

REVIEW: STATINS AND ASTHMA

A Systematic Review of Statin Efficacy in Asthma

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Background. Statins are known for their lipid-lowering effects and role in the treatment of atherosclerotic disease. They also have anti-inflammatory and immunomodulatory properties which could benefit asthma patients. We aimed to review the evidence on the efficacy and safety of statins in asthma-related outcomes. **Methods.** A systematic review of the literature on the effects of statins on asthma-related outcomes was performed following a search of the National Guideline Clearinghouse, Cochrane, Scopus, and Pubmed Medline databases in January 2012. Randomized controlled trials (RCTs) and observational studies (cohort/case-control design) assessing the effect of statins were included. The Grading of Recommendations Assessment Development and Evaluation (GRADE) system was used to rate the levels of evidence and grade of recommendation. **Results.** Twenty-four of the 379 articles retrieved electronically and one article identified by hand search were selected for full-text scrutiny by two independent reviewers. Eight studies were included: six RCTs and two observational studies. Statin use was not associated with consistent, statistical significant improvements in patient outcomes (asthma control, quality of life, steroid-sparing effects) or disease outcomes (lung function, airway responsiveness), and all the studies analyzed had low or very low quality of evidence. Inflammatory outcome improvements were observed in mild allergic asthma. **Conclusion.** Statins do not seem to have any additional benefit in asthma control or steroid-sparing effect in asthma treatment. Considering the prevalence of both statin use and asthma, more, better designed studies are needed to determine whether a specific phenotype of asthma exists that could benefit from statin treatment.

Keywords anti-inflammatory agents, asthma, immunomodulation, inflammation, statins, systematic review, treatment outcome

INTRODUCTION

Statins are one of the most commonly prescribed drugs for cardiovascular disease treatment and prevention (1). Current guidelines from the American College of Cardiology/American Heart Association suggest that statin therapy should be prescribed to reduce low-density lipoprotein (LDL) cholesterol in individuals at high risk for cardiovascular disease (2). However, all hydroxymethylglutaryl coenzyme (HMG-CoA) reductase inhibitors have pleiotropic effects, including immunomodulation, that are independent of their lipid-lowering properties. These effects, however, might vary between statins (3).

Statins have multiple effects that lower both innate and adaptive immune responses, thereby reducing inflammation. These properties seem to be mainly related to the inhibition of isoprenoid synthesis through the mevalonate pathway (3, 4). Additionally, statins block inflammatory responses (5). Results from clinical trials that have tracked inflammatory biomarkers support the concept that the anti-inflammatory effects of statins are of clinical benefit (3).

Asthma is a complex disease with a spectrum of clinical phenotypes that are difficult to define. Different asthma phenotypes have been described, especially in patients with severe asthma (6, 7). They are distinguished by clinical features, triggers, pathophysiology, and inflammatory markers (8–10), all characteristics that are currently being linked to diverse pathogenic mechanisms (11, 12).

Multidimensional approaches using complex statistical nonlinear relation models to define specific asthma endotypes could help to clarify treatment targets (6, 7, 10–12).

The main physiological feature of asthma is intermittent and reversible airway obstruction, while the main pathological feature is airway inflammation, occasionally associated with airway structural changes (13). It is therefore conceivable that the statin-induced effect on immune and inflammatory responses, namely alteration of the T_H1/T_H2 balance and inhibition of interleukin 17 (IL-17) (5, 14), might represent an additional potential therapeutic benefit in asthma phenotypes mediated by these molecular and cellular pathways. Furthermore, the fact that statins reduce systemic inflammation could benefit the cluster of obese asthma patients. Nevertheless, very few studies have analyzed the effects of statins on inflammation in asthma.

Statin therapy has been seen to reduce T_H2 responses in a mouse model of allergic asthma (15), although there have also been reports of polarization from the T_H1 to the T_H2 profile in animal models of autoimmune disease (3), raising additional safety concerns regarding the use of statins in asthma.

The aim of this systematic review was to assess the efficacy and safety of statins on asthma-related outcomes.

METHODS

We selected published reports of randomized controlled trials (RCTs) and observational studies, including case series with either a cohort design (with concurrent

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selection of controls) or a case-control design, comparing or assessing the effect of statins in patients of any age with a clinical diagnosis of asthma, unrestricted by disease severity or previous or current asthma treatment. Expert opinions, classical reviews, animal studies, and studies of individuals not exposed to intervention with statins were excluded.

Patient and disease outcomes were reviewed as primary and secondary outcomes, respectively. Patient outcomes were evaluated through asthma control and quality of life questionnaires, steroid-sparing effects, and asthma symptoms secondary to statin use. Disease outcomes, in turn, were evaluated by changes in lung function, airway hyper-responsiveness, and airway inflammation.

Search Methods for Identification of Studies

In January 2012, electronic searches were undertaken in the following databases: National Guideline Clearinghouse, Cochrane, Scopus, and Medline. Due to the absence of a gold standard definition of asthma, we used the following keywords: “asthma,” “bronchitis,” “respiratory symptoms,” and “lung symptoms” (first group) coupled with “statins” (second group). *A priori* inclusion criteria limited articles to those assessing statin use in individuals with asthma. All the articles retrieved were evaluated to assess correspondence with the entry criteria for the review. Hand searches of the reference lists of selected texts were performed and studies identified. Abstracts from relevant conferences were also searched. After the electronic and hand searches, two review authors independently selected articles for full-text scrutiny based on the title and/or abstract. The authors agreed on a list of articles, which were retrieved and assessed to confirm that they met the review criteria. Information was then extracted from each study in relation to the following factors: design (randomization, blinding, number of study centers and location, number of withdrawals), participants (sample size, age range), intervention (type and dosage, study duration), and outcomes (type of outcome analysis, outcomes analyzed).

Grading System

Analyses for this review were based on outcome measures. For studies with comparable measures, results were pooled using a random effect meta-analysis (16).

The overall quality of evidence was assessed using the Grading of Recommendations Assessment Development and Evaluation (GRADE) approach, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (17). In brief, for each outcome, quality of evidence was evaluated according to (1) study design limitations and potential bias, (2) consistency of the reported outcome results, (3) directness or generalizability of the conclusion, (4) precision, and (5) potential for publication bias. Quality was considered high if multiple RCTs with a low risk of bias had consistent, generalizable results for each outcome; moderate if one of the factors described above was not met; low if two of the factors were not met; and very low if three of the factors were not met. If

just one study measuring an outcome existed, the data were considered sparse and the corresponding evidence was classified as low (18–22). GRADE profiler software (version 3.2) was used for the analysis.

Quality of evidence reflects the extent to which a guideline panel’s confidence in an estimate of an effect is adequate to support a particular recommendation. In the GRADE system, strength of recommendation is classified as strong or weak according to the quality of the supporting evidence, balance of desirable/undesirable outcomes, and patients’ values and preferences (18–22).

RESULTS

The literature search identified 379 potentially relevant publications. Of these, 327 were excluded on the basis of the title and abstract and 24 were selected for full-text scrutiny. One study was retrieved by hand search. Of the 25 studies analyzed, eight (six RCTs and two observational studies) met the entry criteria (Figure 1, Table 1) (23–30). Excluded studies are shown in Table 2.

All the study participants had mild to moderate asthma, and were aged between 18 and 70 years. Use of statins ranged from 4 weeks to 7 years. The longest follow-up periods (2 and 7 years) were seen in the two observational studies (23, 27). Three of the six RCTs assessed the dose-response effect of simvastatin, either in monotherapy (30) or in association with inhaled corticosteroids (25, 26). Effects of a fixed dosage of atorvastatin as add-on therapy to inhaled corticosteroids were evaluated in the other three RCTs, one of which analyzed smokers with asthma (24, 28, 29). None of the RCTs had serious design limitations. Two trials had high withdrawal rates: 34.6% (9/26 participants) and 61.5% (16/36 participants) (29, 30). The two observational studies reported conflicting results. Huang et al. (23), for example, in a nationwide population-based study of nearly 4000 patients, showed a possible risk reduction of hospitalization for asthma with statin use, while Ostroukhova et al. (27), in a retrospective study, showed that statin use over 6 months was associated with increased nocturnal awakenings, increased rescue medication use, and increased office visits due to asthma exacerbations.

Based on the assessment of evidence according to the GRADE approach, all the studies included in this review had a low or very low quality of evidence (Table 3). Both patient and disease outcomes were reported in all the studies.

Asthma control was studied by analysis of asthma symptoms, hospitalizations, and the Asthma Control Questionnaire (ACQ). Of the three studies that evaluated changes in ACQ scores, only one reported improvement (26). The nationwide observational study by Huang et al. (23) reported a decreased number of hospitalizations in asthmatic patients taking statins. Quality of life was measured by the Juniper Asthma Quality of Life Questionnaire in three RCTs (24, 28, 26). One of these showed a significant improvement in asthmatic smokers (24), while the other two found no significant differences between patients

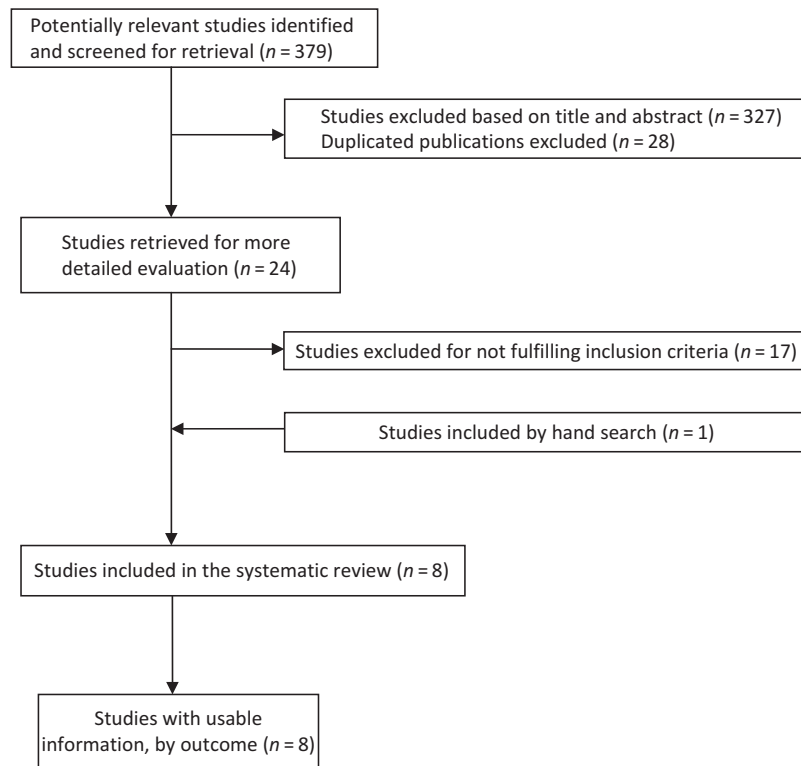


FIGURE 1.—Flow chart of included studies.

receiving statins and those receiving placebo. Neither of these studies had included smokers and the proportion of ex-smokers was low: 28% (26) and 11% (28).

Lung function outcomes (measured by peak expiratory flow and forced expiratory volume in the first second (FEV₁) before and after beta2-agonist administration) were assessed in five RCTs (158 patients) and one observational study (50 patients). Only one of the RCTs showed an association between statin use and improved lung function (FEV₁ of 2.79 L in simvastatin group vs. 2.64 L in control group; $p = .001$) (26). The observational study, by contrast, reported a worsening of lung function with statin use (1%–5% decrease in FEV₁) (27).

Of the two trials that assessed changes in airway responsiveness to methacholine (26, 30), one showed a trend, without statistical significance, toward improvement with simvastatin use (26). Airway inflammation, measured by exhaled nitric oxide, sputum eosinophil and macrophage counts or leukotriene B4 in sputum supernatants, improved in all the trials (25, 26, 28, 30) except the one that studied smokers (24). The improvements observed were significant in two trials (25, 28).

According to our quality of evidence analysis, the strength of recommendation for statin efficacy in asthma is classified as weak. Meta-analysis or data pooling was not possible due to the high heterogeneity among the studies.

DISCUSSION

This systematic review found that statin use was associated with a slight improvement in asthma symptoms, lung

function, and inflammation outcomes, but the data were sometimes contradictory and supported by low-quality evidence. The studies analyzed varied widely in terms of statins used, populations, outcome measures, and design. With respect to patient outcomes, we detected just a slight improvement in asthma control assessed by the ACQ (26), and a reduction in hospitalizations due to asthma exacerbations in one large observational study (23). Improvements were observed in lung function (including airway responsiveness) but they were not consistently significant (24, 26, 28, 30). Furthermore, one study described a worsening of symptoms and lung function with statin use in asthmatic patients (27). The evidence from that study, however, is limited, as it was a retrospective observational study of a small sample. The fact that the RCTs included patients with mild persistent asthma and the observational study analyzed intermittent mild and moderate to severe persistent asthma might have contributed to the differences observed. Data regarding decrease in airway inflammation, assessed by exhaled nitric oxide and sputum eosinophils, were more consistent. In the trial that analyzed asthmatic smokers, no improvements were seen in inflammatory biomarkers (24), possibly because smoking decreases eosinophil and exhaled nitric oxide levels and lowers exhaled nitric oxide measurements (48). The findings of this review support a possible anti-inflammatory role of statins, whose benefits had already been proven in cardiovascular disease, and in atherosclerosis in particular (24,25,28,30). This role could be a new target for the eosinophilic-predominant asthma phenotype, but more evidence is needed.

TABLE 1.—Studies included in the systematic review.

Reference	Study design and participants	Intervention	Outcome measure	Results
Huang et al. (23)	Observational retrospective case-control nationwide population-based study; 3965 individuals aged 60–69 y	Statin use for 7 years (atorvastatin, lovastatin, simvastatin, fluvastatin, pravastatin, and rosuvastatin)	Hospitalization for asthma	Statins reduced asthma hospitalization risk by 18% (0.82, 95% CI 0.71–0.96; $p = .006$)
Braganza et al. (24)	Double-blind RCT in 70 smokers with asthma, aged 34–52 y	Daily atorvastatin 40 mg plus 400 µg inhaled beclomethasone for 4 weeks	Asthma control and quality of life questionnaire scores Lung function Airway responsiveness Airway inflammation Airway inflammation	Improvement in asthma quality of life score (0.52, 95% CI 0.17–0.87; $p = .005$)
Maneechotesuwan et al. (25)	Double-blind crossover RCT in 47 asthmatic patients, aged 46–52 y	Simvastatin 10 mg plus 200 µg inhaled budesonide for 8 weeks		Sputum eosinophilia decreased by 10.0% compared with 6.75% in controls ($p = .02$)
Cowan et al. (26)	Double-blind crossover RCT in 43 asthmatic patients, aged 20–68 y	Daily simvastatin 40 mg for 12 weeks plus the lowest dose of fluticasone for asthma control	Asthma control and quality of life questionnaire scores Lung function Airway inflammation	Asthma control score in simvastatin group was 0.3 comparing to 0.7 with placebo ($p = .171$); pre-BD and post-BD FEV ₁ with no inhaled corticosteroid was 2.79 L and 3.09 L in the simvastatin group compared to 2.64 L and 2.99 L in the control group ($p = .001$ and $p = .010$, respectively); sputum eosinophils were lower with simvastatin than with placebo (9.5% vs. 25.4%, $p = .033$)
Ostroukhova et al. (27)	Observational, retrospective, case-control study with review of 759 medical records of asthma patients and analyses of 50 asthmatic patients, aged 44–64 y	Simvastatin use for 2 years	Asthma control Lung function	Increased use of inhaled corticosteroids maintenance dose by 67%, of rescue medication by 75%, of nocturnal awakenings by 33%, and office visits by 38%
Hothersall et al. (28)	Double-blind RCT crossover in 46 asthmatic patients, aged 18–70 y	Daily 40 mg atorvastatin plus inhaled corticosteroids for 24 weeks	Asthma control and quality of life questionnaire scores Lung function Airway responsiveness Airway inflammation Systemic inflammation Lung function	Median range of 3%–5% worsening of FEV ₁ Reduced sputum macrophage count (mean absolute difference -44.9×10^4 , 95% CI -80.7 to -9.7 ; $p = .029$) and leukotriene B ₄ (mean difference 1.6 ppb, 95% CI -7.1 to 3.9 $p = .014$) in sputum supernatant.
Fahimi (29)	Double-blind RCT crossover in 17 asthmatic patients, aged 16–65 y	Daily 10 mg atorvastatin for 4 weeks and inhaled corticosteroids for 4 weeks.		No significant difference in FEV ₁ and PEF between groups. FEV ₁ difference was -3.07 (95% CI -12.61 to 6.47) and PEF 2.32 (95% CI -8.27 to 12.91)

TABLE 1.—(Continued).

Reference	Study design and participants	Intervention	Outcome measure	Results
Menzies et al. (30)	Double-blind RCT crossover in 16 asthmatic patients, aged 19–56 y	Daily simvastatin 20 mg/day for 2 weeks, then 40 mg for 2 weeks	Lung function Airway responsiveness Airway inflammation	Airway hyperresponsiveness was unchanged by simvastatin treatment with a -0.18 (95% CI -1.90 to 1.55) doubling solution difference in methacholine PC10 compared with placebo; sputum eosinophil count was also unchanged (0.31% (95% CI -5.08 to 5.69); no difference in FENO, geometric mean fold change of 0.86 (95% CI 0.70 – 1.04 , $p = .15$)
Summary	Eight studies; six RCTs and two observational studies	Add-on statins in asthma	Asthma control and quality of life questionnaire scores Lung function Airway responsiveness Airway inflammation Hospitalization	Two out of eight studies showed improvement in asthma control and quality of life; two out of seven studies reported improvement in airway inflammation with decreased sputum eosinophilia; and two studies reported contradictory effects in terms of asthma hospitalization.

Note: CI, confidence interval; NO, nitric oxide; pre-BD FEV1, pre-bronchodilator forced expiratory volume in 1 second; post-BD FEV1, post-bronchodilator forced expiratory volume in 1 second; RCT, randomized clinical trial.

TABLE 2.—Studies excluded from the systematic review.

Reference	Study design and subjects	Intervention	Outcome	Results	Reason for exclusion
Zeki et al. (31)	Expert's literature review	Not applicable	Definitions, epidemiology, diagnosis, and treatment	Descriptive review	No intervention
Zeki et al. (32)	Expert's bibliographic review	Not applicable	Mechanism of action, potential therapeutic use of statins, and recent clinical trials	Descriptive review	No intervention
Schaafsma et al. (33)	Cultured human airway smooth muscle cells obtained from patients with lung adenocarcinoma	Simvastatin, geranyltransferase 1, and farnesyltransferase inhibitors	Effects on fibrotic function of airway mesenchymal cells	Inhibited synthesis and secretion of extracellular matrix.	No asthmatic individuals
Pawlak et al. (34)	Expert's bibliographic review	Not applicable	Beta-blocker effect on chronic asthma, statins anti-inflammatory, and immunomodulatory effects	Descriptive review	No intervention
Royce and Tang (35)	Expert's bibliographic review	Not applicable	Treatment options for preventing airway remodeling	Descriptive review	No intervention
Robinson et al. (36)	Experimental trial	Cultured eosinophils with fluvastatin, pravastatin, mevastatin, and simvastatin	GM-CSF stimulated eosinophil adhesion to inter-cellular adhesion molecule-1 CR3 expression and eosinophil viability and apoptosis	Fluvastatin and lovastatin inhibited GM-CSF-stimulated eosinophil adhesion ($p < .05$)	No asthmatic individuals No patient outcomes
Shyamsundar et al. (37)	Double-blind RCT in 30 healthy volunteers who inhaled 50 µg LPS	Daily 40 and 80 mg of simvastatin 4 days before LPS inhalation	Pulmonary inflammation and systemic inflammation induced by LPS	Reduced upregulation of nuclear NF-κB in monocyte-derived macrophages induced by LPS ($p < .001$)	Population not adequate No disease or patient outcomes
Feldman (38)	Expert's bibliographic review	Descriptive evaluation	Potential benefit of statins in prevention and/or treatment of respiratory conditions	Descriptive review	No intervention
Rubin (39)	Expert's bibliographic review	Not applicable	None	Author's opinion	No intervention
Camoretti-Mercado (40)	Expert's bibliographic review	Not applicable	Description of airway smooth muscle and cellular biology	Descriptive review	No intervention
Al Obaidi and Al Samarai (41)	Observational study in 20 asthmatic patients, aged 17–52 y	Daily 20 mg of simvastatin for 12 weeks	Oxidative and systemic inflammation	Serum malondialdehyde, serum eosinophil cationic protein were reduced ($p < .0001$) and total antioxidant capacity ($p < .0001$) increased	No disease or patient outcomes
Walsh (42)	Expert's bibliographic review	Not applicable	Increased persistence of apoptotic cells in patients with chronic inflammatory lung diseases	Descriptive review	No intervention
Paraskevas et al. (43)	Expert's bibliographic review	Not applicable	Use in allergic asthma	Descriptive review	No intervention
Takizawa (44)	Expert's bibliographic review	Not applicable	Proliferation, differentiation, and activity of myofibroblasts	Descriptive review	No intervention
Emnis (45)	Expert's bibliographic review	None	Modification of mast cell activation	Descriptive review	No intervention
Emnis (46)	Expert's bibliographic review	None	Airway anti-inflammatory and anti-allergic diseases	Descriptive review	No intervention
Samson et al. (47)	Case-control study in seven asthmatic patients, aged 25–32 y	Peripheral blood mononuclear cells after allergic specific (<i>Dermaphagoides farinae</i>) and nonallergen-specific stimulation	Systemic inflammation	Fluvastatin has inhibitory effects on cytokine (IFN-γ and IL-5) and chemokine (CCL10, CCL17) production	No patient outcomes

Note: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; CCL, chemokine (motif L-L); CXL, chemokine (C-X-C motif); Exhaled NO, exhaled fraction of nitric oxide; GITRL, glucocorticoid-inducible TNF receptor ligand; GM-CSF, granulocyte macrophage-colony stimulating factor; HR, hazard ratio; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon γ; IL, interleukin; LPS, lipopolysaccharide; LTb4, leukotriene B4; NF-κB, nuclear factor κB; PC20AMP, provocative concentration of adenosine monophosphate producing a 20% decline in FEV₁; PEFR, morning peak expiratory flow; Pre-BD FEV₁, pre-bronchodilator forced expiratory volume in 1 second; Post-BD FEV₁, post-bronchodilator forced expiratory volume in 1 second; RCT, randomized clinical trial; sICAM, soluble intercellular adhesion molecule; TNF, tumor necrosis factor.

TABLE 3.—Quality rating of studies included according to GRADE analysis.

Question: Should statins be used for asthma?
Settings: Outpatient

Summary of findings												
No. of studies	Quality assessment						Effect					
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Statin	Control	Relative (95% CI)	Absolute	Quality	Importance
Asthma control												
One on asthma symptoms (follow-up, 24 months)	Observational, case-control study (28)	No serious limitations	No serious inconsistencies	Serious ^a	Serious ^b	None	4/24 (12.5%) ^c	0/26 (0%) ^c	Not calculated			
Three on changes in ACQ (follow-up, 6 months)	RCTs, two crossover (26,27,29)	No serious limitations ^d	No serious inconsistencies ^e	Serious ^a	Serious ^b	None	125 ^f	121 ^f	–	Not pooled ^c	++OO	Low
One on the risk of hospitalization for asthma (follow-up, 7 years)	Observational study ^g (23)	Serious ^h	No serious inconsistencies	No serious indirectness	No serious imprecision	None	291/3965 (7.3%) ^c	683/7843 (8.7%) ^c	Not pooled			
Asthma quality of life (mean follow-up 6 months)												
Three	RCT (26, 27, 29)	No serious limitations ^d	No serious inconsistencies ⁱ	Serious ^a	Serious ^b	None	125 ^f	121 ^f	–	Not pooled	++OO	Low
Lung function (follow-up 6 months; better indicated by higher values)												
Five	RCT, three crossover (24, 26, 27, 29, 30)	No serious limitations ^d	Serious ^j	Serious ^a	Serious ^b	None	158 ^f	154 ^f	–	Not pooled	+OOO	Very Low
One	Observational study (28)	No serious limitations	No serious inconsistencies	Serious ^a	Serious ^b	None	15/24 (62.5%) ^c	6/26 (23.1%) ^c	Not calculated			
Airway responsiveness (follow-up, 6 months; better indicated by lower values)												
Three	RCT (24, 26, 27)	No serious limitations ^c	No serious inconsistencies	Serious ^a	Serious ^b	None	98 ^f	94 ^f	–	Not pooled	++OO	Low
Airway inflammation (follow-up, mean 6 months; better indicated by lower values)												
Four on changes in exhaled NO	RCT (24, 26, 27, 29)	No serious limitations ^d	No serious inconsistencies	Serious ^a	Serious ^b	None	141 ^f	137 ^f	–	Not pooled	++OO	Low
Five on changes in sputum eosinophilia	RCT (24–27)	No serious limitations ^d	Serious ^k	No serious indirectness	Serious ^b	None	120 ^f	123 ^f	–	Not pooled	++OO	Low

^aCompared different statins at different doses.

^bSmall population and short washout period.

^cNumber of participants with intervention (control or statins) in which event occurred/ total patients who underwent the intervention; (% patients with event in each group).

^dLoss to follow-up or withdrawals of three to nine patients.

^eMinor improvements in ACQ in one study, using simvastatin alone, but with a small population.

^fNumber of patients submitted to each intervention; as crossover trials were included, some underwent both interventions (statins and placebo), exceeding the total number of participants from each study; no analysis was performed with these data.

^gTaiwan National Health Insurance Database.

^hUnder-matching case and control population, significant differences between them: more hypertension ($p < .001$), diabetes mellitus ($p < .001$), coronary heart disease ($p = .001$), and dysrhythmia ($p = .001$).

ⁱMinor improvement of AQLQ in asthmatic smokers study.

^jSmall significant improvement in pre-BD FEV₁ and post-BD FEV₁ in the statin group in only one of the studies.

^kSputum cell% eosinophil was significantly reduced in two studies.

Note: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; Exhaled NO, exhaled fraction of nitric oxide; pre-BD FEV₁, pre-bronchodilator forced expiratory volume in 1 second; post-BD FEV₁, post-bronchodilator forced expiratory volume in 1 second; RCT, randomized clinical trial.

The evidence of the studies analyzed in this systematic review was classified as low or very low, mainly due to small sample sizes and short washout and follow-up periods. These design features might have introduced bias since the anti-inflammatory properties of statins in asthma might have been overestimated and because short follow-up might reduce the ability to see the true anti-inflammatory potential of these drugs. Furthermore, only patients with mild to moderate asthma were studied. Accordingly, patients with phenotypes that could potentially benefit from statin therapy, such as those with severe or steroid-refractory asthma, or obese patients with asthma were not analyzed. The use of different statins also made it difficult to compare results, since structural differences are associated with differences in metabolism, solubility, and intra-membrane localization. Dose-response effects are also an important consideration. High statin doses have been used in animal models, but these are not suitable for humans due to the risk of adverse effects. The use of statins in different therapeutic strategies also limited the pooling of data and weakened our results. Despite the comprehensive search strategy used, we identified only a small number of articles, which limits the conclusions that can be drawn with regard to implications for clinical practice.

Statins have pleiotropic effects. They have both anti-inflammatory properties, through which they stabilize the lipid raft, and immunomodulatory properties (1, 2). The blockage of HMG-CoA reductase by statins leads to a reduction in levels of intermediate products in the mevalonate pathway that are responsible for the isoprenylation of regulatory proteins, such as GTP-binding proteins (1, 4). This can affect processes such as growth, migration, cytoskeleton organization, and molecular trafficking in many cells (1, 4). However, it does not completely explain the anti-inflammatory effect of statins, which is why other mechanisms and targets are being studied. One of the first recognized immunomodulatory properties of statins was their ability to reduce antigen presentation through the downregulation of interferon γ (IFN- γ)-dependent major histocompatibility complex (MHC) II expression (3, 4). Treatment with simvastatin has also been shown to reduce IFN- γ in mouse models sensitized with ovalbumin (15), a finding supported by an *in vitro* study of peripheral blood mononuclear cells in allergic asthmatic patients (47). Properties such as enhanced expression of endothelial nitric oxide synthase, which interferes with cell binding by reducing leucocyte-endothelial cell adhesion, and suppression of intercellular adhesion molecule (ICAM-I) and lymphocyte function-associated antigen 1 (LFA-1), have also been identified (1, 3, 5, 49). In addition, adaptive immunity is also targeted by modulation of T-cell-mediated responses (1, 5). Statins alter the T_H1/T_H2 balance in mouse models (50) by inducing secretion of T_H2 cytokines (IL-4, IL-5, IL-10) and reducing transforming growth factor- β (TGF- β) and T_H1 cytokines (IL-2, IL-12; IFN- γ , and tumor necrosis factor- α (TNF- α)) (1, 4), but this has not been proven in human cells (3, 51). Production of IL-17, a cytokine with an important role in airway inflammation, is also directly and indirectly inhibited by statins

(5, 14, 52). Moreover, these drugs affect cellular proliferation and increase apoptosis (49). All these immunomodulatory and anti-inflammatory effects of statins may play a role in different structural and inflammatory cells within the lungs.

The potential benefits of statin therapy have been demonstrated in ovalbumin-sensitized mice models of allergic asthma (14, 15, 53–55). Reduced inflammatory cell infiltrate and eosinophilia in bronchoalveolar lavage fluid and decreased production of IFN- γ , IL-4, and IL-5 have been reported in mouse allergic asthma models treated with simvastatin (15, 53, 55). There have also been reports of reduced IgE levels and expression of CD40, CD40 ligand, and vascular cell adhesion molecule 1 (VCAM-1), which are all important for inflammatory cell migration (53). Similar findings have been observed with atorvastatin and pravastatin, supporting lowered pro-inflammatory responses mediated by IL-4, IFN- γ , IL-10, and IL-17 (14, 56, 57). In a study by Imamura et al. (14), pravastatin, besides reducing IL-17, induced regulation of lung dendritic cells by suppression of the antigen presentation capacity of CD11⁺ cells. Several animal studies have shown statins to be associated with a reduction in airway responsiveness and possibly airway remodeling inhibition (55, 58, 59). Chiba et al. (58, 59) reported a decrease in airway responsiveness with lovastatin, with inhibition of geranylgeranyltransferase I in the bronchial smooth muscle. Using simvastatin, Zeki et al. (55) demonstrated an improvement in compliance and airway resistance, as well as in airway remodeling assessed by goblet cell hyperplasia (54). Unspecific mechanisms, namely improved nitric oxide metabolism of bronchial epithelium, were reported by Ahmad et al. (60) in lung epithelial cells *in vitro*. Theoretically thus, based on findings from animal models and considering the anti-inflammatory and immunomodulatory effects of statins, these drugs would appear to be an interesting option for the treatment and control of predominantly inflammatory asthma.

However, there is still insufficient evidence to support the use of statins in asthma, but their use should certainly not be limited to asthmatic patients as they have proven benefits in cardiovascular diseases. Future studies should implement design improvements. More RCTs, larger samples, comparisons of different statins and dosages, and longer studies with washout protocols similar to those used in corticosteroids will help to add to the body of evidence on the potential value of statins in asthma. Finally, future studies should separate and compare the effects of statins on mild, moderate, and severe asthma.

Statins could be targeted to specific asthma phenotypes. The reviewed evidence suggests that statin use might reduce airway inflammation biomarkers, such as sputum eosinophilia and exhaled nitric oxide, raising the possibility that asthma patients with predominantly eosinophilic inflammation might benefit from this add-on therapy. Statins are widely used in obese-dyslipidemic patients, and obesity has long been proposed as a risk factor for asthma (6). Obesity-related systemic inflammation has been linked to asthma development, but the immune

pathophysiology of the obese-asthma phenotype is still unknown (61, 62). Metabolic syndrome could also explain the increased risk of asthma in obese individuals, as insulin resistance, linked to hyperinsulinemia and insulin growth factor 1 upregulation, promotes epithelial proliferation and airway remodeling (61). Furthermore, chronic obstructive pulmonary disease (COPD) involves a progressive chronic inflammatory process that is typically associated with neutrophilic inflammation predominance (63). In a mouse model of smoking-induced emphysema, simvastatin was seen to inhibit lung parenchyma destruction and inflammation (64). The slight improvements seen in ACQ and quality of life scores in smokers with asthma in the study by Braganza et al. (24) might be related to a decreased number of exacerbations, but this outcome was not reported. Patients with asthma-COPD overlap syndrome might also be a target for statin use.

Studies focusing on patient and disease outcomes could help to clarify if statins are an effective option for asthma treatment. Further research on the potential role of statins in airway remodeling is also necessary to better understand their ability to reverse the process of asthma. The identification of new biomarkers will improve long-term evaluation, which, in turn, may help to determine whether statins are a treatment option for asthmatic patients and to identify subgroups that could benefit most.

CONCLUSION

Statins do not seem to have any additional benefit in asthma control or steroid-sparing effect in asthma treatment, although they do appear to decrease airway inflammation in individuals with mild allergic asthma. Although the findings from the studies analyzed in this systematic review are not consistent, the theoretical anti-inflammatory and anti-airway remodeling properties of this drug class were evident. Due to the small number of studies available, an association between statins and airway diseases cannot be ruled out. Given the prevalence of statin use and asthma disease, more studies are needed to confirm these data, in particular, RCTs with larger samples, longer follow-up periods, and proper comparison of different statins, dosages, and asthmatic populations (mild, moderate, and severe asthma). More research is also needed to determine whether statin therapy might benefit certain subpopulations of asthma patients.

DECLARATION OF INTEREST

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