

Statins in the treatment of asthma

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Asthma is a chronic disease that affects more than 22 million Americans.¹ It is an inflammatory disorder of the lungs that results in airflow obstruction and bronchial hyperresponsiveness. Asthma is caused by a variety of factors relating to genetics and the environment and is predominantly a T-helper cell type 2 (Th2) response. A variety of cell types cause the inflammatory state: mast cells, macrophages, lymphocytes, eosinophils, neutrophils, epithelial cells, immunoglobulins, adhesion molecules, and interleukin (IL)-4, IL-5, and IL-13 secreted from Th2 lymphocytes.^{1,2}

An asthma exacerbation has an early phase that occurs during the first hour and a late phase that occurs six hours after the triggering allergic event. In the early phase, allergens trigger the synthesis of immunoglobulin E (IgE) from B cells in a process called isotype switching.³ The cytokines IL-4 and IL-13 (from Th2 cells) and CD40 (from B cells) help to initiate IgE synthesis. IgE then binds to its receptor (Fc epsilon RI) on mast cells, basophils, eosinophils, lymphocytes, platelets, and macrophages. This leads to the release of histamine, prostaglandins, eicosanoids, and reactive oxygen

Purpose. Current evidence on statin agents as potential alternatives or adjuncts to corticosteroid therapy for asthma is reviewed.

Summary. Research showing antiinflammatory and antioxidant effects of statins in animal models suggested that the cholesterol-lowering drugs might be useful in mitigating the adverse effects of long-term corticosteroid therapy in patients with asthma, but studies in humans have yielded mixed results. Two small placebo-controlled clinical trials indicated that statins were not effective in combating asthmatic inflammatory processes, and trials of statins as adjunctive therapy have indicated minimal steroid-sparing benefits. In two studies involving a total of more than 1000 current and former smokers with asthma, statin use correlated with reduced acute asthma exacerbations and a slower decline of lung function in some patients. A large population-based study

($n = 3965$) found that statin therapy was associated with a significantly reduced risk of hospitalization for asthma after an average follow-up period of about 4.5 years; a smaller U.S. retrospective cohort study indicated a significantly lower 1-year rate of asthma-related emergency room visits among patients receiving statins relative to those not using statins (9.08% versus 4.18%). Much of the research on statins and asthma has not controlled for confounding influences such as patient comorbidities and concomitant medication use.

Conclusion. Clinical trials have shown that statin therapy is not superior to and does not enhance the beneficial effects of inhaled corticosteroids for the treatment of asthma. Some evidence suggests that statins may help preserve lung function in cigarette smokers with obstructive pulmonary disease and reduce hospitalizations in asthmatic smokers and nonsmokers.

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species; mucus secretion, vasodilation, and bronchial smooth muscle contraction follow. In the late phase, eosinophils, CD4+ T cells, basophils, neutrophils, and macrophages are recruited to the inflammatory site, where they release cytokines and chemokines and promote the expression of adhesion molecules on epithelial cells. Eosinophils, in particular, in-

crease the severity of asthma by causing the degranulation of basophils and mast cells, altering bronchial responsiveness, and contributing to the damage of epithelial cells.^{3,4} The synthesis of eosinophils, their release, and the prolongation of their survival are mediated in part by Th2 cytokine IL-5.⁴ The inflammatory process is not just caused by eosino-

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phils. The combination of T cells, mast cells, macrophages, and epithelial cells; fibroblast and cell signaling; and the release of proinflammatory mediators, cytotoxic mediators, and cytokines also contribute.^{5,6}

The purpose of asthma treatment is to control symptoms and prevent exacerbations. The severity of asthma can be assessed by measuring peak expiratory flow (PEF) with spirometry or a peak flow meter. Spirometry is a test that measures the volume of air inspired or expired. Forced expiratory volume over one second (FEV₁) and forced vital capacity (FVC) can be determined from a spirometer to diagnose, measure the severity, and assess the risk of exacerbation of asthma. PEF can be used to objectively measure lung function, but it is more commonly used for at-home monitoring.¹

There are several medications used in the treatment of asthma, with inhaled corticosteroids being the medication class that is the most effective in reducing inflammation, inhibiting inflammatory cell migration, blocking late-phase reaction effects, and improving long-term asthma control.¹ Adverse effects of inhaled corticosteroids include oropharyngeal candidiasis, dysphonia, growth suppression, osteoporosis, cataracts, dermal thinning, and adrenal insufficiency.⁷ Due to the adverse effects associated with long-term corticosteroid use, there is a need for treatments employing other classes of medications. Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors,

are a group of medications approved in the United States for cholesterol-lowering treatment in the prevention of cardiovascular disease. These medications have also exhibited pleiotropic effects that include anti-inflammatory effects and may be potentially beneficial in the treatment of asthma. The aim of this article is to review and evaluate research and clinical trials that have evaluated statin therapy in the treatment of asthma.

Statins and murine inflammatory response

Research studies that led to clinical trials in humans used murine models to investigate the effect of statin therapy in the treatment of asthma. Statin treatment was usually given with simvastatin, but lovastatin, atorvastatin, and rosuvastatin were also used. The results of the studies demonstrated the ability of statins to reduce asthma severity by reducing the fraction of exhaled nitric oxide (FE_{NO}) and eosinophil activity.^{8,9} Statin treatment reduced leukocyte, macrophage, and neutrophil influx.¹⁰⁻¹⁴ Several studies demonstrated the ability of statin therapy to reduce the activity of the inflammatory chemokine eotaxin,^{10,15} which is responsible for leukocyte recruitment, endothelial cell activation, and adhesion molecule activation¹⁶⁻¹⁸ and for production of the proinflammatory cytokine IL-6.¹⁹ Statin therapy also reduced levels of the Th2-secreted cytokines IL-4, IL-5, IL-13, tumor necrosis factor α (TNF- α), and IgE.^{10,11,13-15,19,20} Additionally, statin treatment reduced adhesion molecule expression of CD40, CD40 ligand (CD40L), vascular adhesion molecule 1 and goblet cells (mucus-secreting cells).^{14,20} Statin administration to mice also reduced contraction, hyperresponsiveness, and resistance of bronchial smooth muscle²⁰⁻²² while increasing lung compliance.¹⁰ Overall, experiments with statins in animals provided

evidence that statin therapy reduced inflammatory processes that contribute to the severity of asthma. These beneficial results led to experiments to see if the effects seen in animals could be achieved in humans.

Statins and inflammatory response in patients with asthma

Ostroukhova et al. A study by Ostroukhova et al.²³ used a retrospective cohort design to evaluate statin effects in 50 patients who had mild intermittent, mild persistent, moderate persistent, or severe persistent asthma; the majority of patients had mild persistent asthma (treatment regimens were not reported). Compared with the control group ($n = 26$), the statin group ($n = 24$) had a higher mean body mass index ($p = 0.05$) and higher proportions of patients with hypertension ($p = 0.04$) and taking aspirin therapy ($p = 0.04$). The primary outcome was the change from baseline in FEV₁ at 6, 12, and 24 months. The secondary outcomes were albuterol use (for acute relief of asthma symptoms), night awakenings, medication changes, oral corticosteroid use, outpatient visits, emergency department visits, and hospitalizations.

A higher proportion of patients in the statin group, compared with the control group, had a decrease in FEV₁ at 6 months (75% versus 46% of patients, $p = 0.034$), at 12 months (73% versus 42% of patients, $p = 0.038$), and at 24 months (71% versus 23% of patients, $p = 0.037$). The median change in FEV₁ differed significantly between the statin group (5%, 4%, and 3% reductions at 6, 12, and 24 months, respectively) and the control group (no change at 6 and 12 months and an increase of 1.5% at 24 months) ($p = 0.004$, 0.002, and 0.003 for between-group comparisons at 6, 12, and 24 months, respectively). In addition, a significantly higher proportion of patients in the statin group than in the control group had an increase in albuterol use and

an increase in nighttime awakenings at all study times. At the 6- and 12-month evaluations, a significantly higher proportion of statin versus control patients had medication changes for asthma; oral corticosteroid use did not differ significantly between groups at any study time. Statin patients also had significantly more asthma exacerbations resulting in outpatient physician visits at 6 and 12 months; differences between groups in emergency department visits were not significant.

This study had inherent limitations, such as its small number of patients, limited data, and retrospective design. Nevertheless, it suggested that statin therapy in asthmatic patients was not beneficial and might worsen lung function as measured by FEV₁.

Menzies et al. In a placebo-controlled, double-blind crossover study, Menzies et al.²⁴ evaluated the role of simvastatin and its antiinflammatory effects in the treatment of asthma. The primary endpoints were FE_{NO}, the provocation concentration of methacholine causing an FEV₁ reduction of 10% (PC₁₀), the eosinophil count, and the C-reactive protein (CRP) concentration. In this trial, 26 patients (16 completed the study) who had mild-to-moderate asthma with an FEV₁ of $\geq 60\%$ of the predicted value and were taking no more than 2000 μg of inhaled beclomethasone dipropionate or an equivalent therapy were randomly assigned to receive simvastatin 20 mg orally daily for two weeks followed by simvastatin 40 mg orally daily for two weeks or a placebo daily for four weeks. Patients were weaned off antiinflammatory asthma medications in a step-down fashion prior to randomization and maintained on salmeterol 50 μg by inhalation twice daily for palliation of symptoms. After four weeks of treatment with simvastatin or placebo, the participants crossed over to the opposite treatment group. All patients were evaluated with spirometry every 14

days to check their FEV₁, and salmeterol was withheld for 48 hours prior to each measurement. After the four-week treatment period, salmeterol was withheld for 48 hours and short-acting β_2 -agonist therapy was withheld for 6 hours before examination.

Measured FE_{NO} values after withdrawal of antiinflammatory asthma medications increased by a mean of 43%, in comparison with baseline values, in patients taking simvastatin ($p = 0.004$). FE_{NO} measurements after the four-week treatment period revealed no significant difference between the simvastatin and placebo groups and no significant change from baseline in the simvastatin group. There was no significant difference between simvastatin treatment and placebo use with regard to methacholine PC₁₀, sputum eosinophil count, peripheral eosinophil count, salivary eosinophilic cationic protein level, or CRP assay results at the end of the study.

As expected, simvastatin treatment significantly reduced total cholesterol and low-density lipoprotein (LDL) cholesterol in the statin group compared with baseline and placebo measurements ($p < 0.005$ and $p = 0.001$, respectively), demonstrating that the simvastatin dosage and duration of treatment were sufficient to produce a metabolic effect. However, there was no significant reduction of CRP levels, which is typically seen with statin therapy. Also, FE_{NO} is not a specific marker of asthma treatment effectiveness. In summary, this trial showed that a simvastatin dosage of 20 or 40 mg for a period of two weeks each and a total simvastatin treatment period of one month were not effective in reducing markers of asthma inflammation.

Moini et al. In a double-blind randomized clinical trial, Moini et al.²⁵ evaluated asthma control in 62 patients with persistent mild-to-moderate asthma who received 40 mg of atorvastatin orally daily ($n = 31$) or a placebo ($n = 31$) for eight

weeks. The primary outcome was asthma control based on Asthma Control Test (ACT) scores, and the secondary endpoints were improvement in lung function, as determined based on FEV₁ and FVC values, and improvement of inflammation, as determined by eosinophil counts. There was no significant difference in patient demographics, and the patients were not required to discontinue any asthma control medications (specific treatment regimens were not reported).

The results from this study indicated that atorvastatin was not effective in treating persistent mild-to-moderate asthma, as there were no significant differences between the treatment and control groups in ACT scores, FEV₁, FVC, or eosinophil counts after eight weeks of treatment. Limitations of this study included the use of the ACT score as a primary outcome and the fact that the study methods did not account for patient comorbidities or concomitant medication use; study strengths included the use of a placebo that was same weight, size, and shape of an atorvastatin 40-mg tablet and the administration of study medications by a staff member.

Concurrent use of statins and steroids

Hothersall et al. A study by Hothersall et al.²⁶ showed an improvement in antiinflammatory markers in sputum in patients taking atorvastatin 40 mg orally daily. The primary outcome was to show that atorvastatin added to inhaled corticosteroid treatment would improve lung function and reduce the sputum cell count in patients with atopic asthma. Atopy was defined as a positive skin-prick test or elevated specific IgE of >0.35 AU/mL. Like the study of Menzies et al.,²⁴ the design was a randomized double-blind, placebo-controlled crossover trial. Fifty-four patients were randomly assigned to participate for a total of

24 weeks: a 2-week run-in period and two 8-week periods of treatment (atorvastatin or placebo) separated by a 6-week washout period. Subjects were taking the equivalent of 1000 µg of beclomethasone dipropionate by inhalation daily and short-acting β_2 -agonist therapy. Patients recorded morning and evening PEF measurements and symptoms.

The investigators found that changes in PEF compared with baseline did not differ significantly between the atorvastatin and placebo groups ($p = 0.921$). When atorvastatin was used, there was a decrease in the mean absolute sputum macrophage count ($p = 0.029$) and the macrophage percentage ($p < 0.05$) as well as a decrease in levels of the inflammatory biomarker leukotriene B4 ($p = 0.014$) compared with baseline. An increase in sputum neutrophils in the atorvastatin cohort compared with the placebo cohort ($p < 0.025$) was seen, but no differences in the absolute count of these cells or the absolute count of other inflammatory cells were noted. Relative to placebo use, there were atorvastatin-associated decreases in total and high-density lipoprotein (HDL) cholesterol levels ($p < 0.0001$ and $p = 0.026$, respectively). No significant differences in the total sputum cell count or other inflammatory biomarkers, including FE_{NO} , high-sensitivity CRP, intercellular adhesion molecule-1, TNF- α , IL-5, IL-6, and IL-8 were found. Rates of adverse events were similar between the groups; however, one patient in the atorvastatin group needed oral corticosteroid treatment, compared with none in the placebo group, for treatment of an asthma exacerbation. Two patients from each group made unscheduled physician visits, and two patients in the atorvastatin group versus one in the placebo group went to the emergency room due to their asthma.

In summary, asthma treatment with inhaled corticosteroids and

atorvastatin was not associated with evidence of improvement in lung function or a reduction in sputum cell counts, with the exception of a reduction in macrophages and leukotriene B4. It should be noted that in this study, patients on statin therapy had a decrease in HDL, which was not the expected result. Also, there was not definitive evidence that the favorable results seen were due to the statin therapy alone, as a statin was used in combination with an inhaled corticosteroid, a type of drug used to inhibit inflammatory cell function in order to decrease inflammation.

Cowan et al. In a randomized, double-blind, placebo-controlled crossover study involving 43 patients, Cowan et al.²⁷ directly tested the potential use of statins as steroid-sparing therapy. This experiment was conducted in two phases using simvastatin 40 mg orally nightly. The first phase was an open-label two-week run-in period in which inhaled corticosteroids were discontinued until loss of control (LOC) occurred or the patient had received a total of 28 days of therapy. Patients received fluticasone 1000 µg by inhalation for at least 28 days, partly to define the degree of corticosteroid responsiveness. The second phase of the study was limited to patients who demonstrated a 15% fall in FEV_1 in response to a provocative dose of hypertonic saline, a 20% fall in FEV_1 in response to provocative methacholine, or an increase of 12% or greater in FEV_1 in response to a bronchodilator. The primary endpoint was to measure the minimum inhaled corticosteroid dose requirement, and the secondary endpoints were to establish the dose of inhaled corticosteroid at LOC and the number of patients without LOC after inhaled corticosteroid withdrawal.

After patients were randomized to placebo or simvastatin, they were required to use two inhalers that provided a total fluticasone dose of 0 (placebo), 50, 125, 250, or 500 µg per day. If asthma was controlled,

the dosage of fluticasone was reduced monthly until LOC occurred. In patients who were able to step down to 0 µg fluticasone or demonstrated LOC, a sputum induction and adenosine 5'-monophosphate (AMP) challenge test (used to test bronchial hyperresponsiveness in patients with asthma) was performed. Patients then crossed over to the alternative treatment group. Patients also completed the Asthma Control Questionnaire (ACQ), ACT, and Asthma Quality of Life Questionnaire (AQLQ) as well as FE_{NO} testing.

In phase 1 of the study, fluticasone use was associated with a reduction in ACQ score ($p < 0.001$) and increases in FEV_1 ($p < 0.001$) and the provocation concentration of AMP causing an FEV_1 reduction of 20% ($PC_{20}AMP$) ($p < 0.001$). In phase 2, patients maintained on the minimum fluticasone dose—in both the simvastatin and placebo groups—did not show a difference in ACT or AQLQ scores, FEV_1 , or airway hyperresponsiveness; the ACQ results were similar. However, patients taking simvastatin had a lower sputum eosinophil count than placebo users ($p = 0.0047$). At the highest daily fluticasone dose (500 µg), patients taking the placebo had higher PEF than patients taking simvastatin ($p = 0.007$), whereas with 0 µg of fluticasone, patients taking simvastatin had higher FEV_1 values and a lower mean ACQ score before and after bronchodilator therapy. There were no significant differences between the simvastatin and control groups with the other evaluated doses of fluticasone; this indicated that patients receiving simvastatin but not corticosteroid therapy had better asthma control. On average, the simvastatin group had a significantly higher number of sputum lymphocytes relative to placebo users ($p = 0.003$); levels of $PC_{20}AMP$ during phase 2 were not significantly different between the groups. Four patients dropped out of

the study after treatment began due to muscle pain, rash, and relocation.

In this study, there was no difference between the simvastatin and placebo groups in the minimum daily dose of fluticasone, the fluticasone dose at which patients experienced LOC, or the proportion of patients who experienced LOC; therefore, the researchers concluded that simvastatin did not confer a steroid-sparing benefit in asthma management. Simvastatin may, however, have provided some improvement to asthma symptoms and in the reduction of eosinophils in sputum. The open-label design of this study needs to be taken into consideration when interpreting the results. The investigators did try to decrease inhaled corticosteroid use among study participants and delineate the effects of steroid therapy from those of statin use.

Statins and smokers with asthma

Braganza et al. In a randomized placebo-controlled trial, Braganza et al.²⁸ tested the short-term effects of atorvastatin in smokers with mild-to-moderate asthma. The primary outcome measure was PEF, and the secondary outcome measures were asthma control and airway inflammation, as determined by FEV₁, ACQ and AQLQ scores, methacholine provocation, counts of inflammatory cells (macrophages, neutrophils, eosinophils), counts of bronchial epithelial cells, and the presence of inflammatory cytokines (leukotriene B₄, IL-6, IL-8, IL-10, CRP, and myeloperoxidase). Subjects were weaned from long-acting bronchodilators and inhaled corticosteroids over 4–10 weeks and, after a 2-week washout baseline, PEF measurements were taken. Patients were also asked to record their asthma symptoms twice a day. Patients were randomly assigned to take 40 mg of atorvastatin orally daily ($n = 33$) or a placebo ($n = 27$) and were evaluated at weeks 4 and 8. After the fourth week, all patients began beclomethasone

dipropionate 200 µg twice daily by inhalation.

Improvement of asthma in the atorvastatin group relative to placebo users was only seen at the week-4 evaluation, as determined by scores on the full seven-item ACQ ($p = 0.016$), the six-item ACQ, and the total AQLQ ($p = 0.005$). The improvement was not shown to be significant between the atorvastatin group and the placebo group based on PEF, FEV₁, methacholine PC₂₀, and rescue-inhaler puffs per 24 hours. At week 8, there was no improvement seen between the groups based on quantitative or qualitative measurements. There was also not a significant improvement or decline between atorvastatin patients compared with placebo based on measurement of inflammatory cells or inflammatory cytokines. Two patients in the atorvastatin group experienced worsening of asthma compared with one patient in the placebo group.

Overall, this study did not show an improvement in lung function, inflammation due to asthma, or asthma control in patients who smoked and were concurrently taking atorvastatin. One key limitation of this study was the use of patient-recorded PEF values as a primary outcome measure.

Keddissi et al. In a study by Keddissi et al.,²⁹ 418 smokers with asthma were randomly assigned to control ($n = 203$) or statin ($n = 215$) groups. Patients included in the trial had been taking statins for at least three months. Asthma medications taken by patients at baseline included inhaled corticosteroids and long-acting bronchodilators, from which patients were weaned prior to baseline spirometry testing. The majority of the 418 patients (76%) had obstructive findings on baseline spirometry. Most patients in the statin group received simvastatin; other statin medications taken were lovastatin, atorvastatin, and fluvastatin. In the statin group, there were

significantly ($p < 0.01$) more patients with coronary artery disease or congestive heart failure, hypertension, diabetes mellitus, and dyslipidemia; the control group had significantly more patients with inflammatory or autoimmune diseases (7 versus 1, $p = 0.005$). The primary endpoint was the mean annual decline in FEV₁ and FVC values. The secondary endpoint was the need for respiratory-related emergency department visits.

The study also entailed a comparison of statin effects in current and former smokers; lung function, as measured by FEV₁ and FVC, was similar at baseline in the two groups, with no significant difference in the annual rate of lung function decline ($p = 0.06$).

To determine compliance, lipid-profile data were compared between the statin and control groups. A significant decrease was seen in LDL levels between groups, with LDL levels declining in the statin group and increasing in the control group ($p = 0.04$). There were no significant differences between the statin and control groups in the use of various respiratory medications, with the exception of theophylline use, which was significantly higher in the control group (17% versus 8%, $p = 0.008$). Unlike the comparison of smokers with ex-smokers (which evaluated two subgroups of patients with comparable baseline lung function), the control group had higher mean baseline FVC and lower mean FEV₁/FVC values than the statin group. However, FEV₁ was similar between the groups, as was the arterial blood gas level.

The data showed that the statin group had a slower decline in both FEV₁ and FVC ($p < 0.0001$ for both). There was no difference between the statin group and the control group in FEV₁ and FVC. In both current and former smokers who received statins, there were slower declines in FEV₁/FVC. There was also no difference seen in pulmonary function among ex-

smokers in either the statin group or the control group based on the length of time since the quit date. Comparing patients with obstructive versus restrictive pulmonary dysfunction, patients with obstructive pulmonary function who received statins had significantly slower declines in FEV₁ and FVC ($p < 0.0001$ for both).

Patients in this study receiving statins were less likely to be hospitalized or visit the emergency department, but this finding was significant only in patients with obstructive pulmonary dysfunction ($p = 0.02$). There was no difference in mortality between the statin and control groups.

Overall, this study found that statin use was associated with slower declines in FEV₁ and FVC in patients with obstructive or restrictive pulmonary function—both smokers and ex-smokers. A limitation of this study was the inclusion of patients with several comorbidities; throughout the study, these patients continued using several medications, including inhaled and systemic corticosteroids, theophylline, leukotriene inhibitors, and β_2 -agonists, as well as oxygen therapy, which could have contributed to improvement in the primary outcome. The patients were also on medications that have been shown to reduce hospitalization (e.g., angiotensin-converting-enzyme inhibitors, aspirin, β -blockers), which might have influenced the secondary outcome.

Alexeeff et al. In their longitudinal (10-year) study of 803 elderly male patients with asthma, Alexeeff et al.³⁰ measured statin effects to determine if there were differences between smokers and nonsmokers; patient comorbidities included chronic bronchitis, emphysema, and coronary heart disease. Treatments for these conditions were not discontinued and included bronchodilators and inhaled corticosteroids. The primary objective was to show that statins had a protective effect on declining lung function, with other ob-

jectives including an examination of the effect of statins on lung function in current and past smokers and patients who had never smoked. Measurements included FEV₁ and FVC.

Patients were instructed to refrain from smoking the night before pulmonary function testing. Patients not using statins experienced an estimated decline in FEV₁ of 23.9 mL per year compared with an estimated decline of 10.9 mL per year among statin users ($p < 0.001$). FVC declined in nonusers of statins by an estimated 36.2 mL per year, compared with an estimated decline of 14.0 mL per year among statin users ($p < 0.001$).

To examine the effects of statin use in relation to smoking status, the researchers divided the cohort into four groups: never-smokers, longtime quitters (≥ 10 years), recent quitters (< 10 years), and current smokers. The interaction among time since first visit, statin use, and smoking status was significant for both FEV₁ and FVC ($p < 0.001$ for both). Patients in each group who were not taking statins experienced a faster decline in both FEV₁ and FVC, but the size of the effect varied with smoking status. Researchers measured the net difference between statin users and nonusers to determine if there was a relationship between statin use and quit time. The difference between statin and control groups in the rate of decline of FEV₁ was greatest for recent quitters (19.7 mL per year), and the difference in the rate of decline of FVC was greatest for longtime quitters (24.7 mL per year). The greatest differences between the statin and control groups in the rate of decline in FEV₁ (2.5-fold) and FVC (3.0-fold) were observed in longtime quitters.

From this study, researchers concluded that statin use reduced the decline in lung function among current and former smokers and was more beneficial in longtime and recent quitters. Therefore, statin usage may be protective in current or past

smokers with asthma. As this study was observational and the population was predominantly elderly white men, the results are not broadly generalizable. Also, patients continued to receive inhaled corticosteroids and other asthma medications during the study, which may have influenced the results. However, the researchers stated that statistical analyses taking into account inhaled corticosteroid use and race were performed and yielded essentially the same results, although the data were not shown in their published findings.

Statins and asthma-related hospitalizations

Huang et al. A large evaluation of statin treatment for asthma was performed in Taiwan by Huang et al.³¹ to determine if statin use by patients with asthma led to a lower incidence of hospitalizations. A cohort of 1 million patients receiving statin therapy was examined from January 2000 to December 2007. From the overall cohort, 7843 patients with asthma who were not taking statins were selected to be the control group, and 3965 patients with asthma who were taking statins were selected to be the study group. Atorvastatin, used by 30% of patients, was the most commonly used statin; others were lovastatin, simvastatin, fluvastatin, pravastatin, and rosuvastatin. Comparing the statin and control groups, there were significant differences in baseline rates of hypertension, diabetes mellitus, coronary artery disease, dysrhythmia, and chronic kidney disease; in all cases, the statin group had relatively more patients diagnosed with these disease states ($p < 0.001$). There were no significant differences between the groups in regard to age or gender, rates of ischemic stroke and intracerebral hemorrhage, or use of asthma medications including inhaled or oral corticosteroids and nonsteroids (β_2 -agonists, xanthine derivatives, and leukotriene-receptor agonists).

The primary outcome was the incidence of asthma-related hospitalization among statin users. During the follow-up period, which averaged nearly five years, 291 patients (7.3%) receiving statin therapy were hospitalized for asthma, compared with 683 patients (8.7%) in the control group, a significant difference ($p = 0.001$). After adjusting for age, sex, hypertension, diabetes, coronary artery disease, and chronic renal disease, the researchers determined that statin use was independently associated with a decreased risk of hospitalization in patients with asthma (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.71–0.95; $p = 0.006$). The only other variable determined to be associated with hospitalization was increasing age (HR, 1.02; 95% CI, 1.02–1.03; $p < 0.001$). In the follow-up period, 210 patients (5.3%) on statins were admitted to the emergency department for asthma exacerbations, with 80 patients from this group being hospitalized, whereas 395 patients (5.0%) from the control group were admitted to the emergency department and 145 patients from this group were hospitalized. Log-rank analysis did not show a significant difference between the two groups with respect to emergency department admittance.

This research showed that with statin use, there is a decrease in incident hospitalizations for asthma exacerbations. However, as this was a cohort study, there were inherent limitations; patients were allowed to use several medications, including inhaled corticosteroids, which may have influenced the favorable results seen among statin users.

Lokhandwala et al. Using a retrospective matched-cohort design, Lokhandwala et al.³² also examined hospitalization and statin use in patients with asthma receiving inhaled corticosteroid therapy. The primary outcome was the incidence of hospitalizations and emergency room visits during a period of one year.

The study evaluated 479 patients taking a statin and an inhaled corticosteroid and 958 patients taking an inhaled corticosteroid but not receiving a statin. There were significant differences between statin users and nonusers in geographic region, with more residents of rural areas in the statin group ($p = 0.0287$); age (statin users were, on average, older than nonusers) ($p < 0.0001$); and race, with more African Americans among nonusers of statins ($p < 0.0001$); also, before and after matching, the statin group had more patients with comorbidities, as indicated by Charlson Comorbidity Index scores ($p = 0.0001$ before and $p = 0.0300$ after matching).

It was also found that patients on statin therapy were less adherent to inhaled corticosteroid therapy ($p = 0.0146$), averaged a lower number of short-acting β -agonist prescriptions ($p < 0.0001$), and had fewer emergency room visits due to asthma in the six months prior to the index date ($p = 0.063$). Hospitalizations occurred in 3.79% of patients in the statin group, compared with 6.47% of patients not receiving statin therapy. The frequency of emergency room visits was 4.18% in the statin group and 9.08% among nonusers of statins.

The researchers concluded that asthmatic patients using statins were less likely than nonusers to visit the emergency room or be hospitalized for asthma. However, given the inherent limitations of any retrospective study and that the statin group was disproportionately elderly and African American, the study results should be interpreted cautiously.

Discussion

In vivo research in animals has yielded promising evidence of the benefits of statins in the context of asthma; many of these studies demonstrated a reduction in inflammatory markers with the use of statins, supporting the hypothesis that statin

use might reduce the severity of asthma. However, the clinical trials conducted in humans have not supported the overall conclusion that statin therapy is beneficial in the treatment of patients with asthma. It is possible that even though animal trials provided evidence of benefit in a two- to four-week period and a two-week period is sufficient to see lipid lowering, it may take longer to see inflammatory and spirometry changes in humans.

Some of the studies reviewed here found that statin therapy provided positive effects such as improvements in ACQ and AQLQ scores, decreases in emergency department visits for asthma exacerbations, reductions in hospitalization for asthma, and a slowing of the decline of lung function (based on FEV₁ and FVC test results) in smokers.^{28–32}

With regard to patient assessment methods, the ACQ and AQLQ have been validated for the assessment of asthma control and quality of life, respectively.^{33–35} However, although these two questionnaires provided evidence that statin therapy was beneficial by improving asthma symptoms, the use of a similar test (the ACT) did not indicate more favorable outcomes with statin therapy. Research on these questionnaires has shown that ACT and ACQ scores are highly correlated,³⁶ but the ACT is considered a better measurement of control, as patients may overestimate control with the ACQ.^{37,38} However, the ACT has been shown to have poor accuracy due to its weak correlation with FEV₁, PEF, FE_{NO}, and specialist opinion.^{36,38,39} Therefore, neither instrument should be the sole tool used for the assessment of asthma.³⁸ In relation to the research reviewed in this article, the ACQ score should not be considered a reliable measure of asthma control, as ACQ scores did not correlate with FEV₁ or PEF values.^{25,28}

Statin therapy was shown to be protective in smokers with asthma

who were recent quitters or longtime smokers by reducing the decline in FEV₁.²⁸ There are not many studies on this topic; therefore, more research is needed to determine the protective mechanism of action of statins along with the rationale for their use in smokers with asthma.

Hospitalization and emergency department visits were reduced by statin therapy for asthma exacerbations. Perhaps this is the primary role of statins in the treatment of asthma, as statins have already been established as agents for the reduction of adverse events and hospitalizations in the context of cardiovascular disease.⁴⁰⁻⁴⁴ More research is needed to determine whether patients currently not requiring statins would benefit from concurrent therapy.

Without more research, it is difficult to firmly rule out statins as beneficial agents in the treatment of asthma, especially when there is evidence that they are beneficial in other lung disease states such as chronic obstructive pulmonary disease (COPD). There are a few studies that demonstrated that statin therapy can reduce COPD exacerbations, increase quality of life, increase survival, and reduce the risk of COPD-related death in patients with asthma.⁴⁴⁻⁴⁶ Another study has shown that statin therapy was associated with increased survival of lung allografts in lung transplant recipients.⁴⁷

Larger and longer trials, as well as a conclusive review of all statin therapies and prospective clinical studies to adequately determine the role of statins in asthma, are needed. In clinical and animal trials, the main statins studied were simvastatin and atorvastatin. In the clinical trials that indicated positive outcomes of statin use, patients were on a variety of statin medications, so it is possible that other statin therapy besides simvastatin and atorvastatin could provide positive outcomes in the treatment of asthma.

Conclusion

Clinical trials have shown that statin therapy is not superior to and does not enhance the beneficial effects of inhaled corticosteroids for the treatment of asthma. Some evidence suggests that statins may help preserve lung function in cigarette smokers with obstructive pulmonary disease and reduce hospitalizations in asthmatic smokers and nonsmokers.

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