
The effect of statin therapy on allergic patients with asthma

Marina Ostroukhova, MD, PhD*; Ruth W. Kouides, MD, MPH*; and Elizabeth Friedman, MD*†

Background: 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors have significantly improved outcomes in coronary artery disease. They have anti-inflammatory and cholesterol-lowering effects. Statins alter the production of T_H1 cytokines and thus promote a T_H2 response. This immune alteration would promote allergic diseases such as asthma.

Objective: To ascertain whether statin use adversely affects the clinical course of asthma.

Methods: We retrospectively reviewed 759 medical records of consecutive patients with asthma to identify patients with extrinsic asthma who had at least 4 physician visits over 1 year. We compared patients who started receiving statins after their initial asthma evaluation with patients who never received statins. Baseline characteristics; change in forced expiratory volume in 1 second from baseline at 3, 6, 12, and 24 months; and a need for increases in medication and acute asthma visits were compared between the statin and control groups.

Results: We identified 24 patients who started statin therapy and 26 control patients. There was a statistically significant 3% to 5% median worsening of forced expiratory volume in 1 second at all time points for the statin group compared with the controls. At 6 months, more patients in the statin group needed increased maintenance medication (16 [67%] vs 7 [27%]; $P = .005$), used albuterol more frequently (18 [75%] vs 3 [12%]; $P < .001$), had more nocturnal awakenings (8 [33%] vs 0 [0%]; $P < .001$), and were seen more frequently at office visits for acute asthma (9 [38%] vs 1 [4%]; $P = .003$).

Conclusions: This preliminary study demonstrated that patients with asthma who received statins had a worse clinical course than controls. Given the prevalence of both statin use and asthma, further research is needed.

Ann Allergy Asthma Immunol. 2009;103:463–468.

INTRODUCTION

The discovery of the first 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statin) in 1976 drastically improved outcomes in the treatment of hypercholesterolemia. This class of medication has changed the primary and secondary prevention of coronary artery disease. Statins are commonly prescribed worldwide, and use is expected to increase. They are being considered for primary prevention in almost any patient who has any cardiac risk factors.^{1–3} Statin use is so common that atorvastatin calcium (Lipitor) has been the top-selling drug for the past 5 years.

Recently, there has been a large amount of interest in the pharmacologic effects of statins in addition to their lipid-lowering properties. This resulted from the realization that the effect of statins cannot be ascribed solely to their lipid-lowering properties. Cardiovascular disease has an inflammatory component, and it would appear that statins down-regulate the immune response.^{3–6} Several mechanisms have been described to explain the immunomodulatory effects of statins. One of these is the down-regulation of the T_H1 response and the augmentation of the T_H2 cytokine profile. Statins are currently being evaluated as immunomodulators

of T_H1-driven diseases, such as multiple sclerosis and other autoimmune diseases.^{4–8}

Since the early 1990s, it has been recognized that the T_H2 inflammatory response plays a significant role in the pathogenesis of atopic asthma.⁹ T_H2 cytokines have been shown to be upregulated by the addition of statins to T-cell culture and in vivo.^{5,10,11} This naturally leads to the question of what effect statins would have on a T_H2-driven disease such as asthma. Are statins safe to use in patients with allergic asthma? Will increasing statin use lead to the unmasking of or increase in the prevalence of asthma in previously asymptomatic patients, as is seen with β -blockers? To our knowledge, there have been no human studies evaluating these concerns. The purpose of our study was to evaluate the clinical course of asthma in patients who started receiving statin therapy.

METHODS

We conducted a retrospective cohort study involving patients with physician-diagnosed asthma who were observed by the Department of Allergy and Immunology, Rochester General Hospital (RGH), Rochester, New York, between January 1, 2005, and December 31, 2006. Approval was obtained from the RGH institutional review board. We compared the clinical course of asthma among those patients who started receiving statin therapy (statin group) with the clinical course of patients not receiving statin therapy.

Affiliations: * Department of Medicine, Rochester General Hospital, Rochester, New York; † Division of Allergy and Immunology, Rochester General Hospital, Rochester, New York.

Disclosures: Authors have nothing to disclose.

Received for publication September 24, 2008; Received in revised form May 29, 2009; Accepted for publication June 28, 2009.

Patient Identification

The RGH billing database was searched to identify patients with asthma (*International Classification of Diseases, Ninth Revision [ICD-9]* code 493.00) who were between the ages of 30 and 70 years, who underwent skin testing, and who had at least 4 visits to RGH over a period of at least 1 year. We reviewed the medical records of those patients who met these screening criteria to determine if they met the following inclusion and exclusion criteria.

Inclusion Criteria

To be included, patients needed a diagnosis of asthma established by an allergist and a positive skin test result. *Asthma* was defined as episodic wheezing or cough, chest tightness, and/or dyspnea and was objectively confirmed by evidence of reversible airflow obstruction on spirometry (using Knudson Spirometry Prediction Tables for Normal Males and Females¹¹). A positive skin test result required a positive result for at least 2 perennial allergens. Some patients also had seasonal allergens. Prebronchodilator spirometry performed at 6-, 12-, and 24-month intervals was also required for inclusion. Intervening data collected outside these time points were not included in our analysis. All levels of asthma severity were included and managed on standard doses of asthma controller therapy per the 1997 National Heart, Lung, and Blood Institute (NHLBI) guidelines.¹³

Exclusion Criteria

Because we wanted to determine the change in asthma control after beginning statin therapy, we excluded all patients who were receiving a statin at the time of the first visit. Patients diagnosed as having chronic obstructive pulmonary disease, nonallergic asthma (skin test result negative to common allergens), congestive heart failure, or other comorbid lung conditions (eg, sarcoidosis or pulmonary hypertension) were also excluded. We also restricted enrollment based on smoking status: current smokers, ex-smokers who quit within the past year, and ex-smokers who had smoked more than 5 pack-years in their lifetime were excluded. Patients receiving omalizumab (Xolair) and with known immunodeficiencies (primary or secondary) were excluded. Medical records were reviewed for the addition of any medication that would worsen asthma during the study period, such as β -blockers; none were found.

Primary Outcome Measure

Our primary outcome measures were the change in forced expiratory volume in 1 second (FEV₁) from baseline at 6, 12, and 24 months. Prebronchodilator measurements of FEV₁ are done at each visit to the RGH Allergy and Immunology Practice according to American Thoracic Society criteria.¹³ At least 3 spirometry maneuvers were done, and the highest FEV₁ was reported.

Secondary Outcome Measures

Secondary outcome measures included the following. (1) The patient reported an increase in the daytime use of a fast-acting

bronchodilator (excluding prophylactic puffs for exercise) compared with the baseline value. (2) The patient reported an increase in the frequency of night awakening due to asthma in the interval between visits. (3) There was a change in medications per NHLBI guidelines secondary to increased symptoms since the last visit. (4) The patient reported requirement of oral corticosteroids in the interval between visits. (5) The patient reported office visits due to an acute asthma exacerbation since the last visit. (6) The patient reported emergency department visits due to an asthma exacerbation in the interval between visits. (7) The patient reported hospital admissions due to an asthma exacerbation since the last visit.

Data Abstraction

Patients who met all the inclusion and exclusion criteria constituted the study population. Those who started receiving a statin while under our care became the statin group, and those who never received a statin were the nonstatin group. The nonstatin group was selected consecutively from the billing-generated database. In the statin group, the baseline visit was the visit before beginning statin therapy. Follow-up visits were at 3 to 6 months and at 1 and 2 years after starting statin therapy. For the nonstatin group, we reviewed 4 similar points in time; however, the selection of a baseline visit was arbitrary. Patients were also selected consecutively from our patient identification data. Age, sex, race, body mass index (BMI), comorbid illness, medications, asthma severity, and the outcome variables previously outlined were abstracted for each patient and entered in a computer database (Excel).

Statistical Analysis

We compared baseline characteristics between the statin group and the nonstatin group. We calculated the change in FEV₁ as the difference between FEV₁ after statin therapy started and the baseline value. Discrete variables were compared using the χ^2 test and the Fisher exact test as appropriate. For normally distributed continuous variables, the *t* test and an analysis of variance were used. For nonnormally distributed continuous variables, the Kruskal-Wallis test was used.

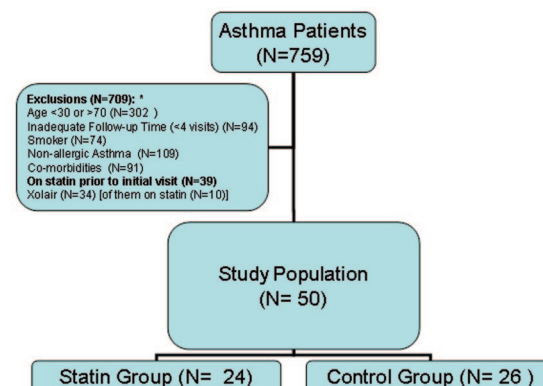


Figure 1. Study patient recruitment. * Some patients may have met more than 1 exclusion criterion. Numbers do not add to 709.

Table 1. Baseline Characteristics of the Statin and Control Groups

Characteristic	Statin group (n = 24) ^a	Control group (n = 26) ^a	P value
Age, y ^b	54 (10)	53 (8)	.50
Male sex	12 (50)	11 (42)	.60
Race			
White	17 (71)	19 (73)	.90
African American	6 (25)	7 (27)	
Other	1 (4)	0	
BMI ^b	32.2 (5.5)	29.0 (6.1)	.05 ^c
Comorbidities			
GERD	6 (25)	4 (15)	.50
Hypertension	11 (46)	5 (19)	.04 ^c
Medications			
PPI	6 (25)	4 (15)	.60
β -Blockers	4 (17)	1 (4)	.20
Aspirin	7 (29)	2 (8)	.04 ^c
Other	15 (62)	15 (58)	.70
Asthma severity			
Mild intermittent	5 (21)	2 (8)	.58
Mild persistent	14 (58)	17 (65)	
Moderate persistent	4 (17)	5 (19)	
Severe persistent	1 (4)	2 (8)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

^a Data are given as number (percentage) of each group unless otherwise indicated.

^b Data are given as mean (SE).

^c Significant difference.

We used computer software (MINITAB version 13.2) for statistical analysis.

RESULTS

Patient Identification

We reviewed 759 medical records (Fig 1) of consecutive patients who were seen at RGH Allergy and Immunology Practice in 2005 and 2006. Of these patients, 457 met the criteria for age. There were 63 patients with asthma receiving statins; patients who had started receiving statins before evaluation in our clinic (n = 39) were excluded. Additional patients were excluded because they did not have positive skin test results, they had comorbidities, they were receiving omalizumab (Xolair), they were smokers, or they did not have the frequency of office visits required for this study. After exclusions, there were 24 patients in the statin group and 26 patients in the nonstatin group.

Baseline Characteristics

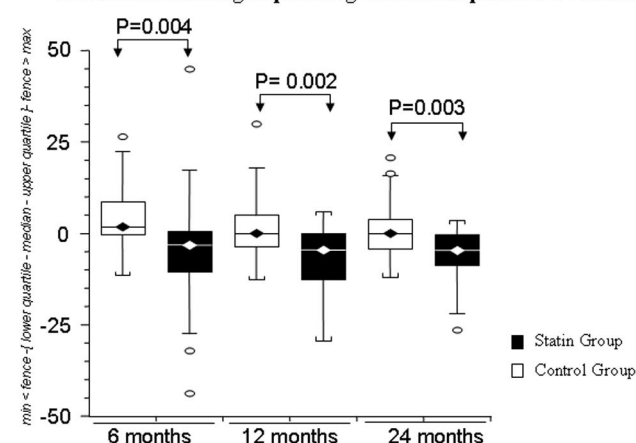
Baseline characteristics are demonstrated in Table 1. Most patients enrolled in this study had mild persistent asthma. There was no difference in asthma severity at baseline between the 2 groups (Table 1). Most patients in both groups were white. The BMI in the statin group was slightly higher than the BMI in the nonstatin group, and more patients in the statin group had hypertension. Except for aspirin, no difference was noted in medication use.

Primary and Secondary Outcomes

The primary outcome, change in FEV₁, at 3 different time points is shown in Figure 2. There was a worsening of FEV₁ compared with baseline at all time points for the statin group compared with the nonstatin group; this difference was statistically significant as demonstrated by the Kruskal-Wallis test. At 6, 12, and 24 months, the FEV₁ decreased by a median of 5%, 4%, and 3%, respectively, compared with no change at 6 and 12 months or a 1.5% increase at 24 months in the nonstatin group (Fig 2A). Most patients in the statin group (18 [75%] at 6 months, 16 [73%] at 12 months, and 15 [71%] at 24 months) had a decrease in FEV₁ compared with those in the nonstatin group (12 [46%] at 6 months, 11 [42%] at 12 months, and 6 [23%] at 24 months) (Fig 2B). More than a 5% FEV₁ decrease was found in 11 (46%) of the patients at 6 months, in 10 (46%) at 12 months, and in 8 (38%) at 24 months ($P = .09$, $P = .05$, and $P = .03$, respectively). In logistic regression models, hypertension and obesity were not significant predictors of more than a 5% FEV₁ decrease at 6, 12, or 24 months.

The secondary outcome analyses are demonstrated in Table 2. Patients in the statin group were more symptomatic at all observed time points, resulting in increased use of albuterol and nocturnal awakenings. The statin group required more frequent medication changes at 6 and 12 months based on the NHLBI guidelines, more courses of oral steroids for acute asthma exacerbations at all time points, and more

A Box & Whisker plot representing Kruskal-Wallis analysis in change of FEV₁ in between groups during observation period of 24 months.



B Percent of Patients with a Worsening of FEV₁ compare to baseline.

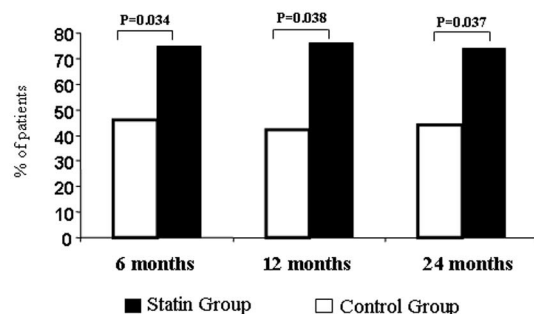


Figure 2. Box-and-whisker plot representing Kruskal-Wallis analysis in the change of forced expiratory volume in 1 second (FEV₁) in between groups during the observation period of 24 months. The central diamond shows the median value, the edges of the boxes are the 25th and 75th percentile points of the data, and the whiskers show the range of the data (not the confidence intervals), excluding the outliers, which are represented by circles. Therefore, at 6 months, the median decrease in FEV₁ in the statin group was 4.7%, the 25th percentile was 8.9%, and the 75th percentile was 0.2%.

frequent office visits for acute asthma at all time points (Table 2). Of the 2 patients who visited the emergency departments secondary to asthma exacerbations, both were in the statin group.

DISCUSSION

The purpose of our study was to examine the clinical course of asthma in patients who recently started receiving statin therapy. As previously shown, the patients receiving statins experienced a loss of control of their disease compared with matched controls who were not receiving this class of medication. To our knowledge, this is the first study to show that statin therapy may have a detrimental effect on asthma control.

In our study, patients were observed retrospectively for 2 years to avoid the confounding factor of seasonal exacerbations related to pollen allergy. We assumed that the patients' asthma was allergic in nature based on their sensitization to perennial allergens. Provocative classification of asthma would be preferable but was not feasible in a retrospective study. The inclusion of nonallergic asthmatic patients in both groups would bias our results toward the null. However, during this time, a small, but statistically significant, decrease in FEV₁ was noted in most patients in the statin group. In addition to this primary end point, statistically significant increases were seen in most of our secondary end points as well. These include an increased frequency of asthma exacerbations, visits for acute asthma, and changes in asthma medication (per NHLBI guidelines¹²). Although the worsening in FEV₁ is small, the changes in the course of the patients' asthma are consistent with a clinically important adverse effect of statins on asthma control. The changes in medication were not sustained at 24 months. Statistical significance in the number of courses of prednisone was also not achieved at 24 months. We hypothesize that the pro-T_H2 effect of statins was overcome by sufficient changes in medication. There was a slight difference in the baseline characteristics of our patient in terms of BMI and hypertension. This likely represents the risk factors that made these patients candidates for statin use in the first place. Although our patients in the statin group were more likely to be obese and hypertensive, regression models failed to show that these factors confounded the relationship between the addition of a statin and the worsening of asthma control.

The findings from our study should be viewed as preliminary given the retrospective design and the lack of other studies showing a consistent effect of statins on asthma control. The limited sample size also precludes analysis by different statin medications and doses. Further research is necessary.

Several mechanisms have been proposed for statins' anti-inflammatory properties, including inhibition of the mevalonate pathway.^{4,5,10,15} These findings suggest that statins could be useful not only in the prevention and treatment of coronary artery disease but also for the treatment of other autoimmune conditions that exhibit a T_H1 cytokine profile (interferon γ and tumor necrosis factor α).⁴⁻⁸ However, the influence of statins on T-cell differentiation results in the polarization away from a T_H1 cytokine profile, which promotes T cells and dendritic cells to differentiate toward a T_H2 cytokine profile; this would be expected to promote allergic diseases, including asthma. To summarize, statins may be helpful in certain kinds of inflammatory processes and detrimental in others.

Animal studies evaluating the effect of statins on T_H2-driven diseases resulted in conflicting data. The initial study by McKay et al¹⁵ showed that high-dose simvastatin, 40 mg/kg, can suppress acute eosinophilic airway inflammation and T_H2 cytokine secretion in a murine asthma model. This study did not propose a mechanism of action, and it used

Table 2. Secondary Outcome Analyses

Variable	Statin group (n = 24) ^a	Control group (n = 26) ^a	P value
Increase in albuterol use			
At 6 mo	18 (75)	3 (12)	<.001
At 12 mo	18 (75)	9 (35)	.004
At 24 mo	8 (33)	2 (8)	.02
Increase in night awakening			
At 6 mo	8 (33)	0 (0)	<.001
At 12 mo	10 (42)	0 (0)	<.001
At 24 mo	3 (12)	0 (0)	<.001
NHLBI medication change			
At 6 mo	16 (67)	7 (27)	.005
At 12 mo	19 (79)	10 (38)	.004
At 24 mo	9 (38)	11 (42)	.64
Interval steroid use			
At 6 mo	5 (21)	2 (8)	.24
At 12 mo	7 (29)	3 (12)	.16
At 24 mo	4 (17)	1 (4)	.13
Acute asthma outpatient visit			
At 6 mo	9 (38)	1 (4)	.003
At 12 mo	6 (25)	1 (4)	.03
At 24 mo	5 (21)	2 (8)	.24
Emergency department visit			
At 6 mo	0	0	NA
At 12 mo	2 (8)	0	NA
At 24 mo	0	0	NA

Abbreviations: NA, not applicable; NHLBI, National Heart, Lung, and Blood Institute.

^a Data are given as number (percentage) of each group.

suprathreshold doses. The highest dose used in humans is 80 mg/d of atorvastatin; for a 70-kg adult, this equals approximately 1.1 mg/kg. The doses in the study by McKay et al were almost 40 times higher.

Arora et al¹⁰ showed that the effects of statins are dose dependent. They investigated the effect of simvastatin on cell viability. Simvastatin treatment did not induce cell death in dendritic cells at lower doses (1- μ M equivalent to 0.3 mg/kg), but cell death was observed at higher doses (10- μ M equivalent to 3.3 mg/kg). In a murine model of asthma using small doses (0.3 mg/kg), they found a T_H2-promoting effect of simvastatin in vivo. Not only did they show a dose response, they identified a novel mechanism by which simvastatin promotes a T_H2-type response. Statins worked through the induction of the chitinase family member, Ym1, in dendritic cells, which through presentation of antigen is crucial to the initiation of the immune response.

The apparently conflicting data in murine models may be explained by the various doses tested. The suprathreshold doses in the study by McKay et al¹⁵ may have killed dendritic cells, thus impairing the entire immune response with resulting improvement in asthma. The lower doses used by Arora et al¹⁰ selectively increased T_H2 function and resulted in a worsening of asthma.

To our knowledge, the only human randomized, controlled, clinical trial of statins that investigated the use of simvastatin as an anti-inflammatory agent in patients with

asthma was performed by Menzies et al.¹⁶ This trial was designed to optimize the treatment effect of statins by withdrawing all anti-inflammatory treatment for the duration of the study and compared patients receiving simvastatin with those receiving placebo, rather than using statins as an adjuvant therapy. This trial failed to show a benefit of simvastatin in the clinical course of asthma. Conversely, it did not show a detrimental effect because the objective of this study was not to evaluate if statin therapy worsened asthma; in fact, the patients were already experiencing worsening of their asthma as a result of the withdrawal of their controller therapy. In addition, although most patients were allergic to seasonal and perennial allergens, some of them were nonatopic, which, based on our understanding of statins' mechanism, would give conflicting data.

The novel immunomodulatory aspects of statins in conjunction with the wide use of these medications highlight the importance of examining the potential effects of these medications. The benefit of statin therapy for hyperlipidemia encourages primary care physicians to initiate therapy early. Fully understanding the interaction of statins on multiple disease processes may elucidate the beneficial effects of some disease states and avoid difficulty in controlling others. It may be that, as with β -blockers and angiotensin-converting enzyme inhibitors, statins will need to be approached with caution in the atopic patient with asthma. Without a doubt,

more information is needed before we “put them in the drinking water.”

Once the retrospective data demonstrated a statistically significant result and supported our hypothesis, we determined that the appropriate next step would be to generate prospective data because more patients studied prospectively would provide more valuable data. Asthma is a complex syndrome, and the reliability of FEV₁, the objective criterion frequently used to evaluate severity, has been questioned as an adequate marker of asthma control. A larger prospective study would have the advantages of more uniform timing of data collection and the ability to collect validated questionnaires such as the Asthma Control Test in addition to clinical and spirometric end points. Given the increasing prevalence of both asthma and the use of statins, a better understanding of the possible interactions is crucial.

ACKNOWLEDGMENTS

We thank Anuradha Ray, PhD, Prabir Ray, PhD, and Mitchell Grayson, MD, for critical reading of the manuscript.

REFERENCES

1. Topol E. Intensive statin therapy: a sea change in cardiovascular prevention [editorial]. *N Engl J Med*. 2004;350:1562–1564.
2. Strom BL. Statins and over-the-counter availability [perspective]. *N Engl J Med*. 2005;352:1403–1405.
3. Ehrenstein MR, Jury EC, Mauri C. Statins for atherosclerosis: as good as it gets [editorial]? *N Engl J Med*. 2005;352:73–75.
4. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nat Rev Immunol*. 2006;6:358–370.
5. Youssef S, Stüve O, Patarroyo RC, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune diseases. *Nature*. 2002;420:78–84.
6. Palinski W. Immunomodulation: a new role for statins? *Nat Med*. 2000;6:1311–1312.
7. Albert MA, Danielson E, Rifai N, Ridker PM; PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA*. 2001;286:64–70.
8. Leung BP, Sattar N, Crilly A, et al. A novel anti-inflammatory role for simvastatin in inflammatory arthritis. *J Immunol*. 2003;170:1524–1530.
9. Robinson DS, Hamid Q, Ying S, et al. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med*. 1992;326:298–304.
10. Arora M, Chen L, Paglia M, et al. Simvastatin promotes Th2-type responses through the induction of the chitinase family member Ym1 in dendritic cells. *Proc Natl Acad Sci U S A*. 2006;103:7777–7782.
11. Hakamada-Taguchi R, Uehara Y, Kuribayashi K, et al. Inhibition of hydroxymethylglutaryl-coenzyme A reductase reduces Th1 development and promotes Th2 development. *Circ Res*. 2003;93:948–956.
12. *Stepwise Approach for Managing Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2003. NIH publication 03–5074.
13. *Pulmonary Function Laboratory Management and Procedure Manual*. 2nd ed. New York, NY: American Thoracic Society; 2005.
14. Weitz-Schmidt G, Welzenbach K, Brinkman V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. *Nat Med*. 2001;7:687–692.
15. McKay A, Leung BP, McInnes IB, Thomson NC, Liew FY. A novel anti-inflammatory role of simvastatin in a murine model of allergic asthma. *J Immunol*. 2004;172:2903–2908.
16. Menzies D, Nair A, Meldrum KT, Fleming D, Barnes M, Lipworth BJ. Simvastatin does not exhibit therapeutic anti-inflammatory effects in asthma. *J Allergy Clin Immunol*. 2007;119:328–335.

Requests for reprints should be addressed to:
Elizabeth Friedman, MD
Genesee Health Service
222 Alexander St
Monroe Court
Rochester, NY 14607
E-mail: elizabeth.friedman@viahealth.org