Title

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Journal

American Journal of Ophthalmology, 159(4)

ISSN

0002-9394

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Publication Date

2015-04-01

DOI

10.1016/j.ajo.2015.01.009

Peer reviewed

Published in final edited form as:

Am J Ophthalmol. 2015 April ; 159(4): 707–713.e2. doi:10.1016/j.ajo.2015.01.009.

Association between Statin Use and Uveitis: Results from the Pacific Ocular Inflammation Study

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Abstract

Purpose—To assess whether there is a protective association between statin use and uveitis diagnosis

Design—Retrospective, population-based case-control study

Methods—Medical records of all patients in the Kaiser Permanente Hawaii health plan between January 1, 2006 and December 31, 2007 (N=217,061) were searched electronically for International Classification of Diseases, 9th Revision, diagnosis codes related to uveitis. Chart review was done to confirm incident uveitis diagnosis during the study period. Two control groups were each randomly selected at a 5:1 ratio to cases, and controls were assigned an index date to match their respective case diagnosis date. One control group was selected from the general Kaiser Permanente Hawaii population that had at least one healthcare visit during the study period. Another control group was selected from the population of Kaiser Permanente Hawaii members who had at least one visit to the ophthalmology clinic during the study period. Statin use was defined as filling a prescription for statin medication in the year prior to the diagnosis or index date based on an electronic search of the Kaiser Permanente Hawaii pharmacy database for Generic Product Identification codes. A conditional logistic regression model with clinical diagnosis of uveitis as the outcome was used to assess the relationship between statin use and uveitis.

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Results—One hundred eight incident cases of uveitis were identified. Nineteen percent of uveitis patients had used statin medication in the year prior to diagnosis compared to 30% of patients in the general Kaiser population control (p=0.03) and 38% of patients in the ophthalmology clinic control (p<0.001). Using the general Kaiser population control and adjusting for age, gender, race, and autoimmune diseases, the odds of a statin user developing uveitis were 48% less than the odds of a non-statin user developing uveitis (OR: 0.52, 95% CI: 0.29 to 0.94, p=0.03). Similarly, the odds of developing uveitis were 33% less for statin users compared to non-statin users (OR: 0.67, 95% CI: 0.38 to 1.19, p=0.17) when adjusting for these factors and using the ophthalmology clinic control group.

Conclusions—Statin use may be protective against the development of uveitis. Several anti-inflammatory and immunomodulatory mechanisms may explain this association.

Introduction

Uveitis is a set of conditions defined by inflammation of the uveal tract and accounts for approximately ten percent of legal blindness in the United States.[1–4] The exact mechanism by which uveitis occurs is not well defined. Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors, are primarily used for decreasing low-density lipoprotein (LDL) cholesterol, as well as for reducing cardiovascular and cerebrovascular disease risk, and the side effects are generally minimal in most patients.[5–8] Numerous studies have shown additional anti-inflammatory and immunomodulatory benefits of statins in a variety of systemic diseases, including multiple types of cancer, inflammatory bowel disease, and rheumatoid arthritis.[9–15]

In the ophthalmology literature, several studies have investigated whether there is an association between statin use and age-related macular degeneration, as well as glaucoma, cataract, and diabetic retinopathy. While the results have been varied, some studies have shown a protective effect of this class of medications.[16–27] Multiple laboratory studies have been done suggesting anti-inflammatory properties of statins in animal models with experimental autoimmune uveitis, and one clinical case-control study found a non-significant protective association between statin use and all types of ocular inflammatory disease.[28–31] However, a population-based study focusing specifically on the association between statin use and uveitis is lacking.

The Pacific Ocular Inflammation study aims to elucidate details about the epidemiology of ocular inflammatory disease in the Hawaiian islands. Kaiser Permanente Hawaii provides an optimal setting for this population-based study as it is comprised of more than fifteen percent of the general Hawaiian population with centers throughout the Hawaiian islands. The goal of this specific case-control study was to assess whether there is a protective association between statin use and uveitis diagnosis.

Methods

Institutional Review Board and Ethics Committee approval was obtained at Kaiser Permanente Hawaii and the University of California, San Francisco, respectively. All work was HIPAA-compliant and adhered to the tenets of the Declaration of Helsinki. Detailed

methods for identification of uveitis cases, including a complete list of International Classification of Diseases, 9th Revision (ICD-9) codes used, have been described previously.[32] Briefly, all clinical encounters between January 1, 2006 and December 31, 2007 in the electronic database of Kaiser Permanente Hawaii were queried for ICD-9 diagnosis codes associated with uveitis. The medical records of patients identified by this initial search were individually reviewed by a uveitis fellowship-trained ophthalmologist to exclude patients without a confirmed diagnosis of uveitis. Additionally, incident cases were identified as patients whose first diagnosis of uveitis was within the study period based on comprehensive chart review. All patients with a confirmed incident diagnosis of uveitis were included in this study.

Two control groups were each randomly selected at a 5:1 ratio to incident uveitis cases. One control group was selected from the general Kaiser Hawaii membership who had at least one healthcare visit during the study period. An ophthalmology control group was selected from the population of Kaiser patients who were 18 years of age or older as of January 1, 2007, and had at least one visit to the Kaiser ophthalmology clinic during the study period. Each control patient was assigned an index date to match the diagnosis date for its respective case.

Statin use was determined based on an electronic search of the Kaiser Hawaii pharmacy database for all Generic Product Identification (GPI) codes corresponding to this class of medications. Patients were considered statin users if they had filled a prescription for atorvastatin, lovastatin, fluvastatin, rosuvastatin, pravastatin, simvastatin, or ezetimibe-simvastatin in the year prior to the diagnosis or index date. Use of other lipid-lowering agents was based on a similar search for cholestyramine, colestipol, ezetimibe, fenofibrate, gemfibrozil, and vitamin B_3. High dose statin use was defined as having a prescription filled for statin medication at a dosage shown to reduce low-density lipoprotein (LDL) cholesterol by at least fifty percent.[33]

Demographic information, diagnosis of hyperlipidemia, hypertension, diabetes, or autoimmune disease, and smoking status were collected electronically for both cases and controls. Smoking status was determined based on information provided at physician visits, and each patient's smoking status closest to the diagnosis or index date was used. Infectious uveitis was defined as having an associated diagnosis of herpes simplex virus, herpes zoster virus, histoplasmosis, toxoplasmosis, human immunodeficiency virus, Bartonella, tuberculosis, syphilis, cytomegalovirus retinitis, or Lyme disease determined by electronic ICD-9 code search or individual chart review.

Demographic data and clinical characteristics for cases and controls were compared using Fisher's exact test or a two-sample t-test for categorical and continuous variables, respectively. Conditional logistic regression with diagnosis of uveitis as the outcome was used to assess the association between statin use and uveitis for each control group. Age, gender, race, diagnosis of autoimmune disease, and smoking status were used as covariates in the main regression model and sensitivity analyses to evaluate the effect of these factors on the association. A p-value less than 0.05 was considered statistically significant. All analyses were performed using STATA 12.0 (StataCorp, College Station, TX).

Results

The total population of Kaiser Permanente Hawaii was 217,061 people at the midpoint of the study period, January 1, 2007. Out of this population, 224 patients had a confirmed diagnosis of uveitis, and of these, 108 were confirmed incident cases. Location of inflammation, disease course, and associated diagnoses have been presented previously.[32] A majority of incident cases were anterior (n=88, 81%) and non-infectious (n=82, 76%).

For both the general Kaiser Hawaii population control and the ophthalmology clinic control, 540 patients were randomly selected for comparison to the uveitis patients. Demographic data were compared between uveitis patients and control patients (Table 1). Compared to both the general control group and the ophthalmology control, cases were not significantly different with respect to age and gender with the exception that uveitis patients were significantly younger than the ophthalmology control group (mean age: 49.9 years vs. 62.5 years, $p<0.001$).

Table 2 presents the clinical characteristics of both cases and controls. Nineteen percent of uveitis patients had used statin medication in the year prior to uveitis diagnosis. This was significantly lower than both the general Kaiser population control (30%, $p=0.03$, Table 2) and the ophthalmology control (38%, $p<0.001$, Table 2). Use of high dose statins or other lipid-lowering agents were not significantly different between cases and either control group. For the general population control, the proportions of cases and controls with lipid metabolism disorders, hypertension, or diabetes did not differ significantly. Patients in the ophthalmology control group had higher rates of these diseases compared to uveitis patients (Table 2). After adjusting for age, lipid metabolism disorders (OR: 1.22, 95% CI: 0.73 to 2.03, $p=0.45$), hypertension (OR: 0.90, 95% CI: 0.54 to 1.50, $p=0.69$), and diabetes (OR: 0.63, 95% CI: 0.35 to 1.14, $p=0.13$) were not associated with case status.

Multivariate conditional logistic regressions were used to compare uveitis patients to each control group adjusting for the effects of age, gender, race, and autoimmune disease (Table 3). Using the general population control, the odds of a statin user developing uveitis were 48% less than the odds of developing uveitis for a patient not taking this class of medications (OR: 0.52, 95% CI: 0.29 to 0.94, $p=0.03$, Table 3). Similarly, the odds of a statin user developing uveitis were 33% less than the odds for a non-statin user when using the ophthalmology clinic control (OR: 0.67, 95% CI: 0.38 to 1.19, $p=0.17$, Table 3); however, this association was not significant.

A sensitivity analysis was done to evaluate the effect of current smoking status on this association. Controlling for smoking status in addition to age, gender, race, and autoimmune disease did not affect the protective association between statin use and uveitis when using both the general population (OR: 0.52, 95% CI: 0.29 to 0.95, $p=0.03$) and ophthalmology clinic control groups (OR: 0.65, 95% CI: 0.36 to 1.16, $p=0.15$). Adjusting for current and prior smoking status rather than current smoking status alone also did not impact the results for either control group.

Additional sensitivity analyses were done to evaluate this association for non-infectious uveitis. Using only patients with non-infectious uveitis and their respective general

population controls, the odds of developing uveitis were 56% less in statin users compared to non-statin users (OR: 0.44, 95% CI: 0.22 to 0.88, p=0.02) when adjusting for age, gender, race, current smoking status, and autoimmune disease. A similar association, which trended toward significance, was found using the ophthalmology clinic control group and adjusting for these factors (OR: 0.52, 95% CI: 0.26 to 1.02, p=0.057).

Discussion

Prior to this, several studies suggested beneficial anti-inflammatory and immunomodulatory properties of statin medications for multiple systemic diseases, as well as various ophthalmic conditions, including age-related macular degeneration, glaucoma, and diabetic retinopathy.[9–17,20,22,23,25,26,34,35] In this study, the odds of developing uveitis were approximately fifty percent less for statin users compared to patients not taking this class of medications. This association was significant using a general Kaiser population control group, and a significant association remained when considering only cases of non-infectious uveitis. This is a novel finding and suggests that statin medications may be protective in the development of uveitis.

Previously, one clinical study investigated a similar research question.[31] This study included all cases of ocular inflammatory disease and found a non-significant protective association between statin use and ocular inflammatory disease. A large proportion of cases in that study were uveitis patients, and the overall effect size was similar to the current study. Of note, the prior study was done in a Veterans Affairs hospital population comprised mainly of White males. Our population was significantly different from this with regard to both gender and racial demographics, suggesting that a protective association between statin medications and uveitis may be present in diverse populations.

A number of immunomodulatory and anti-inflammatory mechanisms could explain these findings. Specifically, statins have been shown to reduce levels of key inflammatory cytokines, such as interleukins 6 and 8 and TNF-alpha, as well as C-reactive protein.[36,37] Additionally, this class of medications has been shown to decrease interactions between leukocytes and endothelial cells via the intercellular adhesion molecule-1 (ICAM-1) pathway.[38] This can prevent leukocyte migration across the blood-retinal barrier, thus decreasing intraocular inflammation.[39–41] Similarly, statins can help to strengthen the blood-retinal barrier by decreasing the formation of oxygen free radicals and increasing levels of nitric oxide. Both of these mechanisms have been shown to stabilize endothelial cells in the vasculature.[42–44]

Many of these mechanisms have been demonstrated in prior studies using animal models of experimental autoimmune uveitis (EAU).[28–30] Two prior studies have shown decreased levels of proinflammatory cytokines on histological examination of lymph nodes from EAU mice treated with statin medication.[28,29] Similarly, these studies found a significant reduction in leukocyte infiltration into the retina with treatment with lovastatin; one study also showed a similar effect with atorvastatin. Although one study found no overall reduction in proiflammatory cytokines in statin-treated EAU mouse models, the results still showed mildly decreased inflammation on histological examination of the retina in

atorvastatin-treated mice.[30] All three of these studies suggest that the anti-inflammatory benefits of statins for intraocular disease could be most directly related to actual inhibition of lymphocyte migration through retinal endothelial cell monolayers. Although the greatest effects in these studies were observed with parenteral administration of statin medications, it is possible that similar mechanisms could explain a protective association between oral administration of statins and uveitis in humans.

There are some limitations to acknowledge. Like all case control studies, the results suggest an association between statin use and uveitis but do not establish causation. Similar to other studies using electronic data, it is possible that all statin users were not captured using GPI codes secondary to miscoding or prescriptions being filled elsewhere. However, less than five percent of Kaiser Hawaii members had dual insurance during the study period that would facilitate receiving healthcare, including prescription medications, outside of the Kaiser system. Additionally, it is unlikely that uveitis patients preferentially filled prescriptions for statin medications outside of the Kaiser system.

Another limitation that may have affected the estimate of actual statin use is compliance since pharmacy dispensing data was used as a surrogate marker for statin use. However, there is no reason to believe that rates of medication compliance would be different in cases and controls, particularly prior to uveitis diagnosis. Other information that was not available but would be interesting to investigate further is duration and dosage of statin use. A prior study suggested that longer duration of statin use may increase the protective association between statin use and ocular inflammatory disease.[31] Also, results of animal studies have shown that statin dosage may impact the degree of intraocular anti-inflammatory effects in experimental autoimmune uveitis.[29,30]

Additionally, it is possible that other confounding demographic and clinical characteristics could affect the association found in this study. However, multiple important confounding factors have been adjusted for in our analyses. Statins have been shown to have a protective association with several autoimmune diseases, such as inflammatory bowel disease, that are also positively associated with uveitis.[13] However, the protective association between statins and uveitis was persistent even after accounting for other autoimmune diseases.

Similarly, smoking has been positively associated with both uveitis and cardiovascular disease, a common indication for statin use.[45–47] A sensitivity analysis was done to adjust for smoking status, and this did not affect the association between statin use and uveitis. Information on history of stroke or myocardial infarction was not available for our population of patients. However, these comorbidities are unlikely to be confounders. A prior study investigating the association between statin use and ocular inflammatory disease adjusted for these comorbidities and found no significant effect.[31] Additionally, while there is a clear association between stroke and myocardial infarction and statin use, there is no association between these comorbidities and uveitis to our knowledge.[5–8] Furthermore, it is possible that there may be unknown confounders that have not been adjusted for in this study, but this is the case in all case control studies.

Despite these limitations, this study has several strengths. The charts of all uveitis patients in this study were individually reviewed by a uveitis specialist (NRA) to confirm that patients had an incident diagnosis of uveitis during the study period. Additionally, the results are strengthened by the population-based design since uveitis studies done in tertiary care centers may not be applicable to the general population.[48] Furthermore, Kaiser Hawaii has a racially diverse membership, providing data on a population which has not been studied frequently. Because only five percent of Kaiser Hawaii members had dual insurance that would facilitate receiving outside care, the Kaiser Hawaii electronic medical record likely provides comprehensive healthcare information on the membership during the study period.

In summary, the odds of developing uveitis for statin users were approximately half the odds for patients not taking this class of medications. In contrast to many other ophthalmic conditions that have previously been associated with statin use, such as glaucoma or age-related macular degeneration, uveitis disproportionately causes significant visual impairment in a younger population who may not already be on statin medications. These findings also raise the question of whether there could be a therapeutic benefit of statins once the diagnosis of uveitis is made with respect to the severity and course of disease. Prospective studies may be useful to investigate the role of statins in moderating the severity of prevalent disease. This is especially warranted given the relatively benign side effect profile of this class of medications compared to the systemic immunosuppressant therapies that are often required to treat more severe cases of uveitis.

Acknowledgments

A. **Funding/Support:** Dr. Acharya is supported by National Eye Institute grant U10 EY021125-01 (Bethesda, MD) and a UCSF Research Evaluation and Allocation Committee Award (San Francisco, CA). The UCSF Department of Ophthalmology is supported by National Eye Institute grant EY06190 (Bethesda, MD), That Man May See Foundation (San Francisco, CA), and an unrestricted grant from the Research to Prevent Blindness Foundation (New York, NY). The sponsors or funding organizations had no role in the design or conduct of this research.

B. **Financial Disclosures:** None of the authors have any financial or personal disclosures to report.

C. **Contributions of Authors in each of these areas:** Design of the study (DSB, NRA); Conduct of the study (DSB, VMT, ES, JVP, ACV, AU, NRA); Collection of data (DSB, VMT, ES, JVP, ACV, AU, NRA); Management of data (DSB, NRA); Analysis and interpretation of data (DSB, VMT, ES, JVP, ACV, AU, NRA); Preparation of manuscript (DSB, NRA); Review of manuscript (DSB, VMT, ES, JVP, ACV, AU, NRA); Approval of manuscript (DSB, VMT, ES, JVP, ACV, AU, NRA); Responsibility for the integrity of the entire study and manuscript (DSB, NRA).

D. **Other Acknowledgements:** none

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Biographies

Durga Borkar, MD, is a first year resident in ophthalmology at Massachusetts Eye and Ear Infirmary. She earned both her undergraduate and medical degrees at Northwestern University. During medical school, she completed a predoctoral research fellowship at the F.I. Proctor Foundation at UCSF, where she studied clinical outcomes in bacterial keratitis and the epidemiology of ocular inflammatory disease under the mentorship of Dr. Nisha Acharya and Dr. Thomas Lietman. She plans a career in academic ophthalmology.

Nisha R. Acharya, MD, MS, is Director of the Uveitis Service at the F.I. Proctor Foundation and Associate Professor in the Departments of Ophthalmology and Epidemiology and Biostatistics at the University of California, San Francisco. Dr. Acharya’s research interests include designing and implementing clinical trials and epidemiologic studies in the field of ocular infection and inflammation.

Table 1

Association between Statin Use and Uveitis: Demographic Data for Incident Uveitis Cases and Controls

	Incident Cases	General Controls	p-value	Ophthalmology Controls	p-value
Total	**108**	**540**		**540**	
Female	52 (48%)	302 (56%)	0.14[a]	291 (54%)	0.29[a]
Mean Age (years)	49.9	52.1	0.27[b]	62.5	<0.001[b]
Current Smoker	21 (19%)	75 (14%)	0.14[a]	47 (9%)	0.002[a]
Race[3]	N=82 (76%)	N=446 (83%)	0.04[a]	457 (85%)	0.28[a]
Alaskan/Native American	1 (1%)	10 (2%)		5 (1%)	
Asian	39 (48%)	166 (37%)		211 (46%)	
African American	2 (2%)	1 (<1%)		6 (1%)	
Pacific Islander	18 (22%)	134 (30%)		97 (21%)	
White	22 (27%)	135 (30%)		138 (30%)	

[a] P-value obtained by Fisher's exact test

[b] P-value obtained by two-sample mean comparison t-test

[c] Percentages for each race subgroup are listed in parentheses using the number of patients reporting race as the denominator

Table 2

Association between Statin Use and Uveitis: Clinical Characteristics of Incident Uveitis Cases and Controls

	Incident Cases	General Controls	p-value[a]	Ophthalmology Controls	p-value[a]
Total	**108**	**540**		**540**	
Medications					
Statins	21 (19%)	160 (30%)	0.03	204 (38%)	<0.001
High Dose Statins	2 (2%)	17 (3%)	0.75	14 (3%)	1.00
Other Lipid Lowering Agents	4 (4%)	25 (5%)	0.80	17 (3%)	0.77
Chronic Conditions					
Lipid Metabolism Disorder	44 (41%)	231 (43%)	0.75	295 (55%)	0.01
Diabetes	15 (14%)	118 (22%)	0.07	139 (26%)	0.01
Hypertension	36 (33%)	224 (41%)	0.13	280 (52%)	<0.001
Autoimmune Diseases[b]	8 (7%)	17 (3%)	0.051	20 (4%)	0.11

[a] P-values obtained by Fisher's exact test

[b] Includes reactive arthritis, sarcoidosis, Behcet's disease, multiple sclerosis, polyarteritis nodosa, granulomatosis with polyangiitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, inflammatory bowel disease, juvenile idiopathic arthritis, and systemic lupus erythematosus

Table 3

Association between Statin Use and Uveitis: Conditional Logistic Regression Models Predicting Incident Uveitis Diagnosis

	Cases vs. General Controls			Cases vs. Ophthalmology Controls		
	Odds Ratio	**95% CI**	**p-value**	**Odds Ratio**	**95% CI**	**p-value**
Statin Use	**0.5**	**0.3–0.9**	**0.03**	**0.7**	**0.4–1.2**	**0.17**
Age (by decade)	1.0	0.9–1.1	0.80	0.7	0.6–0.8	<0.001
Female	0.7	0.5–1.1	0.11	0.8	0.5–1.2	0.20
Race (ref=White)						
Alaskan/Native American	0.6	0.1–4.8	0.61	0.5	0.1–5.1	0.58
Asian	1.5	0.8–2.7	0.17	1.3	0.7–2.4	0.41
African American	10.4	0.9–123.0	0.06	1.4	0.2–8.2	0.71
Pacific Islander	0.8	0.4–1.6	0.49	0.9	0.4–1.9	0.81
Unknown	1.5	0.8–2.9	0.23	1.1	0.6–2.2	0.78
Autoimmune Disease	3.0	1.2–7.7	0.02	3.2	1.3–8.0	0.02