). Lancet 360 (9326):7-22.
5. **Gurevich VS, Shovman O, Slutzky L, Meroni PL, Shoenfeld Y**. Statins and autoimmune diseases. Autoimmun Rev 2005;4:123–9.
6. **Abeles AM, Pillinger MH** (2006) Statins as antiinflammatory and immunomodulatory agents: a future in rheumatologic therapy? Arthritis Rheum 54(2):393–407.
7. **Blanco-Colio LM, Villa A, Ortego M, Hernandez-Presa MA, Pascual A, Plaza JJ, Egido J**. 3-Hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors, atorvastatin and simvastatin, induce apoptosis of vascular smooth muscle cells by downregulation of Bcl-2expression and Rho A prenylation. Atherosclerosis 2002;161(1):17-26.
8. **Hakamada-Taguchi R, Uehara Y, Kuribayashi K, Numabe A,Saito K, Negoro H, Fujita T, Toyo-oka T, Kato T.** Inhibition of hydroxymethylglutaryl-coenzyme a reductase reduces Th1 development and promotesTh2 development. Circ Res 2003;93(10):948-56.
9. **Zhou X, Bailey-Bucktrout SL, Jeker LT, Penaranda C, Martinez-Llordella M, Ashby M, Nakayama M, Rosenthal W, Bluestone JA.** Instability of the transcription factor Foxp3 leads to the generation of pathogenic memory T cells in vivo. Nat Immunol 2009;10(9):1000-7.
10. **McCarey DW, McInnes IB, Madhok R, et al.** Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet 2004;363:2015–21.
11. **Paul F, Waiczies S, Wuerfel J, et al.** Oral high-dose atorvastatin treatment in relapsing-remitting multiple sclerosis. PLoS ONE 2008;3:e1928.
12. **Abud-Mendoza C, de la Fuente H, Cuevas-Orta E, Baranda L, Cruz- Rizo J, Gonzalez-Amaro R** (2003) Therapy with statins in patients with refractory rheumatic diseases: a preliminary study. Lupus 12(8): 607–611.
13. **de Kruif MD, Limper M, Hansen HR, de Ruiter J, Spek CA, van Gorp EC, ten Berge IJ, Rowshani AT, ten Cate H, Meesters EW** (2009) Effects of a 3-month course of rosuvastatin in patients with systemic lupus erythematosus. Ann Rheum Dis 68(10):1654.
14. **Costenbader KH, Liang MH, Chibnik LB, Aizer J, Kwon H, Gall V, Karlson EW** (2007) A pravastatin dose-escalation study in systemic lupus erythematosus. Rheumatol Int 27(11):1071–1077.
15. **Moher D, Liberati A, Tetzlaff J, Altman DG**; PRISMA Group. Reprint – preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Phys Ther. 2009;89:873–880.
16. **Petri MA, Kiani AN, Post W, Christopher-Stine L, Magder LS.** Lupus Atherosclerosis Prevention Study (LAPS). Ann Rheum Dis 2010 70(5):760–765.
17. **Plazak W, Gryga K, Dziedzic H, Tomkiewicz-Pajak L, Konieczynska M, Podelec P, Musial J.** Influence of atorvastatin on coronary calcifications and myocardial perfusion defects in systemic lupus erythematosus patients: a prospective, randomized, double-masked, placebo-controlled study. Arthritis Research & Therapy 2011 13:R117.
18. **Fatemi A, Moosavi M, Sayedbonakdar Z, Farajzadegan Z, Kazemi M, Smiley A**. Atorvastatin effect on systemic lupus erythematosus disease activity: a double-blind randomized clinical trial. Clin Rheumatol (2014) 33:1273–1278.