Statin Use in Giant Cell Arteritis: A Retrospective Study

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ABSTRACT. ***Objective.*** (1) To examine the association between statin use and giant cell arteritis (GCA); (2) to compare the clinical features and disease course of GCA among statin users and nonusers.

Methods. For this retrospective study, we reviewed the medical records of all patients with biopsy-positive GCA diagnosed between 1998 and 2008. Using a case-control design, we compared the frequency of statin use in GCA patients to non-GCA population-based subjects who were randomly selected and individually matched by sex, age, and calendar year to the GCA cases. Statin use at diagnosis or index date and during followup was abstracted. In subjects with GCA, clinical information at diagnosis and followup was collected.

Results. We included 594 patients, 297 with GCA (73% female), mean age at diagnosis 75 years. The rate of statin exposure at index date was 18.1% for GCA patients versus 33.3% for controls ($p < 0.001$). Patients using statins were less likely to develop GCA compared with patients not using statins (OR 0.31, 95% CI 0.15–0.6, $p < 0.001$), even after adjustment for cardiovascular risk factors. Among patients with GCA, the presenting clinical features and acute-phase reactants were similar in patients receiving statins compared to those not on statin therapy. These 2 groups were also similar with regard to relapse rate, prednisone tapering, and overall survival.

Conclusion. Patients using statins may be less likely to develop GCA compared to patients who are not using statins. Statin use does not appear to modify the clinical presentation or the course of the disease. (J Rheumatol First Release April 1 2013; doi:10.3899/jrheum.121150)

Key Indexing Terms:
GIANT CELL ARTERITIS VASCULITIS EPIDEMIOLOGY
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In addition to their lipid-lowering properties, HMG-CoA reductase inhibitors (statins) are known to have immunomodulatory and antiinflammatory effects[1]. Statins inhibit the mevalonate pathway and block cholesterol synthesis, but also interfere with the generation of isoprenoids[2]. Isoprenoids are important for signal transduction pathways in all cell types through their action on small guanosine triphosphate hydroxylases (GTPases)[2]. This ability of statins to block isoprenoid synthesis may have beneficial cardiovascular effects that extend beyond their cholesterol-lowering properties[3]. Because of these pleiotropic effects, statins have been studied in several inflammatory and autoimmune disorders such as rheumatoid arthritis (RA)[4], systemic lupus erythematosus[5], and multiple sclerosis[6]. There are conflicting data regarding the effect of statins on disease activity in patients with RA[7,8]. A study found that the use of statins may be associated with a reduction in the incidence of RA[9].

Giant cell arteritis (GCA) is an inflammatory condition affecting large arteries that occurs in people over the age of 50 years[10]. It is the most common form of vasculitis in adults, and a recent study estimated the lifetime risk of GCA is about 1% for women and 0.5% for men[11]. Morbidity associated with the disease or its treatment is well recognized[12,13]. The pathophysiology of GCA involves the activation of dendritic cells in the adventitial layer of the artery, resulting in activation of T cells and generation of a local and systemic inflammatory response[14,15]. Statins may influence the inflammatory process in GCA. The main goal of our study was to examine the potential association

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between statin exposure and a diagnosis of GCA. We also evaluated whether statins influence disease presentation and disease course in patients with GCA.

MATERIALS AND METHODS

The study was approved by the institutional review boards at Mayo Clinic and at Olmsted Medical Center. The need for informed consent was waived in this retrospective, medical record review study. Patients who denied authorization of the use of their medical records for research purposes were excluded.

For this retrospective study, we identified all patients who underwent temporal artery biopsy (TAB) at Mayo Clinic, Rochester, between January 1, 1998, and December 31, 2008. Histopathology reports were reviewed and all patients with a TAB interpreted as being consistent with GCA were identified. Each medical record was reviewed to confirm the diagnosis according to the American College of Rheumatology classification criteria[16]. The date of TAB was considered as the date of GCA diagnosis.

To evaluate statin use and risk of GCA, we performed a case-control study. Using resources of the Rochester Epidemiology Project (REP), controls were randomly selected from the general population of Olmsted County, Minnesota, where the Mayo Clinic is located. The REP is a unique record-linkage system whose database allows access to all inpatient and outpatient medical records from all healthcare providers for the population of Olmsted County[17]. This resource is well suited for population-based epidemiologic studies. One control without GCA was matched with each GCA case by sex, age, and calendar year of diagnosis. Each control was assigned an index date corresponding to the date of diagnosis of the GCA case. Risk set sampling was chosen and controls were limited to those free of disease at the index date only. Subjects from the pool of possible controls that later developed GCA were designated controls until the time they themselves became a case.

The medical records of both groups were reviewed and a standardized case report form was used to collect the following data: patient demographics (age at index date, sex), use of statin at index date and during followup (for GCA patients only), body mass index (BMI) at index date, and cardiovascular (CV) risk factors at index date. CV risk factors included a clinical diagnosis of hypertension, diabetes, smoking status, family history of CV disease, dyslipidemia, and personal history of CV disease [angina or myocardial infarction (MI), stroke or transient ischemic attack, lower limb arterial disease].

To evaluate whether statin use was associated with clinical differences among patients with GCA, we abstracted detailed clinical data on each patient with GCA. The clinical features at the time of diagnosis [new onset of headache, temporal artery abnormality, jaw claudication, polymyalgia rheumatica, visual symptoms, and constitutional syndrome (fatigue, weight loss, low grade fever)], laboratory testing before corticosteroid treatment [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count, and lipid profile], and data regarding disease course including relapses were abstracted. Relapse was defined as (1) new onset of symptoms more than 1 month after diagnosis; or (2) elevation of ESR > 50 mm after a period of normal ESR; or (3) the need for the treating clinician to increase the corticosteroid dose (in the absence of other conditions contributing to the above). Elevated ESR was defined as > 30 mm/h, and elevated CRP as > 8 mg/dl (laboratory reference values).

For the purposes of our study, statin use was defined as a prescription of statin medication, as determined from the patient's medication list. Subjects who were taking statins but discontinued the medication up to 1 week prior to index date were still considered statin users. Patients who started treatment with a statin within 1 week before index date were considered statin nonusers.

Descriptive statistics were used to summarize the data including percentage, means with SD, and medians with first and third quartiles of the distributions. To compare proportions between the 2 patient groups, McNemar's test was used. Proportions within the group of patients with GCA were compared with the chi-square test or Fisher's exact test when appropriate. Continuous variables were compared between groups with the Wilcoxon rank-sum test. The association between statin exposure and diagnosis of GCA was analyzed with a conditional logistic regression model, allowing for adjustment for CV risk factors. All explanatory variables introduced in the model were binary variables. Smoking status was coded as ever/never smoker, and BMI was coded as ≥ 25 kg/m^2 or < 25 kg/m^2. We also tested for an interaction between BMI and statin use.

In addition to the conditional logistic regression models, several approaches were used to adjust for differences in the frequency of CV risk factors between cases and controls when examining the association between statin use and case/control status. First, logistic regression models were used, stratified by the number of CV risk factors (including smoking, hypertension, hyperlipidemia, diabetes mellitus, and history of MI) and adjusted for age and sex. In an alternative approach, a propensity score predicting the probability of receiving a statin was developed using CV risk factors. Inverse probability of treatment weights was determined from the propensity scores and a weighted analysis was performed[18].

Overall survival, time to first relapse, and time to taper steroids to a dose of 10 mg/day were estimated using the Kaplan-Meier method, and statin users were compared to nonusers using the log-rank test. The rates of GCA relapses among statin users and nonusers were compared using Cox models with a time-dependent covariate to account for statin exposure that may begin after the diagnosis of GCA. All tests were 2-sided with a significance level of $p < 0.05$. Statistical analysis was performed using SAS software (version 9.1; SAS Institute).

RESULTS

The study included 297 patients with biopsy-positive GCA and 297 control subjects. Both groups were predominantly female (73%), and the mean age at TAB (or index date) was 75 years (± 7.4).

Statin use in patients with GCA versus controls. Using a case-control design, we examined the association between statin exposure and GCA diagnosis. The rate of statin exposure at index date was 18.1% for the cases versus 33.3% for controls ($p < 0.0001$). However, CV risk factors including hypertension, diabetes, tobacco smoking, BMI ≥ 25 kg/m^2, and history of MI were more frequent in the control group (Table 1).

Patients using statins were significantly less likely to develop GCA (OR 0.31, 95% CI 0.15–0.6; $p = 0.0006$), after adjustment for hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, personal history of MI, stroke, lower limb claudication, BMI ≥ 25 kg/m^2, and family history of ischemic heart disease. In a second analysis stratified by the number of CV risk factors and adjusted for age and sex, the association between statin use and case/control status remained significant (OR 0.55, 95% CI 0.35–0.87; $p = 0.010$). We also calculated the OR for each strata and found that it was similar across the strata, indicating that the relationship between statin use and case/control status was similar across the levels of CV risk (data not shown). In a third analysis, inverse probability of treatment weighting was used to adjust for confounding due to differences in the frequency of CV risk factors between the groups, and the results remained similar (OR 0.53, 95% CI 0.34–0.82; $p = 0.004$).

Table 1. Demographic characteristics, cardiovascular risk factors, and treatment at the date of temporal artery biopsy/index date among patients with giant cell arteritis (GCA) and a population-based comparison group.

Characteristic	GCA, n (%), n = 297	Comparison, n (%), n = 297	p, McNemar test
Age at index date, yrs	75.1 (± 7.4)	75 (± 7.5)	
Female	217 (73)	217 (73)	
Hypertension	136 (45.9)	169 (56.8)	0.011*
Diabetes	23 (7.8)	42 (14.2)	0.018*
Dyslipidemia	100 (34.1)	119 (39.9)	0.161
Family history	55 (20.8)	67 (24.2)	0.401
Tobacco (ever smoker)	113 (40.4)	138 (48.9)	0.048*
History of myocardial infarction	42 (14.2)	66 (22.4)	0.010*
Stroke history	22 (7.5)	23 (7.8)	1
Claudication history	10 (3.4)	8 (2.7)	0.790
Body mass index ≥ 25 kg/m^2	118 (42.5)	199 (69.6)	< 0.0001*
Statin use	54 (18.1)	99 (33.3)	< 0.0001*
Nonstatin lipid-lowering agent	6 (2)	18 (6.1)	0.022*
Aspirin	118 (39.7)	140 (47.1)	0.075

* $p < 0.05$.

We also performed a subset analysis restricting the cases to only those patients with GCA who were Olmsted County residents at the time of diagnosis (n = 52 patients). Each case was matched on age, sex, and index date to 2 controls (also from Olmsted County). CV risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking status, and history of MI) did not differ significantly between cases and controls, but BMI was significantly lower in patients with GCA compared to controls (p = 0.002). Among the cases, 14 (27%) were exposed to statins and among the controls 35 (34%) were exposed to statins. The association between statin use and development of GCA was not significant (OR 0.71, 95% CI 0.33, 1.53; p = 0.38 using conditional logistic regression), likely because of the small sample size.

The types of statin medications used were similar between patients with GCA and the population-based comparison group. Simvastatin (41% cases vs 45% controls) and atorvastatin (46% cases vs 38% controls) were most commonly prescribed. The remaining prescriptions were distributed between pravastatin, lovastatin, rosuvastatin, fluvastatin, and cerivastatin.

Statin use and clinical features at diagnosis in patients with GCA. In a cross-sectional analysis of patients with GCA, we examined the association between statin use and disease features at diagnosis. Among subjects with GCA, the presenting clinical features were similar between patients receiving statins at diagnosis and those who were not (Table 2). Acute-phase reactants (ESR and CRP) were slightly less elevated in patients with GCA receiving statins at the time of diagnosis. However, this difference was not statistically significant. The median ESR for patients with GCA taking statins was 64 mm/h (53–96) versus 69 mm/h (43–95) for those not taking statins (p = 0.92, Wilcoxon rank-sum test), and the median CRP for statin users was 48.7 mg/l (35–94) versus 56.5 mg/l (27–100) for nonusers (p = 0.88, Wilcoxon rank-sum test). Among patients with GCA, an elevated ESR and/or CRP at baseline was present in 94.4% of statin users versus 91.6% of nonusers (p = 0.58, Fisher's exact test). The

Table 2. Clinical features of patients with giant cell arteritis at the time of temporal artery biopsy, comparing statin users and nonusers.

Sign/Symptom	Statin Users, n (%) n = 54	Nonusers, n (%) n = 243	p, chi-square
New-onset headache	33 (63.46)	166 (68.88)	0.44
Abnormal temporal artery	17 (32.69)	55 (22.82)	0.13
Jaw claudication	25 (48.08)	127 (52.70)	0.54
Polymyalgia rheumatica	18 (34.62)	93 (38.59)	0.59
Visual symptoms	14 (26.92)	68 (28.22)	0.85
Constitutional signs	26 (50)	128 (53.11)	0.68
Other*	5 (9.62)	45 (19.07)	0.10
Elevation of ESR and/or CRP	51 (94.44)	217 (91.56)	0.58**

* Dry cough, tongue claudication, limb claudication, arthralgia, arthritis, ear pain, pericarditis. ** Fisher's exact test. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

laboratory findings at the time of diagnosis of GCA are displayed in Table 3. Although treatment with statins was not associated with a reduction in inflammatory markers, it was associated with lower cholesterol levels, and especially low-density lipoprotein (LDL) cholesterol.

Statin use and outcomes in patients with GCA. In the longitudinal portion of our study, we evaluated whether statin use influenced the clinical course of GCA. Among the GCA cases, the median followup was 3.7 years for statin users and 4.0 years for nonusers. Followup data with at least 6 months of followup after diagnosis were available for the majority of cases (n = 197). While not statistically significant, statin users may be more likely to experience a first relapse (HR 1.40, 95% CI 0.96, 2.03; p = 0.07). There was no association between statin exposure and the ability to achieve a steroid dose < 10 mg/day (HR 0.87, 95% CI 0.61, 1.26; p = 0.87). The 5-year survival rates for GCA patients taking statins and GCA patients not taking statins were similar (73% and 79%, respectively; p = 0.9). There was also no association between statin exposure and mortality (HR 1.02, 95% CI 0.59, 1.75; p = 0.95). There was no difference in the rate of large artery stenosis or aneurysm formation between statin users and nonusers (data not shown).

DISCUSSION

In this retrospective study, patients using statins were less likely to develop GCA compared with patients not using statins. Specifically, patients using statins were about half as likely to develop GCA compared to those not using statins. However, among patients with GCA, treatment with statins did not appear to modify the clinical presentation of the disease, or to significantly affect the inflammatory markers at the time of diagnosis. The clinical course of the disease was also not significantly affected by exposure to statins at the time of diagnosis.

The rate of treatment with statin in our control group (33%) is consistent with expected rates in the US general population. The use of lipid-lowering agents increases with age and calendar year[19]. During the 1999-2002 period, the rate of use of lipid-lowering agents in the US general population over age 60 years was estimated to be 24.3% in men and 21.6% in women[19]. A population-based study from the Seattle region enrolling more than 3000 elderly people (mean age 74 yrs) during the 1994-2002 period found the rate of statin use to be about 23%[20]. A more recent study enrolled more than 24,000 subjects from the general population in the Southeast region of the United States during the 2002-2008 period. The rate of statin use in the 65–84 age group was around 35%[21].

We recorded CV risk factors to better evaluate them as potential confounding variables in our analysis. This was important because we found that patients with GCA had fewer CV risk factors prior to diagnosis compared to the controls from the general population. At index date, GCA patients had lower rates of arterial hypertension, diabetes, tobacco smoking, and history of MI, and also had a lower BMI. The lower BMI at the time of diagnosis may be explained in part by weight loss frequently seen as a constitutional symptom of GCA.

The lower frequency of CV risk factors in patients with GCA may to some extent explain the lower frequency of statin prescriptions in the patients with GCA, despite similar frequency of dyslipidemia. This finding is somewhat in contrast to other studies[22,23]. In one case-control study, tobacco use and an arterial bruit were associated with GCA, but only in women[22]. In a population-based case-control study of 88 patients with newly diagnosed GCA between 1950 and 1985, tobacco smoking was associated with increased risk of GCA[23]. However, the percentage of smokers in the general population in that study was low compared to our findings (27% vs 49%).

It is not clear whether risk factors for atherosclerosis modulate the risk for developing GCA. Even after

Table 3. Laboratory tests at the time of diagnosis of giant cell arteritis (GCA), comparing statin users and nonusers (Wilcoxon rank-sum test). N is the number of subjects with result available for the variable considered. Data are median (25th percentile, 75th percentile).

Test	GCA with Statin, n = 54	n	GCA without Statin, n = 243	n	p
ESR, mm/h	64 (53–96)	54	69 (43–95)	237	0.9
CRP, mg/l	48.7 (35–94.6)	38	56.5 (27–100)	150	0.8
Hemoglobin, g/dl	11.6 (10.5–12.5)	47	11.7 (10.7–12.8)	227	0.4
Platelets, $\times 10^9$/l	383 (301–438)	47	378 (318–462)	226	0.4
Leukocytes, $\times 10^9$/l	8.6 (6.8–10.3)	47	8.9 (7.4–11.3)	226	0.1
Cholesterol total, mg/dl	170 (146.5–207.5)	36	190 (166–219)	134	0.04
HDL-cholesterol, mg/dl	59 (41.5–70.5)	36	58 (45–72)	133	0.6
LDL-cholesterol, mg/dl	88 (75–108)	36	107 (88–130)	133	0.004
Triglycerides, mg/dl	107 (87–161)	36	101 (75–142)	133	0.3

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

adjustment for the above CV risk factors, the negative association between GCA and statin use remained statistically significant.

When evaluating clinical differences at diagnosis of GCA among statin users and nonusers, ESR and CRP levels in patients taking statins were lower than in patients who were not on statins, but the difference was neither statistically nor clinically significant. Statins have been shown to lower high-sensitivity CRP in patients without overt inflammation[24,25], but the effect of statins on inflammatory processes with high levels of CRP is unknown. A recent study found that the median ESR at the time of diagnosis of GCA was lower in patients taking statins compared to nonusers (57.5 mm/h vs 85 mm/h)[26]. However, the number of patients receiving statins in the study by Hegg, *et al*[26] was small (24/161 patients with GCA), and most of the patients received concomitant statins and nonsteroidal antiinflammatory drugs (NSAID; 19/24). Therefore, it was difficult to draw conclusions regarding the role of NSAID or statins on levels of inflammatory markers in the study reported by Hegg, *et al*[26].

Previous studies have examined the role of adjunctive treatment with statins for patients with GCA[27,28]. These retrospective studies compared statin users with nonusers among a cohort of patients with GCA. Treatment with statins was not associated with a corticosteroid-sparing effect, reduction of ischemic complications of the disease, reduction of disease duration, or with decrease in relapse rates. Our findings are consistent with these studies. From these results, it appears that once the disease is established, statins do not modify the course of the disease.

Our study has limitations that need to be considered when interpreting our findings. We analyzed exposure to statins only at the time of diagnosis of GCA as data regarding the duration and cumulative use of statins were not consistently available. This was a retrospective study and data for statin use were abstracted based on the medical record. However, among patients with GCA, patients who were classified as taking statins at diagnosis had a lower LDL (statistically significant) and CRP (statistically not significant) than patients who were not taking statins. This suggests that the group classified as statin users were exposed to this medication. The patients with GCA were from a referral population, while the comparison group was population-based. Therefore we cannot exclude that inherent differences between the cases and controls could influence our results. In our subset analysis of cases and controls from Olmsted County, no association between statin use and development of GCA was found. Further, we included only cases of biopsy-positive GCA. Because this was a retrospective study, we relied on the recording of pertinent information in the medical record. CV risk factors were considered present based on documentation in the medical record by the treating physician. Statin exposure was also evaluated based on information from medical records of both cases and controls. It is possible that statin use would be asymmetrically documented in the medical records for cases and controls because the controls also received their primary care at Mayo Clinic. However, because this information was abstracted from review of medical records, recall bias would be minimized. While we adjusted for CV risk factors as potential confounders, the possibility of other unknown confounders accounting for our findings cannot be excluded.

The strengths of our study include the large number of patients. We included only incident cases of GCA evaluated at our center. We included a comparison group randomly selected from the general population. We also abstracted information on multiple CV risk factors.

Our findings suggest that statin use is lower in patients with GCA and does not appear to simply reflect a lower rate of CV risk factors in this population. The observation of higher rate of statin exposure among non-GCA comparators is intriguing. Based on the current study design, no conclusive inference can be made about whether statins themselves modify the risk of developing GCA. This would require more robust studies. It is conceivable that statin use may lower the likelihood of developing GCA by virtue of their antiinflammatory and immunomodulatory properties, which may interfere with the pathophysiological process of the disease, prior to clinical disease onset. One potential mechanism is the induction of differentiation of Foxp3-positive CD4-positive regulatory T cells by statins with decreased differentiation of Th17 cells[29]. Statins may also be able to reduce the inflammatory function of T cells and interferon-γ (IFN-γ) expression[30]. Both IFN-γ-producing Th1 cells and interleukin 17-producing Th17 cells are implicated in the pathogenesis of GCA[15]. Theoretically, by interfering with this early step of the disease, statins may modulate risk of developing GCA in some patients.

Given the relatively low frequency of GCA in the general population, a prospective clinical trial examining the effect of statin use on future risk of GCA would not be logistically feasible. However, in the future, if our data are replicated and biomarkers that predict the risk of GCA are discovered, high-risk individuals could be identified as subjects for primary prevention studies.

Patients using statins may be less likely to develop GCA compared to patients not using statins. However, statin use does not appear to modify the clinical presentation or the course of the disease. Our findings are intriguing and warrant further investigation to determine whether statin use can modulate the risk of developing GCA.

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