Effect of 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Inhibitor on Disease Activity in Patients With Rheumatoid Arthritis: A Meta-Analysis

Bin Xing, MD, Yu-Feng Yin, MD, Li-Dan Zhao, MD, Li Wang, MD, Wen-Jie Zheng, MD, Hua Chen, MD, Qing-Jun Wu, MD, Fu-Lin Tang, MD, Feng-Chun Zhang, MD, Guangliang Shan, PhD, and Xuan Zhang, MD

Abstract: HMG-CoA reductase inhibitors (also known as statins) are widely used as lipid-lowering agents in patients with rheumatoid arthritis (RA) to reduce their cardiovascular risk. However, whether they have an effect on RA disease activity is controversial. This study aimed to investigate the effect of statins on disease activity in RA patients.

A systematic literature review was performed using the MEDLINE, EMBASE, Cochrane Library, ISI WEB of Knowledge, Scopus, and Clinical Trials Register databases. Only prospective randomized controlled trials or controlled clinical trials comparing the efficacy of statins with placebo on adult RA patients were included. The efficacy was measured according to the ACR criteria, EULAR criteria, DAS28, HAQ score, ESR, or CRP. The Jadad score was used for quality assessment. The inverse variance method was used to analyze continuous outcomes. A fixed-effects model was used when there was no significant heterogeneity; otherwise, a random-effects model was used. For stability of results, we performed leave-one-study-out sensitivity analysis by omitting individual studies one at a time from the meta-analysis. Publication bias was assessed using Egger test.

A total 13 studies involving 737 patients were included in the meta-analysis; 11 studies were included in the meta-analysis based on DAS28, while the other 2 studies were only included in the meta-analysis based on ESR or CRP. The standardized mean difference (SMD) in DAS28 between the statin group and the placebo group was −0.55 (95% CI [−0.83, −0.26], P = 0.0002), with an I² value of 68%. Subgroup analysis showed that patients with more active disease tended to benefit more from statin therapy (SMD −0.73, P = 0.01) than patients with moderate or low disease activity (SMD −0.38, P = 0.03). Statin therapy also significantly reduced tender joint counts, swollen joint counts, ESR, and CRP compared with placebo, but the reduction in HAQ score and VAS was not significant (P > 0.05).

This meta-analysis suggested that statin therapy might be effective in the reduction of RA disease activity measured by DAS28, TJC, SJC, as well as ESR and CRP.

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INTRODUCTION

3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, also known as statins, are a class of drugs that are used to lower cholesterol levels by inhibiting the HMG-CoA reductase enzyme, which plays a central role in the production of cholesterol. Due to their cholesterol-lowering effects, statins are widely used in the treatment of cardiovascular diseases (CVDs), the latter accounts for approximately 30% of all deaths globally. Recently experimental and clinical evidence suggests that the beneficial effects of statins are pleiotropic, extending beyond their cholesterol-lowering effects. Statins have been shown to possess many anti-inflammatory and immunomodulatory properties that can influence multiple steps in the inflammatory process. Some clinical studies also support these findings. The JUPITER trial showed that statins are effective in the primary prevention of CVDs in patients with elevated CRP levels but relatively low cholesterol levels and other cardiovascular risks, suggesting a non-cholesterol-dependent effect of statins because the reduction in CRP by rosuvastatin was not related to the reduction in low-density lipoprotein (LDL) cholesterol. The recent COSMOS trial
found that rosuvastatin significantly reduces intravascular ultrasound-detected intracoronary plaque volume, unrelated to the reduction in plasma LDL, supporting the idea of effects beyond cholesterol-lowering effects.8

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that primarily affects the synovial tissue, but it is also a systemic disease that can affect many systems. The etiology of RA is unclear. However, it is accepted that autoimmune responses, the dysregulation of T-helper 1-mediated immune responses in particular, play distinct roles in the pathogenesis of RA. Aberrant T-cell activation stimulates monocytes and macrophages to produce inflammatory cytokines and proteolytic enzymes, initiating the destruction.

Recent studies show that in addition to their effects in reducing cardiovascular risks, statins may provide mild anti-inflammatory benefits in RA.10–12 These studies have suggested that statin treatment has a promising effect on disease activity in RA patients, which may be partly due to the immunomodulatory and anti-inflammatory properties. However, the results of these studies are controversial, and they consist largely of single-center studies with small sample sizes. Therefore, in this study, we conducted a comprehensive meta-analysis to evaluate the effect of statins on disease activity in RA patients.

METHODS

The meta-analysis was performed according to the recommendations of the Cochrane Collaboration,13 and the findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.14 As this study is a meta-analysis, ethical approval was not required.

Search Strategy

The following databases were searched on March 20, 2014: MEDLINE (PubMed), EMBASE (Ovid), the Cochrane Central Register of controlled trials, Scopus (Elsevier), and ISI Web of Knowledge. A combination of the following terms was used: “Rheumatoid arthritis”, AND “HMG-CoA reductase inhibitor”, “Anticholesteremic Agents”, “statin, simvastatin, pravastatin, rosuvastatin, atorvastatin, fluvastatin, lovastatin, or pitavastatin. There was a limitation with regard to language in that we only considered English publications, but the year of publication was not limited. Type filters provided by the databases were not used during the search to ensure sensitivity. We also used references from the reports, clinical trial registers (ClinicalTrials.gov), and Internet browsers.

Inclusion and Exclusion Criteria

A study was included in the meta-analysis if it fulfilled the following criteria: the patients enrolled were adult (older than 16 years old) RA patients diagnosed using the American College of Rheumatology (ACR) criteria; the study had a prospective randomized controlled trial (RCT) or controlled clinical trial (CCT) design, in which the effects of statins were compared to placebo; and the efficacy was measured according to the American College of Rheumatology criteria (ACR20, ACR50, ACR70), European League Against Rheumatism (EULAR) criteria, disease activity score in 28 joints (DAS28), functionality assessment according to the health assessment questionnaire (HAQ), or inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The definitions of RCT and CCT were based on the Cochrane Handbook; that is, a trial was eligible if the individuals followed in the trial were assigned prospectively to 1 of 2 (or more) alternative forms of intervention using either random allocation or some quasi-random method of allocation (such as alternation, date of birth, or case record number). Single-arm clinical trials, reviews, and reports involving only laboratory findings, underlying disease mechanisms, and treatment mechanisms were excluded.

Trial Selection and Data Extraction

The titles and abstracts of the trials were assessed independently by 2 of the authors (B.X. and L.Z.). The full-text version of all publications that potentially qualified for the review was assessed in detail based on the inclusion and exclusion criteria. Data extraction was performed independently by 2 of the authors (B.X. and Y.Y.). The following information was extracted from each study: the study design, patient characteristics, interventions, outcomes, and study duration. For studies with multiple time points, 1 time point was chosen for improved consistency with the other studies. For each outcome measure of interest, the following data were extracted from each intervention group: number of patients, the mean change in the outcome measure, and the standard deviation of the change. The standard deviations of continuous data were either extracted from the reports directly or calculated using a 95% CI interval, standard error, or the P value of the t-test reported using the statistical methods provided in the Cochrane Handbook.13 For studies presenting only baseline values and final values, the change values were imputed using the method provided in the Cochrane Handbook.13 The extracted data were compared. The protocol assumed that in the case of discrepancies between the investigators, another investigator would act as an arbiter until consensus was achieved.

Assessment of Trial Quality

The methodology of the trials included in the review was assessed using the Jadad score.15 By definition, the scores ranged from 0 to 5, with higher scores indicating less likelihood of bias in the results.

Statistical Methods of Meta-Analysis

We calculated the standardized mean differences (SMD) for DAS28 to account for the possible use of different versions. Mean differences were calculated for other continuous data, such as ESR, CRP, HAQ, tender joint counts (TJC), swollen joint counts (SJC), and visual analog score (VAS). A mean difference lower than zero indicated that the patients from the experimental group had lower disease activity than those from the control group. By default, a fixed data model was applied. Heterogeneity of the trials was then assessed using the χ2 and I2 tests. When compared trials had a high heterogeneity (I2 > 50%), the random-effects model was applied instead. The results were considered statistically significant at a level of P < 0.05. RevMan 5.2 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to conduct the meta-analysis, and STATA 12.0 (StatCorp LP, College Station, TX) was used for the analysis of sensitivity and publication bias.

RESULTS

 Characteristics of the Included Studies

Figure 1 describes the flowchart of the literature search. A total of 13 studies (737 patients) were finally included in the
meta-analysis: 10 were full-text articles, and 3 were abstracts. Attempts were done to contact the investigators of these 3 studies to gain more information. The risk of bias of the included studies was assessed using the Jadad score (Table 1). All studies included were single-center studies (Table 1), and the number of patients enrolled ranged from 20 to 116. Twelve studies enrolled RA patients with active disease, with a mean baseline DAS28 ranging from 3.5 to 6.5. One study enrolled stable RA patients, with a mean baseline DAS28 of 2.7. Atorvastatin was used in 7 studies (414 patients) at a dose ranging from 10 to 80 mg qd. Simvastatin was used in 2 studies (129 patients) at a dose of 20 mg qd. Rosuvastatin was used in 3 studies (138 patients) at a dose of 10 mg qd. Lovastatin was used in only 1 study (56 patients) at a dose of 80 mg qd. The duration of therapy ranged from 4 weeks to as long as 48 weeks. As 11 of the studies used DAS28 to measure the final outcome, we performed the meta-analysis mainly based on DAS28. HAQ, EULAR criteria, ACR criteria, CRP, and ESR were used to measure outcomes in some of the studies (shown in Table 1).

The Effect of Statins Based on DAS28

A total of 11 studies used DAS28 to evaluate the effect of statins: 9 presented the DAS28 change from baseline, and 2 presented only baseline and final
The results are shown in Figure 2. The overall SMD of DAS28 was \(-0.55\) (95% CI \([-0.83, -0.26]\), \(P = 0.0002\)), which indicated that the DAS28 reduction in the statin group was 0.55 lower than that in the placebo group. This result was statistically significant. The I\(^2\) was 68\%, suggesting a high heterogeneity. A subgroup analysis was conducted based on the statin used and the disease activity presented by baseline DAS28 score; the results showed that atorvastatin significantly reduced disease activity measured based on DAS28 (SMD = -0.77, 95% CI [-1.17, -0.36], \(P = 0.0002\), I\(^2\) = 71\%) (shown in Figure 3A). No dose-dependent reduction of disease activity was observed. Furthermore, the patients with higher disease activity (defined as baseline DAS28 \(\geq 5.1\)) tended to benefit more from statin therapy (SMD = -0.73, 95% CI [-1.28, -0.18], \(P = 0.0007\), I\(^2\) = 79\%) than the patients with moderate and low activity (shown in Figure 3B).

**The Effect of Statins Based on Other Measures**

Other outcome measurements, including CRP, ESR, TJC, SJC, HAQ, and pain evaluated based on VAS, were also analyzed as continuous outcomes using the inverse variance method. The results are shown in Table 2. The fixed-effects model or the random-effects model was chosen according to the heterogeneity. The results showed that statin therapy significantly reduced CRP (mean difference = -5.32, 95% CI [-8.05, -2.60], \(P = 0.0001\)), ESR (mean difference = -5.71, 95% CI [-7.14, -4.27], \(P < 0.00001\)), TJC (mean difference = -2.09, 95% CI [-2.99, -1.28], \(P = 0.0002\), I\(^2\) = 68\%) when compared with placebo.

**Table 1. Characteristics of the Included Studies**

| Author         | Year | Type of Statins (Dosage, mg qd) | Duration (wk) | Number of Patients | Mean Baseline DAS28 | Outcome Measurements                  | Jadad score |
|---------------|------|---------------------------------|---------------|-------------------|--------------------|--------------------------------------|-------------|
| McCarey, DW   | 2004 | Atorvastatin (40)               | 24            | 116\*             | 5.83               | DAS28, HAQ, CRP, ESR, TJC, SJC, VAS  | 5           |
| Tikiz, C      | 2005 | Simvastatin (20)                | 8             | 29                | 4.6                | CRP                                  | 3           |
| Charles-Schoeman, C | 2007 | Atorvastatin (80)              | 12            | 20                | 5.2                | DAS28, HAQ, CRP, ESR, TJC, SJC, VAS  | 4           |
| Ljung, L      | 2009 | Atorvastatin (40)               | 24            | 51                | 4.2                | DAS28, CRP, ESR                       | -           |
| El-Barbary, AM | 2011 | Atorvastatin (40)               | 24            | 30                | 6.1                | DAS28, CRP, ESR, EULAR, VAS, TJC, SJC | 2           |
| Tang, TT      | 2011 | Atorvastatin (20)               | 12            | 55                | 5.67               | DAS28, CRP, ESR                       | 2           |
| Tam, LS       | 2011 | Rosuvastatin (10)               | 24.48\*       | 50\*              | 2.7                | DAS28, CRP, ESR, VAS, TJC, SJC        | 3           |
| Kumar, P      | 2012 | Rosuvastatin (10)               | 24            | 48                | 4.5                | DAS28, HAQ                            | 5           |
| Mikhail, EM   | 2013 | Rosuvastatin (10)               | 8             | 40                | 6.1                | ESR                                  | 3           |
| Cojocaru, L   | 2013 | Simvastatin (20)                | 12.24\*       | 100\*             | 3.2                | DAS28, HAQ, EULAR, CRP, ESR, TJC, SJC | 2           |
|                |      |                                 |               |                   |                    | VAS, CDAI, SDAI                       |             |
| Singh, H      | 2013 | Atorvastatin (20)               | 12            | 50                | –                  | DAS28                                | 1           |
| Aranow, C     | 2013 | Lovastatin (80)                 | 12            | 56                | 3.5                | DAS28, ACR20, EULAR, CRP              | 3           |
| McInnes, IB   | 2014 | Atorvastatin (10)               | 6.12\*        | 92\*              | 6.5                | DAS28, HAQ, CRP, ACR20, ACR50, ACR70  | 4           |

ACR = American College of Rheumatology criteria, CDAI = clinical disease activity index, CRP = C-reactive protein, DAS = disease activity score, ESR = erythrocyte sedimentation rate, EULAR = European League Against Rheumatism criteria, HAQ = health assessment questionnaire, SDAI = simplified disease activity index, SJC = swollen joint counts, TJC = tender joint counts, VAS = visual analog score.

\* Intention to treat method used.

\^ One time point was chosen for studies with multiple time points for improved consistency with the other studies.

\^\^ Full analysis set method used; the number of patients analyzed at 6 and 12 weeks was 97 and 92, respectively.

**Figure 2.** Forest graph of the meta-analysis of the effect of statins versus placebo on DAS28 in RA patients. The pooled standardized mean difference was \(-0.55\), 95% CI \([-0.83, -0.26]\), \(P = 0.0002\), I\(^2\) = 68\%. CI = confidence interval, SD = standard deviation.
1.18], P < 0.00001), and SJC (mean difference −1.42, 95% CI [−2.50, −0.35], P = 0.009) (Table 2). Although statin therapy also reduced the HAQ score (mean difference −0.08, 95% CI [−0.18, 0.02], P = 0.13) and VAS (mean difference −7.58, 95% CI [−18.01, 2.86], P = 0.15), the reductions were not significant (Table 2).

**Analysis of Sensitivity and Publication Bias**

Analyses of sensitivity and publication bias were conducted using the Stata 12.0 software. The sensitivity analysis showed that the sequential omission of individual studies did not alter the overall effect (upper limit of 95% CI interval lower

**FIGURE 3.** Subgroup analysis based on type of statin (A) and disease activity (B). A. Atorvastatin produced a greater reduction in DAS28 in RA patients (SMD −0.77, 95% CI [−1.77, −0.36], P = 0.002, I² = 71%). B. Patients with highly active disease (defined as baseline DAS28 > 5.1) tended to benefit more from statin therapy compared with patients with moderate and low disease activity (SMD −0.73, 95% CI [−1.28, −0.18], P = 0.01, I² = 79%). CI = confidence interval, DAS28 = disease activity score in 28 joints, SMD = standardized mean difference.
than 0 in all cases). The results are shown in Figure 4. The publication bias was evaluated using a funnel plot, which showed no significant evidence of asymmetry (Figure 5). We also performed an Egger test to quantify the publication bias, and the P value was 0.324, suggesting no significant bias of the analysis (Figure 5).

### DISCUSSION

Hyperlipidemia, together with other cardiovascular risk factors, plays important roles in the pathogenesis of CVD. Stains are used in RA patients with hyperlipidemia for the prevention of CVD. RA is associated with an increased risk of CVD, which can only be partially explained by traditional cardiac risk factors. RA and atherosclerosis share many inflammatory mechanisms, and the extent of inflammation associated with RA predicts both CVD and overall mortality rates in RA. This meta-analysis aimed to answer the question of whether statins benefit RA patients more than originally thought via other than lipid-lowering effects. The previous literature search was comprehensive, and efforts were taken to obtain more data. Therefore, it is reasonable to draw conclusions based on this meta-analysis. The studies included are almost all single-center studies with a small number of patients. The types of stains used in each study, the difference in the dosage, the duration of the treatment, and the disease activity also added to the heterogeneity. In the 7 studies about atorvastatin, the dosage varied from 10 to 80 mg per day, and the other lipid-lowering drugs with regard to changes in most results of these 2 studies showed no difference between statins and the other lipid-lowering drugs: ezetimibe and fenofibrate. The results of these 2 studies showed no difference between statins and the other lipid-lowering drugs with regard to changes in most outcome measurements (ESR, CRP, and DAS28). Fenofibrate has also been reported to have anti-inflammatory activity, whereas ezetimibe is a drug that only acts locally and is not absorbed into the circulation. The results suggested that cholesterol reduction per se may result in an anti-inflammatory effect. However, other studies with statins and ezetimibe reached a different conclusion. One recent study compared the cholesterol-lowering efficacy of high-dose statin monotherapy with the same statin at a lower dose plus ezetimibe. The high-dose statins alone improved flow-mediated dilation more than dual therapy with low-dose statins and ezetimibe despite comparable reductions in LDL cholesterol. Therefore, whether the disease-modifying activity of statins is due to their pleiotropic effects or lipid-lowering effects is still difficult to determine.

### LIMITATIONS

This meta-analysis has limitations. Only 13 studies qualifying for the inclusion criteria were finally included. However, the literature search was comprehensive, and efforts were taken to obtain more data. Therefore, it is reasonable to draw conclusions based on this meta-analysis. The studies included are almost all single-center studies with a small number of patients. The types of stains used in each study, the difference in the dosage, the duration of the treatment, and the disease activity also added to the heterogeneity. In the 7 studies about atorvastatin, the dosage varied from 10 to 80 mg per day, and

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**TABLE 2. Meta-Analysis of the Effect of Statins on Other Measures in RA Patients**

| Measure     | Number of trials | Number of patients | Pooled mean difference (95% CI) | P value | Heterogeneity I² | Model |
|-------------|------------------|--------------------|---------------------------------|---------|------------------|-------|
| CRP         | 9                | 475                | -5.32 [-8.05, -2.60]            | 0.0001  | 59%              | R     |
| ESR         | 8                | 462                | -5.71 [-7.14, -4.27]            | <0.00001| 6%               | F     |
| HAQ         | 5                | 374                | -0.08 [-0.18, 0.02]             | 0.13    | 0%               | F     |
| TJC         | 6                | 364                | -2.09 [-2.99, -1.18]            | <0.00001| 33%              | F     |
| SJC         | 6                | 364                | -1.42 [-2.50, -0.35]            | 0.009   | 74%              | R     |
| VAS         | 5                | 316                | -7.58 [-18.01, 2.86]            | 0.15    | 91%              | R     |

CI = confidence interval, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, HAQ = health assessment questionnaire, RA = rheumatoid arthritis, SJC = swollen joint counts, TJC = tender joint counts, VAS = visual analog score.

R for random-effects model, F for fixed-effects model.
did not seem to correlate with DAS28 reduction. The different baseline disease activity and disease-modifying antirheumatic drugs (DMARDs) therapy applied in different studies also complicated the effect of statin dosage on DAS28 reduction. Random-effects models may not fully account for the heterogeneity. Therefore, caution should be taken when interpreting the results of this meta-analysis. The results of our analysis should be confirmed with new and larger studies in the future. The TRACE-RA (Trial of Atorvastatin in the Primary Prevention of Cardiovascular Endpoints in Rheumatoid Arthritis) study, which was a multicenter, placebo-controlled study that aimed to enroll over 3000 patients with RA, tried to investigate whether atorvastatin could reduce the occurrence of CVDs. Although this trial has been stopped because of low number of cardiovascular endpoints, its substudy, TRACE RA DAS, tried to answer the question of whether atorvastatin could reduce inflammation and disease activity in RA patients, and its results merit expectation.

CONCLUSIONS

In summary, our meta-analysis suggested that statin therapy might be effective in the reduction of RA disease activity measured by DAS28, TJC, SJC, as well as ESR and CRP.

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