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Remission of Non-Infectious Anterior Scleritis: Incidence and Predictive Factors

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• PURPOSE: To assess how often non-infectious anterior scleritis remits and identify predictive factors.

• METHODS: Our retrospective cohort study at four ocular inflammation subspecialty centers collected data for each affected eye/patient at every visit from center inception (1978, 1978, 1984, 2005) until 2010. Remission was defined as inactivity of disease off all suppressive medications at all visits spanning at least three consecutive months or at all visits up to the last visit (to avoid censoring patients stopping follow-up after remission). Factors potentially predictive of remission were assessed using Cox regression models.

• RESULTS: During 1,906 years' aggregate follow-up of 832 affected eyes, remission occurred in 214 (170 of 584 patients). Median time-to-remission of scleritis = 7.8 years (95% confidence interval [CI]: 5.7, 9.5). More remissions occurred earlier than later during follow-up. Factors predictive of less scleritis remission included scleritis bilaterality (adjusted hazard ratio [aHR] = 0.46, 95% CI: 0.32-0.65); and diagnosis with any systemic inflammatory disease (aHR = 0.36, 95% CI: 0.23-0.58), or specifically with Rheumatoid Arthritis (aHR = 0.22), or Granulomatosis with Polyangiitis (aHR = 0.08). Statin treatment (aHR = 1.53, 95% CI: 1.03-2.26) within ≤90 days was associated with more remission incidence.

• CONCLUSIONS: Our results suggest scleritis remission occurs more slowly in anterior scleritis than in newly diagnosed anterior uveitis or chronic anterior uveitis, suggesting that attempts at tapering suppressive medications is warranted after long intervals of suppression. Remission is less frequently achieved when systemic inflammatory diseases are present. Confirmatory studies of whether adjunctive statin treatment truly can enhance scleritis remission (as suggested here) are needed. (Am J Ophthalmol 2021;223:377–395. © 2019 Published by Elsevier Inc.)

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INTRODUCTION

SCLERITIS IS DEFINED AS INFLAMMATION WITHIN THE scleral wall of the eye. Anterior scleritis usually creates symptoms of continuous deep, boring pain in the eye, associated with intense redness. Scleritis is potentially blinding via destruction of the eye wall, secondary intraocular and corneal inflammation, secondary glaucoma (often a complication of trabeculitis occurring as part of scleritis or of prolonged corticosteroid use), vision-

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threatening posterior segment complications such as exudative retinal detachment, and from other intraocular complications of corticosteroid treatment.[1–7] In a large series, nearly 60% of patients with scleritis developed ocular complications, with 16% developing visual loss over an unknown amount of follow-up time.[1] Scleritis is associated with a known underlying systemic immune-mediated disease in approximately 40% of cases.[1,3] Even when systemic disease is present, scleritis often requires treatment above and beyond what is needed for systemic disease management, increasing the burden of immunosuppressive therapy for affected patients. The classification system of Watson and Hayreh[7] subdivides scleritis into anterior and posterior scleritis. Anterior scleritis is further subdivided into "diffuse," "nodular," and "necrotizing" subtypes. The large majority of cases, approximately 80%, are non-infectious, non-necrotizing anterior scleritis, presumably of autoimmune etiology.[1]

• **PREVALENCE OF SCLERITIS:** Scleritis is an uncommon disease. If one accepts the conservative assumptions that one-third of scleritis patients have Rheumatoid Arthritis (RA),[2] that 0.7% of patients with RA have scleritis,[2] and that RA patients are adults, an estimate of the US prevalence of scleritis can be calculated from reports of the prevalence of RA in the US. The estimated US prevalence of RA in adults was 1,300,000 as of 2008.[8]

(1) Prevalence (RA) = 1,300,000.
(2) Number of Cases (Scleritis) = [Prev(RA)*0.007]/(1/3) = [(1,300,000)*0.007)]/(1/3) = 27,300 US cases.

In 2008, the US population was approximately 304,090,000 (http://www.multpl.com/united-states-population/table, accessed on March 20, 2018). Approximately 24% of these are children under 18 years (https://www.census.gov/quickfacts/fact/table/US/PST045217, accessed on March 20, 2018). Thus, the prevalence of scleritis among adults can be estimated:

(3) Prevalence in Adults (Scleritis) = (#Cases Scleritis)/(US Adult Popn) = (27,300/[(304,090,000)(0.76)] = 0.012%

A prevalence of 0.012% among adults in 2018, when the total population was 329, 429,111 (www.census.gov, accessed on March 28, 2018), would correspond to 39,531 cases of scleritis in adults. Because this estimate makes conservative assumptions, the true US prevalence may be higher, likely in the range of 45,000 individuals affected.

• **MANAGEMENT OF SCLERITIS:** Management of scleritis typically involves a sequential approach to suppress active disease and thus avoid inflammatory sequelae, beginning with oral non-steroidal anti-inflammatory drugs, progressing to oral corticosteroids and immunosuppressive agents for severe or recalcitrant disease.[9] The few available clinical trials regarding scleritis are early phase trials evaluating candidate treatments.[10–15] Initial use of immunosuppressive agents has been advocated for specific circumstances, e.g., patients with necrotizing scleritis.[16] Although only a small proportion of patients meet criteria for immediate use of immunosuppressive therapy, nearly two-thirds of cases in tertiary centers ultimately require oral corticosteroids and/or immunosuppressive agents.[1] Furthermore, a substantial number of cases exist which either are not successfully controlled with such therapy, or in which such therapy cannot be tolerated.[17] Scleritis also has been managed at times with local injections of depot corticosteroids,[18,19] which are controversial,[20,21] and sometimes with topical corticosteroids, which have limited effectiveness.[14]

Avoidance of the potential side effects of suppressive treatment is an important aspect of scleritis management. Oral non-steroidal anti-inflammatory drugs, which are effective only for a minority of patients with scleritis,[1] usually have few side effects but might increase the risk of life-threatening vascular disease with chronic use,[22] and can cause clinically important gastrointestinal toxicity in a substantial number of patients.[23] Among patients successfully controlled by systemic corticosteroids, a proportion of patients experience weight gain, sleeplessness, and Cushingoid habitus. In one report, complications of corticosteroid therapy included hyperglycemia (10%), osteoporosis (4.9% [possibly underestimated—bone densitometry was not done]), corticosteroid myopathy (2.4%) and psychosis (7.3%).[1] Immunosuppressive drugs also have potential toxicities which have to be avoided by use of monitoring protocols.[16] Concerns about increased cancer risk have been reported,[24] especially with alkylating agents[25] and possibly with Tumor Necrosis Factor inhibitors.[26] Periocular injections[27] and topical corticosteroid eye drops also have a substantial risk of side effects.[28,29]

However, it is important to note that side effects are infrequent with standard management protocols making side effect avoidance a priority. A recent prospective controlled clinical trial among intermediate, posterior and panuveitis patients suggests that with use of recommended approaches to use of systemic corticosteroids and immunosuppressants[16] the risk of such side effects are not significantly higher than with long-lasting intraocular therapy.[30] An evidence-based review concluded that the risk of cancer with immunosuppressive drugs likely is low (except perhaps with alkylating agents),[25] and primary data indicate that the risk of mortality does not seem to be affected with the more commonly used immunosuppressive drugs.[31]

• **REMISSION OF SCLERITIS:** Suppression of inflammation with active treatment is highly beneficial for patients with scleritis. Side effects can be minimized by appropriate management following the rheumatology paradigm, the

constraints imposed by limited effectiveness and side effect avoidance make scleritis management challenging, especially when ongoing therapy is required. Also, the approach has costs,[32] and is complicated to implement.[16] For this reason, remission (prolonged inactivity of scleritis off of suppressive medications) is the most desirable outcome of ocular inflammatory disease management.

Existing information on the remission of scleritis is limited to small case series. We previously reported that cyclophosphamide induces remission in about 63.1% of ocular inflammatory disease patients (about one-fourth with scleritis) within two years; however many patients were unable to tolerate cyclophosphamide, with 33.5% stopping within one year due to side effects.[33] Prior reports have not evaluated potentially predictive factors for remission. Such information would allow clinicians and patients to predict the chances of remission, decide when more aggressive therapy is justified, potentially modulate other modifiable risk factors to improve outcomes, and guide when to stop therapy after suppression of scleritis with active treatments. The risk of relapse after such remission is unknown.

• **GOALS OF THE THESIS:** This thesis holds forth that remission of scleritis is the ideal outcome of management and should be better characterized to see whether primary suppressive management could be supplemented to better enhance remission, and to better counsel patients regarding the likely incidence of remission in their case. We undertook an analysis of a large group of scleritis patients in order to characterize the clinical course of scleritis vis-à-vis remission incidence, and to identify potentially modifiable risk or protective factors. This work is undertaken as part of a larger assessment of the incidence of and risk factors for remission in various ocular inflammatory diseases.[34] We hypothesized that: a) The incidence of remission can be estimated with good precision; b) Alkylating agent but not other immunosuppressive therapies will be associated with a higher incidence of remission; c) Use of statins and angiotensin converting enzyme (ACE) inhibitors will be associated with a higher incidence of remission; and d) Other clinically relevant demographic and clinical predictors of remission will be identified. Our hypothesis regarding cyclophosphamide was based on the prior report mentioned above.[33] Our hypotheses regarding statins and ACE inhibitors were based on prior reports that use of statins is associated with a lower incidence of ocular inflammatory and systemic inflammatory disease,[35–39] and that ACE inhibitors have anti-inflammatory properties relevant to eye inflammation[40,41] and systemic disease.[39,42]

METHODS

• **HUMAN SUBJECTS PROTECTION:** The research was done as part of a large retrospective cohort study, the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study.[27,31,33,34,43–64] The SITE Cohort Study was initiated after approval by the governing institutional review boards at the collaborating centers. The principal collaborating centers included the University of Pennsylvania (Scheie Eye Institute), the Massachusetts Eye and Ear Infirmary, the Massachusetts Eye Research and Surgery Institute, the Johns Hopkins University School of Medicine (Wilmer Eye Institute), the Oregon Health and Sciences University (Casey Eye Institute), and the National Eye Institute. The primary institutional review board for the study initially was JHM-IRB 3 of the Johns Hopkins University School of Medicine (2004-2005), and subsequently was IRB#1 of the University of Pennsylvania Perelman School of Medicine (2005-present). All other participating centers' governing IRBs provided approval for the study, which was annually renewed to date. All centers granted approval for conduct of this retrospective cohort study (which did not involve any contact with study subjects), with exemption of consent and also provided HIPAA waivers. The approved study protocol involved review of medical records and linkage to the National Death Index and state cancer registries, although the linkage aspects are not relevant to the current report. The research was conducted in accordance with the Declaration of Helsinki and applicable United States federal and state laws. Although the study was not a clinical trial, as a National Eye Institute-funded clinically-oriented study it was registered at www.clinicaltrials.gov (NCT00116090).

• **STUDY POPULATION:** The SITE Cohort Study is a retrospective cohort study of patients with ocular inflammatory diseases seen at tertiary ocular inflammation centers. The participating centers were selected because they were frequent users of immunosuppressive therapy for ocular inflammatory diseases, which has become a standard of care for severe cases of ocular inflammation.[16,30] As part of the parent study (which is evaluating the risk of mortality and of cancer in association with immunosuppressive drugs),[31,44] we obtained data on every of eye of every patient meeting eligibility criteria at participating centers from the inception of the center's ocular inflammation subspecialty practice through December 31, 2010. Clinical centers contributing to this analysis, in order of the number of patients enrolled, included: the ocular inflammation practice of C. Stephen Foster, MD at Massachusetts Eye and Ear (Boston, Massachusetts, 1978-2005) and the Massachusetts Eye Research and Surgery Institution (Cambridge, Massachusetts, 2005-2010, now located in Waltham, Massachusetts); the Ocular Immunology Service of the Wilmer Eye Institute, Johns Hopkins University (JHU) School of Medicine, Baltimore, Maryland (1984-2010); the clinical service of the Laboratory of Immunology, National Eye Institute (NEI, Bethesda, Maryland, 1978-2010); and the Ocular Inflammation Service of the Scheie Eye Institute, University of Pennsylvania Perelman

School of Medicine (Penn) (2005-2010). Because the OHSU center participating in the mortality and cancer assessments of the study took a consultative, co-management approach for much of its history in which patients returned mostly if they were not doing well, time-to-remission data from that center are artificially long, and hence that center was excluded from this analysis. In the second phase of the SITE Cohort Study, additional data were collected from additional "ancillary" centers specifically to evaluate the safety of Tumor Necrosis Factor (TNF) inhibitors. Because data only were collected regarding TNF inhibitor-treated and matched patients as a comparison group rather than from the centers' entire experience, these data also were excluded on grounds that such patients may not be representative.

For the parent SITE Cohort Study, patients with any form of non-infectious, non-necrotizing anterior scleritis or other form of non-infectious ocular inflammation seen at a participating center during the study period had been included. Exclusion criteria for the parent study included; 1) infectious ocular disease; and 2) diagnosis with human immunodeficiency virus infection.[44] At each participating center, charts of eligible patients were identified either by manual search of all the service's records (during the paper record era), or by a search of electronic medical records for patients seen by the ocular inflammation specialist clinicians at each center. At JHU and Penn, manual search was aided by a prospectively generated comprehensive list of individuals seen at the center (done under a separate IRB approval at.JHU and under this study's IRB approval at Penn). Medical records thus identified were evaluated for eligibility; eligible patients were entered into the study as subjects. Prior publications report use of random sampling of a subset of patients at Dr. Foster's practice; nevertheless, the unsampled cases subsequently were entered to complete data entry for the entire experience of cases at all these centers through the end of 2010.

In summary, for this thesis, the subset of the SITE Cohort of eyes/patients at the Foster, Wilmer, NEI, and Scheie sites diagnosed with non-necrotizing anterior scleritis that was not currently in remission (active scleritis and/or using suppressive drugs) make up the cohort of interest.

• **DATA COLLECTION:** Data were obtained by standardized chart review conducted by expert reviewers under a standard protocol.[44] Expert reviewers included a total of nine ophthalmologists, one non-ophthalmologist physician, and two ophthalmic technicians, each trained in the study protocol, who entered data between 2004-2014 (see Credit Roster). To facilitate a highly structured, protocol-driven review process, a comprehensive Manual of Procedures was prepared, and a customized database prepared in Microsoft Access (Microsoft Corporation, Redmond, Washington, USA). The database includes internal checks in order to minimize erroneous data entry, allowing for real-time rectification of errors prior to chart closure. Data collected relevant to this analysis has included identifiers (kept only locally under protocol controls); and (as we have reported previously):

> "1) demographic characteristics; 2) primary and secondary ocular inflammatory diagnoses (with dates of diagnoses); 3) whether and over what time interval the patient received immunosuppressive therapy…; 4) whether eye disease was the indication for such treatment, and if so which eye disease(s);…6) what (if any) systemic disease diagnoses were carried by the patient at cohort entry and during follow-up (with date of diagnosis);….10) smoking status; and 11) all ocular surgeries with dates of surgery……In addition, data are collected at every visit regarding: 1) all medications in use [at every visit for every eye]… 4) inflammatory disease activity…".Credit Roster[44]

Data were entered based on the medical record, as read by the expert reviewer. In cases of uncertainty, queries were adjudicated by the ocular inflammation specialist directing the clinical center or by the Principal Investigator. The data were cleaned and reviewed for consistency; missing or incorrect values/charts were reviewed and corrected when possible. In addition, periodic in person and phone site visits to the study team members were conducted by the Principal Investigator to check samples of data against the medical records, especially during the early phases of each data enterer's work.

• **FOLLOW-UP AND STUDY VARIABLES OF INTEREST:** *Follow-up*. Observations of patients (or of eyes with ocular inflammation) included in the parent cohort were available from the time of their first visit at a participating center, and continued until their last visit at a participating center or until the end of the study period (December 31, 2010). Cases with active scleritis, or with inactive scleritis while taking suppressive medications at the first visit, were (retrospectively) followed over time. For those with non-necrotizing anterior scleritis not in remission at the first visit, person-time observed for remission of scleritis began from the person's first visit until the definition of scleritis remission (see below) was met for all eyes with scleritis or until the last visit. Similarly, eye-time observed for remission of scleritis began from the first visit when the eye began to be observed until remission was observed or follow-up ceased. Because some patients had one eye and some had two eyes with scleritis, and some of the risk factors of interest were characteristics of eyes, follow-up of eyes was the primary focus of the analysis.

To assess the occurrence of relapse of scleritis after remission, patients and their eyes were followed from the point of diagnosis with remission until scleritis activity or use of suppressive medications was observed, with person-time being

the corresponding follow-up time for patients and eye-time for eyes.

Observations for remission or relapse and for covariates of interest were entered for every visit. In by-eye analyses, patient-specific attributes were counted as covariates for each eye of the patient which had scleritis.

Primary definition of scleritis remission. The primary definition of scleritis *remission* is: "inactivity of scleritis off all suppressive medications at all visits spanning at least three consecutive months or else at all visits until and including the last visit in the study." This definition is a modification of the SUN Working Group expert consensus definition[65] which we adopted recognizing that some patients cease traveling for tertiary care as soon as quiescence of disease off medication occurs, such that remission is likely to be under-ascertained if only patients who continue follow-up after their disease is quiescent off treatment are counted.[60] "Suppressive medications" included oral non-steroidal anti-inflammatory drugs, systemic corticosteroids, topical corticosteroids, injected corticosteroids (within the last three months), immunosuppressive drugs (antimetabolites, T-cell inhibitors, alkylating agents or biologic immune response modifiers).[16,66,67]

Factors potentially predictive of scleritis remission. In order to explore the hypotheses of interest regarding the association of remission with characteristics and treatments of interest, the association of the following covariates to scleritis remission was assessed. Demographic characteristics studied included age at the beginning of follow-up; sex; and race/ethnicity. The categories of race/ethnicity were: White, Black, Hispanic (Hispanic ethnicity regardless of the race reported), or other. Additional patient-specific characteristics included smoking status (never smoked; former smoker; current smoker; or unknown smoking status); bilaterality of scleritis (bilateral vs. unilateral); and diagnosis with systemic inflammatory disease(s). The systemic inflammatory diseases evaluated included RA, spondyloarthropathy, Granulomatosis with Polyangiitis (GPA), Systemic Lupus Erythematosus (SLE) and others. In addition, other systemic diseases which have been suggested to be associated with ocular inflammation (diabetes mellitus)[68] or which are indications for medications of interest (hypertension, hyperlipidemia) were studied.

Medication use characteristics studied included the use within the last 90 days of statins, ACE inhibitors, and aspirin. Statins used by participants included: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin. ACE inhibitors used by participants included: zofenopril, perindopril, trandolapril, captopril, enalapril(at), fosinopril, monopril, lisinopril, prinivil, ramipril, benazepril, moexipril, quinapril, perindopril arginine, perindopril erbumine.

Treatment with alternative categories of immunosuppressive drugs also were evaluated, with alkylating agents, antimetabolites, TNF inhibitors, rituximab, and other immunosuppressants each compared with those treated with any of the remaining categories of immunosuppressives, to evaluate the hypothesis that alkylating agents are more likely than other immunosuppressants to cause remission.

Eye-specific characteristics of interest included the time since scleritis diagnosis at the time of presentation; severity of inflammation at the time of presentation (inactive, slightly active, active); and history of prior cataract surgery. "Slightly active" scleritis was defined as "Activity that is minimally present, described also by terms such as mild, few, trace etc." Prior glaucoma surgery and vitrectomy surgery also were considered, but were too rare to evaluate (five eyes and one eye respectively).

• **STATISTICAL ANALYSIS:** The incidence of remission of scleritis was estimated as the number of observed remissions divided by the eye-time or person-time observed for remission; 95% confidence intervals were constructed assuming a Poisson distribution. Eye-time observed for remission was used for assessment of eye-specific events, including remission of scleritis. Person-time observed for remission was used for assessment of person-specific events. The association of potentially predictive factors with scleritis remission was assessed through Cox regression, to account for various lengths of follow-up across eyes with scleritis. Graphs illustrating associations between covariates associated with remission were generated using the Kaplan-Meier method.

Because some risk factors are at eye level, the statistical analysis was an analysis of the outcome of eyes with non-necrotizing anterior scleritis; the method of Lin and Wei[69] was used to adjust Cox regression for non-independence (correlation) of eyes of the same patient. Patient-specific factors were counted as present for both eyes of the same patient when both eyes were included in the analysis. Time-updating of covariates that vary over time was done as indicated above. The 90 day lag to allow time for statins, ACE inhibitors and aspirin potentially to induce remission of scleritis to act was selected in favor of instantaneous effects based on exploratory data analysis. For the comparison of the immunosuppressive drugs in inducing remission, in order to account for treatment that began prior to the first visit in the study, a staggered entry Cox regression was used, adjusted for the same factors as in the primary analysis. We did not compare immunosuppressant-treated cases with non-immunosuppressant cases because of the large indication-for-treatment bias expected with such a comparison.

Sensitivity analyses were conducted repeating the analyses with two alternative outcome definitions, to evaluate whether results were consistent across potential alternative definiitions. First, a stricter definition of the outcome was

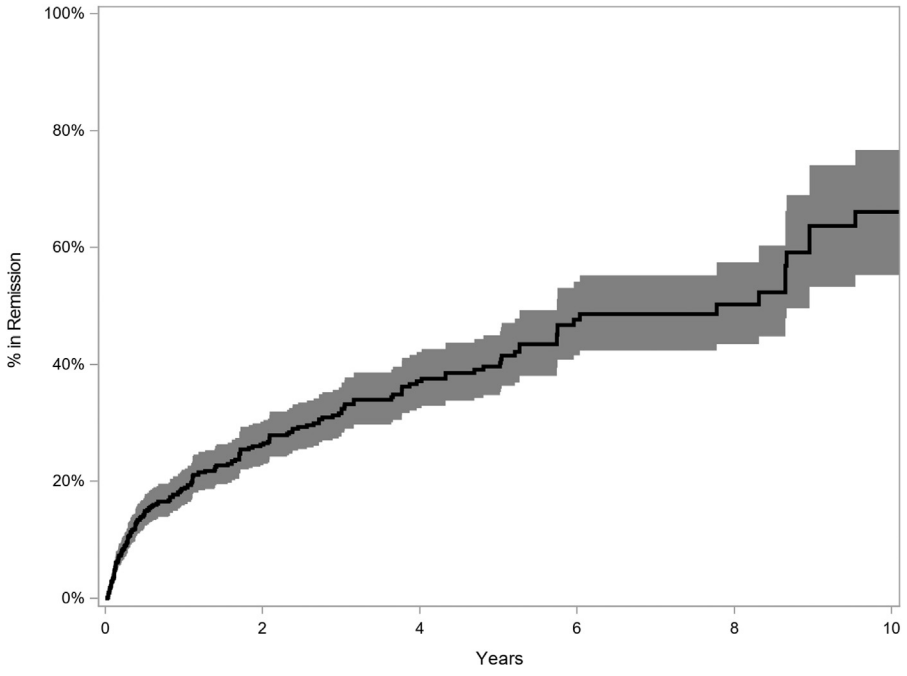

FIGURE 1. Overall Time-to-Remission of Scleritis: Estimated overall time-to-remission among participants in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study; eyes with non-infectious, non-necrotizing scleritis. 95% confidence bands are indicated in gray. The median time-to-remission was 7.8 years.

used, in which remission was not counted unless three consecutive months of inactivity off all suppressive medications was observed before follow-up ended, corresponding to the SUN Working Group's definition of remission of ocular inflammatory disease.[65] Second, a sensitivity analysis counting eyes graded as either inactive or slightly active off suppressive medications as in remission according to the strict definition was conducted.

RESULTS

DATA REGARDING 842 PATIENTS (1,208 AFFECTED EYES) with scleritis were available in the database from the four sites. Among these, 43 patients/79 affected eyes already met criteria for remission at the initial visit; because these were not at "risk" of remission during follow-up, they were excluded. An additional 215 patients/297 eyes had no follow-up after initial consultation. Thus, there were 584 patients (69% of those not in remission at the first visit) with 832 eyes with non-necrotizing anterior scleritis in at least one eye which was active and/or on suppressive medication with sufficient follow-up to be assessed for remission in this report. These were followed for a total of 1,251 person-years (1,906 eye-years) for remission. During this time, remission was observed in 170 patients (see Figure 1), an incidence of 16.4% per person-year (95% confidence interval (CI): 13.8%-19.4%)). Remission occurred more often in the early years of follow-up, but there were progressively more cases of remission in each passing year. Using the more strict definition of remission, 116 remissions were observed, with an incidence of 8.8% per person-year (95% CI: 7.1%-10.9%), with the same general pattern of progressively more remission over time.

From an eye-specific perspective, 214 remissions were observed, with 18.7%, 26.2% and 39.6% estimated remission by one, five and ten years, and estimated 50% remission by 7.8 years (95% CI on median: 5.7-9.5 years), with progressively more cases of remission with each passing year. The overall remission incidence was similar across the four centers (overall $P = .20$). Excluding scleritic eyes of patients with systemic inflammatory disease, the time-to-remission was shorter/more favorable (see predictive factor analysis below), with a median time-to-remission of 3.9 years (95% CI on median: 3.0-5.8 years; interquartile range 0.86 years to 8.67 years).

• **CHARACTERISTICS OF THE STUDY COHORT:** Regarding patients (n = 584), most were middle aged or older adults (155 [26.5%] age > 60 years, 288 (49.3%) ages 40-59 years vs. 141 (24.1%) 39 years or less at presentation). There were more females (387, 66.3%) than males (197, 33.7%), and more persons of white (361, 61.8%) than of other races/ethnicities. About half of patients (297, 50.9%) had bilateral scleritis. Most patients presented with active inflammation in at least one eye: 398 active (69.5%), 44 (7.7%) slightly active, and 131 (22.7%)

TABLE 1. Association of Demographic Characteristics with Remission of Non-infections, Non-Necrotizing Anterior Scleritis, Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study[a]

		Remission		Crude		Adjusted[b]	
	Total	No	Yes	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Age at presentation, Years							
<40	195 (23%)	167 (86%)	28 (14%)	Ref	.004	Ref	.02
40+	637 (77%)	451 (71%)	186 (29%)	2.09 (1.27, 3.45)		1.83 (1.12, 3.01)	
Sex							
Male	284 (34%)	213 (75%)	71 (25%)	Ref	.12	Ref	.17
Female	548 (66%)	405 (74%)	143 (26%)	1.33 (0.93, 1.90)		1.30 (0.89, 1.90)	
Race/Ethnicity category							
White	503 (60%)	363 (72%)	140 (28%)	Ref	.89	Ref	.83
Black	127 (15%)	92 (72%)	35 (28%)	0.96 (0.63, 1.48)		1.04 (0.70, 1.54)	
Hispanic	24 (3%)	17 (71%)	7 (29%)	1.23 (0.52, 2.91)		0.72 (0.23, 2.26)	
Other	178 (21%)	146 (82%)	32 (18%)	0.87 (0.54, 1.40)		0.85 (0.51, 1.39)	

CI = Confidence Interval; Ref = Reference Group.

[a]Eyes with scleritis.

[b]Adjusted for baseline inflammatory activity, bilateral disease, duration of scleritis prior to presentation, baseline inflammatory activity, rheumatoid arthritis, and statin use

inactive while taking suppressive medication. Most also presented taking suppressive medications (even though many were not suppressed at the time of presentation): 197 (33.7%) on NSAIDs, 325 (55.7%) on corticosteroids, and 112 (19.2%) on immunosuppressive drugs; in all, 443 (75.9%) were on one or more of the three medication categories at presentation. Among the patients, 210 (36.0%) had an associated inflammatory systemic disease, of which the most common diagnoses were RA (97 persons, 16.6%), SLE (26 persons, 4.4%), and GPA (20 persons, 3.5%). In addition, 53 (9.1%) had diabetes mellitus; 187 (32.0%) had hypertension and 83 (14.2%) had hyperlipidemia (diseases for which medications of interest are used as treatments).

Tables 1-5 describe the study cohort eyes, wherein characteristics of patients are counted as characteristics of each of their eyes with scleritis for bilateral cases. Regarding eyes (E = 822), about two thirds were from patients with bilateral scleritis (544, 65.4%), as expected given that about half of patients had bilateral scleritis. The majority of eyes were of patients who presented for clinical care within less than six months after onset of disease (457, 54.7%), with 171 (20.6%) presenting at six months or later but before two years, 111 (13.3%) presenting at two years or later but before five years, and 93 (11.2%) presenting five or more years after onset of symptoms. Most cases of scleritis by eye had a diffuse pattern (677, 81.4%); the remainder had a nodular pattern (155, 18.6%) [necrotizing cases were excluded, see methods]. Few eyes had undergone ocular surgery prior to presentation, only 44 (5.3%) having undergone cataract surgery, 5 (0.6%) glaucoma surgery and 1 (0.1%) vitrectomy surgery.

• **FACTORS PREDICTIVE OF REMISSION:** Associations were assessed for the primary outcome and two sensitivity analyses using the by-eye assessment, because some factors were eye-specific. The sensitivity analysis with a more strict outcome definition (remission off of suppressive medications observed over visits spanning 90 days or more) had fewer cases which sometimes resulted in non-significance of results significant in other analyses, but otherwise the results were similar in all three analyses unless otherwise noted below. The sensitivity analysis counting "slightly active" as "inactive" in general had very similar results to the primary analysis.

Demographic characteristics. The relationship between demographic factors studied and the incidence of scleritis remission is summarized in Table 1. Higher age tended to be associated with a higher incidence of remission in the crude analysis, but after adjustment for other factors (see adjustment factors, footnote Table 1) the association was mitigated and not statistically significant. Incidence of remission was similar among males and females, and among White, Black, Hispanic, and Other races/ethnicities.

Clinical characteristics. The relationship between clinical characteristics of eyes and scleritis remission is given in Table 2. A similar number of patients with unilateral (88, 30.7%) and bilateral (83, 27.9%) had remission in at least one eye. Among bilateral cases, 43 had bilateral remission, and 40 had remission in one of two eyes, making the remission incidence among eyes of bilaterally affected patients lower (aHR = 0.46, 95% CI: 0.32, 0.65, see Figure 2). Eyes with a shorter clinical history of

TABLE 2. Association of Clinical Characteristics with Remission of Non-Infections, Non-Necrotizing Anterior Scleritis, Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study[a]

		Remission		Crude		Adjusted[b]	
	Total	No	Yes	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Smoking							
Never	554 (67%)	409 (74%)	145 (26%)	Ref	.61	Ref	.67
Past	95 (11%)	68 (72%)	27 (28%)	1.07 (0.68, 1.70)		0.87 (0.56, 1.35)	
Current	132 (16%)	100 (76%)	32 (24%)	0.92 (0.59, 1.44)		0.89 (0.57, 1.39)	
Unknown	51 (6%)	41 (80%)	10 (20%)	0.61 (0.28, 1.32)		0.64 (0.29, 1.44)	
Nodular/Diffuse							
Diffuse	677 (81%)	504 (74%)	173 (26%)	Ref	.92	Ref	.47
Nodular	155 (19%)	114 (74%)	41 (26%)	1.02 (0.68, 1.53)		0.85 (0.55, 1.31)	
Bilateral Scleritis							
No	288 (35%)	200 (69%)	88 (31%)	Ref	<.001	Ref	<.001
Yes	544 (65%)	418 (77%)	126 (23%)	0.42 (0.31, 0.58)		0.46 (0.32, 0.65)	
Prior Duration of Scleritis							
<6 Months	457 (55%)	314 (69%)	143 (31%)	Ref	.007	Ref	.03
6 Months to <2 Years	171 (21%)	141 (82%)	30 (18%)	0.57 (0.35, 0.93)		0.66 (0.40, 1.09)	
2 to <5 Years	111 (13%)	99 (89%)	12 (11%)	0.36 (0.18, 0.72)		0.36 (0.18, 0.76)	
5+ Years	93 (11%)	64 (69%)	29 (31%)	0.77 (0.49, 1.21)		0.80 (0.49, 1.31)	
Prior Cataract Surgery							
No	788 (95%)	583 (74%)	205 (26%)	Ref	.66	Ref	.57
Yes	44 (5%)	35 (80%)	9 (20%)	1.16 (0.59, 2.27)		0.81 (0.39, 1.68)	
Inflammatory Activity at Baseline							
Inactive	226 (29%)	175 (77%)	51 (23%)	Ref	.03	Ref	.04
Slightly active	59 (8%)	39 (66%)	20 (34%)	2.11 (1.21, 3.67)		1.92 (1.14, 3.24)	
Active	492 (63%)	368 (75%)	124 (25%)	1.26 (0.88, 1.79)		1.07 (0.75, 1.54)	

CI=Confidence Interval; Ref = Reference Group.

[a]Eyes with scleritis.

[b]Adjusted for baseline inflammatory activity, bilateral disease, duration of scleritis prior to presentation, baseline inflammatory activity, rheumatoid arthritis, and statin use

scleritis prior to presentation had a higher incidence of remission than longstanding cases (overall $P = .03$; Figure 3). In the sensitivity analyses, a similar pattern was seen. Prior ocular surgery was infrequent, limiting power to assess association between prior surgery and incidence of remission. Prior cataract surgery was not associated with remission. In addition, presentation with slightly active inflammation was associated with a higher incidence of remission than presenting with inactive inflammation while taking suppressive treatment (aHR = 1.92, 95% CI: 1.14, 3.24, Figure 4) or active inflammation. However, this pattern of association was not observed in the strict sensitivity analysis. Nodular vs. diffuse patterns of scleritis did not have substantial differences in the incidence of remission, nor was smoking associated with significant differences in the incidence of remission.

Associated systemic inflammatory diseases. The relationship between diagnosis with systemic inflammatory diseases and scleritis remission is given in Table 3. Diagnosis with a systemic inflammatory disease in aggregate was associated with an approximate 64% lower (less favorable) incidence of remission (aHR = 0.36, 95% CI: 0.23, 0.58, Figure 5). The most common systemic inflammatory disease, RA, was associated with a 78% lower incidence of remission (aHR = 0.22, 95% CI: 0.11, 0.43, Figure 6); in the sensitivity analyses a similar association was seen. Granulomatosis with Polyangiitis—like RA a disease which often requires therapy with drugs used to suppress scleritis—also was associated with lower incidence of scleritis remission (aHR = 0.08, 95% CI: 0.01-0.59, Figure 7). Relapsing Polychondritis (aHR = 0.14, 95% CI: 0.02, 1.10) and SLE (aHR = 0.57, 95% CI: 0.22, 1.46) also tended to have a lower scleritis remission incidence, but not to a statistically significant degree. Crohn's disease and Ulcerative Colitis did not have a strong association with remission incidence after adjusting for other variables. Sjögren Syndrome and spondyloarthropathies in general showed little association with scleritis incidence. Several other inflammatory diagnoses listed in the Characteristics section above tended to have lower incidences for remission, but with very small

TABLE 3. Association of Coexisting Systemic Inflammatory Diseases with Remission of Non-infections, Non-Necrotizing Anterior Scleritis, Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study[a]

		Remission		Crude		Adjusted[b]	
	Total	No	Yes	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Any Systemic Inflammatory Disease[c]							
No	517 (62%)	350 (68%)	167 (32%)	Ref	<.001	Ref	<.001
Yes	315 (38%)	268 (85%)	47 (15%)	0.28 (0.19, 0.41)		0.36 (0.23, 0.58)	
Rheumatoid Arthritis							
No	682 (82%)	480 (70%)	202 (30%)	Ref	<.001	Ref	<.001
Yes	150 (18%)	138 (92%)	12 (8%)	0.21 (0.11, 0.41)		0.22 (0.11, 0.43)	
Granulomatosis with Polyangiitis							
No	802 (96%)	589 (73%)	213 (27%)	Ref	.02	Ref	.01
Yes	30 (4%)	29 (97%)	1 (3%)	0.10 (0.01, 0.71)		0.08 (0.01, 0.59)	
Systemic Lupus Erythematosus							
No	791 (95%)	583 (74%)	208 (26%)	Ref	.08	Ref	.24
Yes	41 (5%)	35 (85%)	6 (15%)	0.43 (0.17, 1.10)		0.57 (0.22, 1.46)	
Relapsing Polychondritis							
No	812 (98%)	599 (74%)	213 (26%)	Ref	.06	Ref	.06
Yes	20 (2%)	19 (95%)	1 (5%)	0.14 (0.02, 1.06)		0.14 (0.02, 1.10)	
Spondyloarthropathy							
No	812 (98%)	604 (74%)	208 (26%)	Ref	.85	Ref	.97
Yes	20 (2%)	14 (70%)	6 (30%)	0.90 (0.32, 2.54)		1.02 (0.35, 3.02)	
Sjögren Syndrome							
No	817 (98%)	606 (74%)	211 (26%)	Ref	.55	Ref	.63
Yes	15 (2%)	12 (80%)	3 (20%)	0.68 (0.19, 2.40)		0.73 (0.19, 2.72)	
Crohn's Disease							
No	817 (98%)	609 (75%)	208 (25%)	Ref	.76	Ref	.98
Yes	15 (2%)	9 (60%)	6 (40%)	0.86 (0.33, 2.22)		1.01 (0.48, 2.11)	
Ulcerative Colitis							
No	823 (99%)	612 (74%)	211 (26%)	Ref	.56	Ref	.97
Yes	9 (1%)	6 (67%)	3 (33%)	1.47 (0.41, 5.32)		1.02 (0.37, 2.83)	

CI=Confidence Interval; Ref=Reference Group.

[a]Eyes with scleritis.

[b]Adjusted for baseline inflammatory activity, bilateral disease, duration of disease prior to presentation, baseline inflammatory activity, rheumatoid arthritis, and statin use.

[c]Any Systemic Inflammatory Disease = Rheumatoid Arthrtis, Systemic Lupus Erythematosus, Granulomatosis with Polyangiitis, Relapsing Polychondritis, Spondyloarthropathy (any form), Sjögren Syndrome, Crohn's Disease, Ulcerative Colitis, Sarcoidosis, Giant cell arteritis, Scleroderma, Juvenile Idiopathic Arthritis, Polymyositis, Polyarteritis Nodosum, Behçet Disease, and/or Dermatomyositis. Among these diseases, those not listed separately in this Table had five or fewer Observations each.

numbers of cases their relationship to remission incidence was inconclusive.

Diabetes mellitus, hypertension, hyperlipidemia, and use of selected medications. The association of diagnosis with diabetes mellitus, hypertension, hyperlipidemia, or use of ACE Inhibitors, statins, or aspirin and scleritis remission is given in Table 4. Diagnosis with diabetes mellitus (aHR = 0.79, 95% CI: 0.47-1.33) was not associated with differences in scleritis remission incidence. Diagnosis with hypertension (aHR = 0.92, 95% CI: 0.65-1.31) was not associated with a higher incidence of remission compared with patients not carrying such a diagnosis. Diagnosis with hyperlipidemia was not associated with a higher incidence of remission (aHR = 1.36, 95% CI: 0.84-2.22). Results were similarly negative in the sensitivity analyses.

Eyes of patients taking statin drugs within the last 90 days experienced a higher incidence of remission than those not taking statins (aHR = 1.53, 95% CI: 1.03, 2.26, Figure 8). The sensitivity analyses were consistent with this result. Use of ACE inhibitors (aHR = 1.16, 95% CI: 0.71-1.89), aspirin (aHR = 0.81, 95% CI: 0.40, 1.62), and topical non-steroidal anti-inflammatory drugs (aHR = 0.59, 95% CI: 0.08, 4.66) within the last 90 days were not associated with differences in the incidence of scleritis remission.

Use of Immunosuppressive Medications. The relationship between use of immunosuppressive therapies (comparing

TABLE 4. Association of Diabetes, Hypertension, Hyperlipidemia and Use of Selected Medications with Remission of Non-Infections, Non-Necrotizing Anterior Scleritis, Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study[a]

Cox Model of Remission (Including for <90 Days if Final Visits)

		Remission		Crude		Adjusted[b]	
	Total	No	Yes	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Diabetes Mellitus							
No	753 (91%)	559 (74%)	194 (26%)	Ref	.73	Ref	.38
Yes	79 (9%)	59 (75%)	20 (25%)	0.92 (0.56, 1.49)		0.79 (0.47, 1.33)	
Hypertension							
No	557 (67%)	420 (75%)	137 (25%)	Ref	.93	Ref	.64
Yes	275 (33%)	198 (72%)	77 (28%)	0.98 (0.70, 1.38)		0.92 (0.65, 1.31)	
ACE Inhibitors Within 90 days							
No	755 (91%)	568 (75%)	187 (25%)	Ref	.36	Ref	.55
Yes	77 (9%)	50 (65%)	27 (35%)	1.24 (0.79, 1.94)		1.16 (0.71, 1.89)	
Hyperlipidemia							
No	712 (86%)	545 (77%)	167 (23%)	Ref	.003	Ref	.21
Yes	120 (14%)	73 (61%)	47 (39%)	1.77 (1.21, 2.60)		1.36 (0.84, 2.22)	
Statins Within 90 days							
No	737 (89%)	560 (76%)	177 (24%)	Ref	.01	Ref	.03
Yes	95 (11%)	58 (61%)	37 (39%)	1.69 (1.11, 2.55)		1.53 (1.03, 2.26)	
Aspirin Within 90 days							
No	779 (94%)	574 (74%)	205 (26%)	Ref	.77	Ref	.54
Yes	53 (6%)	44 (83%)	9 (17%)	0.90 (0.45, 1.81)		0.81 (0.40, 1.62)	

CI = Confidence Interval; Ref = Reference Group; ACE = Angiotensin Converting Enzyme.

[a]Eyes with scleritis.

[b]Adjusted for baseline inflammatory activity, bilateral disease, duration of disease prior to presentation, baseline inflammatory activity, rheumatoid arthritis, and statin use

one class to the other classes combined) and scleritis remission is given in Table 5. In comparing the outcomes of alternative immunosuppressive drugs started from the beginning of observation, all the drugs tended to be associated with lower incidence of remission in the crude analysis compared to the adjusted analysis—as expected given that such drugs typically are given for severe cases and those associated with systemic inflammatory disease. After adjustment, the incidence of remission was not significantly higher for any immunosuppressive category compared with the others combined. Results were similar comparing immunosuppressants to each other looking at outcomes beyond two years (so as to take into account practice patterns of not tapering certain immunosuppressants until that point).

• **RELAPSE OF SCLERITIS AFTER REMISSION:** Patients who continued to follow-up after experiencing remission met the strict definition of remission (no activity observed over visits spanning at least three months with no suppressive medications), given that they continued to follow-up. Among these 214 eyes of 170 patients, 98 eyes of 80 patients had no further follow-up after meeting the strict definition of remission, leaving 116 eyes of 90 patients followed prospectively for relapse over 169 person-years (231 eye-years).

Among those who continued follow-up, the incidence of relapse among these eyes is described in Figure 9. 86.0% remained in remission after one year. The median time-to-relapse after remission was 5.81 years (95% CI: 2.03, 11.8), and the estimated proportion relapse free through five years was 54.1%.

DISCUSSION

IN THIS LARGE STUDY OF THE INCIDENCE OF REMISSION among eyes with non-infectious, non-necrotizing anterior scleritis, we found that a substantial number of remissions occur over time. In fact, the results suggest that the majority of cases remit given enough follow-up time. The proportion remaining active and/or on medication declined over time, with a tendency for more cases going into remission early on after presentation to the ocular inflammation subspecialty clinic and less remissions as time went on. Nevertheless, additional cases went into remission with each passing year through at least ten years. Taking a more strict definition (in which cases were not counted unless observed to be inactive off medications for at least 90 days rather than counting cases if they met criteria for

TABLE 5. Association Between Use of Classes of Immunosuppressive Therapies (Compared with Alternative Immunosuppressive Therapy Classes) and Remission of Non-infections, Non-Necrotizing Anterior Scleritis, Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study[a]

Cox Model of Remission (Including for <90 Days if Final Visits)

		Remission		Crude		Adjusted[b]	
	Total	No	Yes	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Alkylating agent							
No	134 (74%)	127 (95%)	7 (5%)	Ref	.82	Ref	.79
Yes	46 (26%)	43 (93%)	3 (7%)	1.18 (0.27, 5.19)		0.85 (0.26, 2.78)	
TNF inhibitor							
No	110 (61%)	100 (91%)	10 (9%)	Ref	[c]	Ref	[c]
Yes	70 (39%)	70 (100%)	0 (0%)	[c]		[c]	
Antimetabolite							
No	29 (16%)	27 (93%)	2 (7%)	Ref	.93	Ref	[d]
Yes	151 (84%)	143 (95%)	8 (5%)	0.91 (0.13, 6.41)		[d]	
Rituximab							
No	177 (98%)	167 (94%)	10 (6%)	Ref	[c]	Ref	[c]
Yes	3 (2%)	3 (100%)	0 (0%)	[c]		[c]	
Other IST							
No	161 (89%)	152 (94%)	9 (6%)	Ref	.71	Ref	.98
Yes	19 (11%)	18 (95%)	1 (5%)	0.63 (0.06, 7.15)		1.02 (0.22, 4.76)	

[a]Adjusted for age, bilateral disease, duration of disease prior to presentation, baseline inflammatory activity, rheumatoid arthritis, and statin use.
[b]IMTs are time-updated and reflect current or any previous use, n (%) reflect the number of patients at time of censor or remission.
[c]There were insufficient numbers of TNF inhibitor- and rituximab-treated cases to derive stable hazard ratio estimates.
[d]Due to perfect correlation with adjustment variables, adjusted hazard ratio could not be estimated.

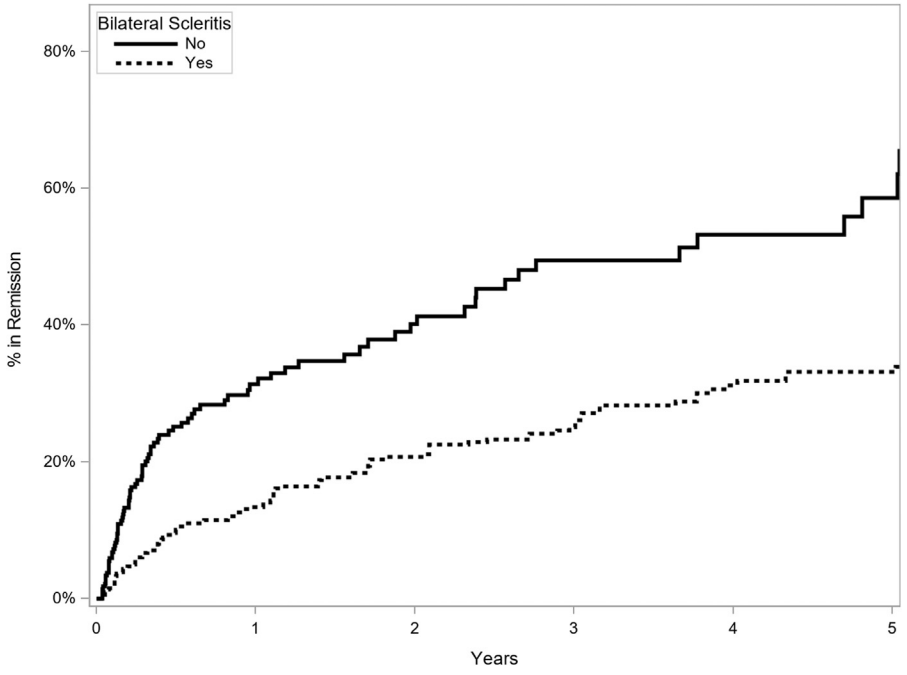

FIGURE 2. Remission of Scleritis by Bilaterality vs. Unilaterality of Scleritis: Estimate of the time-to-remission by whether the contralateral eye was involved with scleritis (bilateral) or not (unilateral). Eyes with contralateral eye involvement had a 54% lower rate of incidence of remission ($P < .001$). [Among participants in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study; eyes with non-infectious, non-necrotizing scleritis.]

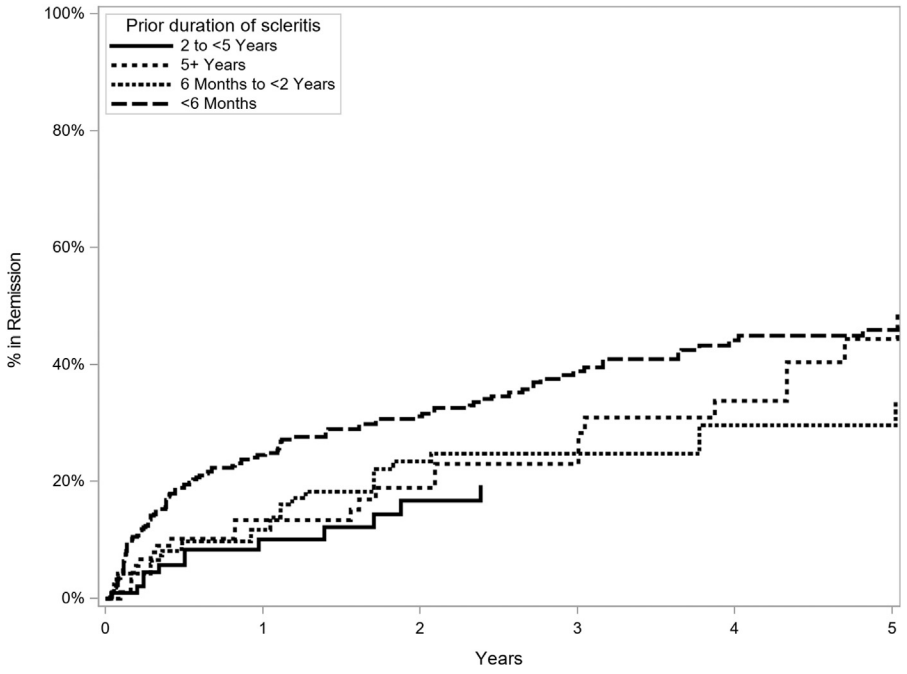

FIGURE 3. Remission of Scleritis by Duration of Disease: Estimated time-to-remission by time since diagnosis of scleritis as of the time of cohort entry. Eyes diagnosed with scleritis within six months prior to cohort entry had the most favorable incidence of scleritis remission.

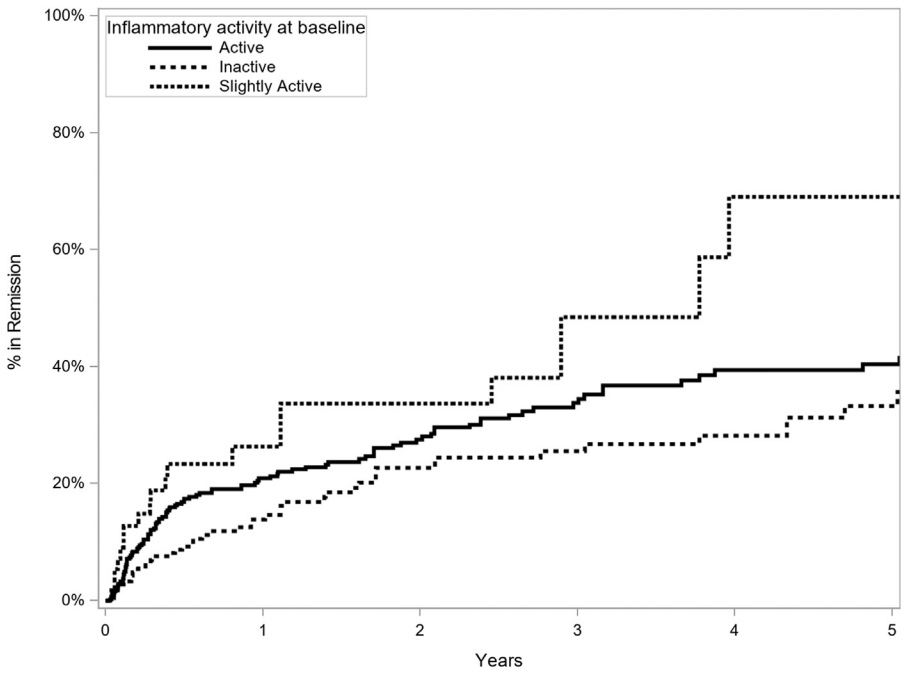

FIGURE 4. Remission of Scleritis by Level of Activity at Baseline: Estimate of the time-to-remission by whether the eye with scleritis presented with inactive inflammation while taking suppressive therapy (inactive, count of eyes [E] = 226), minimally active inflammation (Slightly active, E = 59), or clearly active inflammation (Active, E = 492). Eyes with slightly active inflammation tended to have a higher incidence of remission (overall P = .04). [Among participants in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study; eyes with non-infectious, non-necrotizing scleritis.]

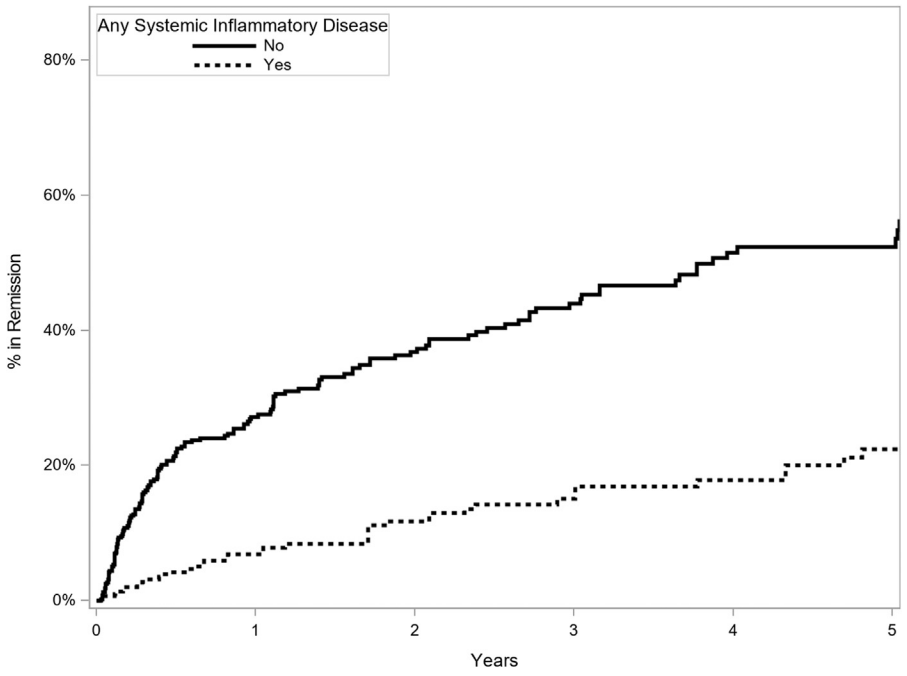

FIGURE 5. Remission of Scleritis by the Presence or Absence of a Systemic Inflammatory Disease: Estimate of the time-to-remission by whether the patient whose eye was assessed had a systemic inflammatory disease or not. Systemic inflammatory diseases considered are listed in the text. Eyes of patients with systemic inflammatory diseases had an approximate 64% lower incidence of remission ($P < .001$). [Among participants in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study; eyes with non-infectious, non-necrotizing scleritis.]

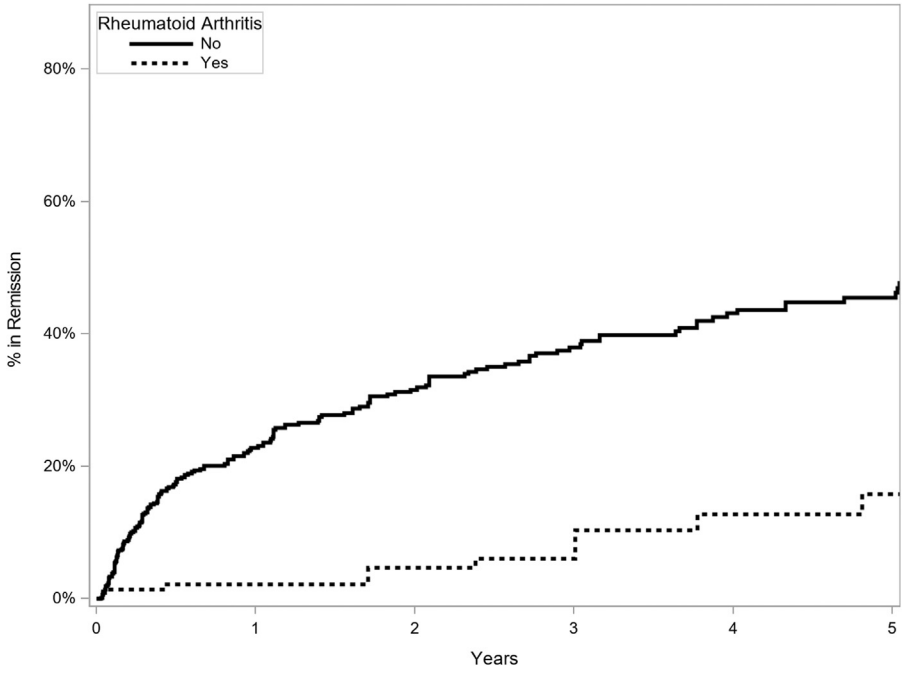

FIGURE 6. Remission of Scleritis by the Presence or Absence of Rheumatoid Arthritis: Estimate of the time-to-remission by whether the patient whose eye was assessed had rheumatoid arthritis or not. Eyes of patients with rheumatoid arthritis had an approximate 78% lower incidence of remission ($P < .001$). [Among participants in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study; eyes with non-infectious, non-necrotizing scleritis.]

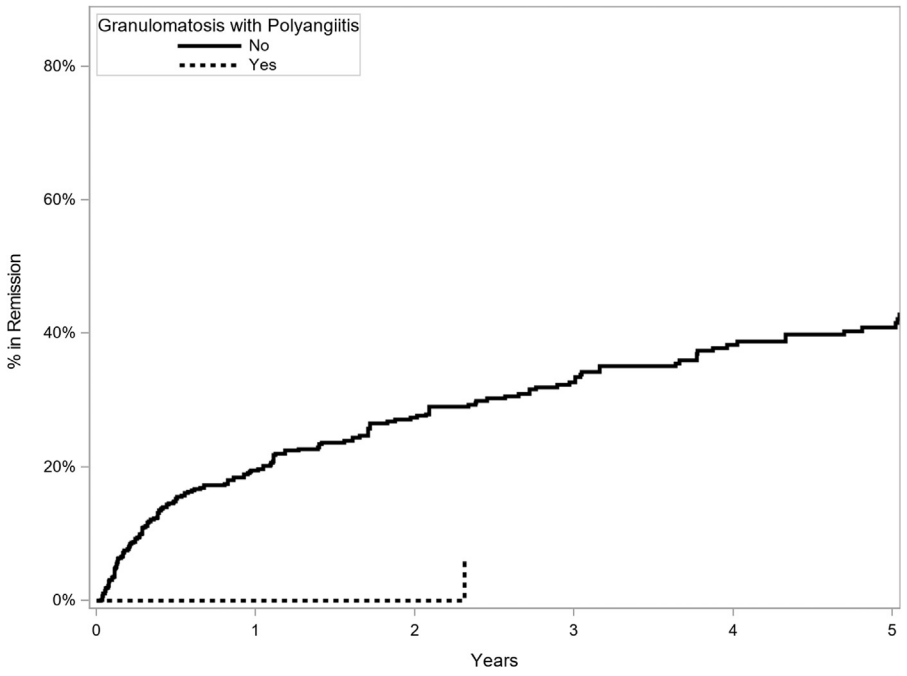

FIGURE 7. Remission of Scleritis by the Presence or Absence of Granulomatosis with Polyangiitis: Estimate of the time-to-remission by whether the patient whose eye was assessed had Granulomatosis with Polyangiitis or not. Eyes of patients with Granulomatosis with Polyangiitis had an approximate 92% lower incidence of remission ($P = .01$). [Among participants in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study; eyes with non-infectious, non-necrotizing scleritis.]

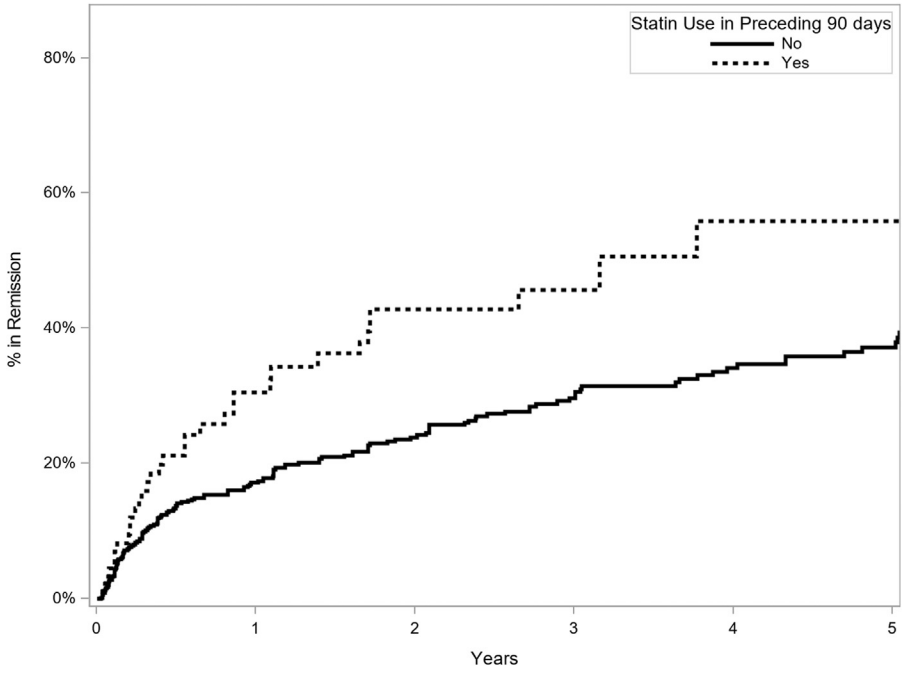

FIGURE 8. Remission of Scleritis by Use vs. Non-Use of Statins: Estimate of the time-to-remission by whether the patient whose eye was assessed had taken statins (HMG-CoA Reductase Inhibitors) in the last 90 days or not (time-updated analysis). Eyes of patients taking statins tended to have a higher incidence of remission, best estimated as a 53% higher incidence of remission ($P = .03$). [Among participants in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study; eyes with non-infectious, non-necrotizing scleritis.]

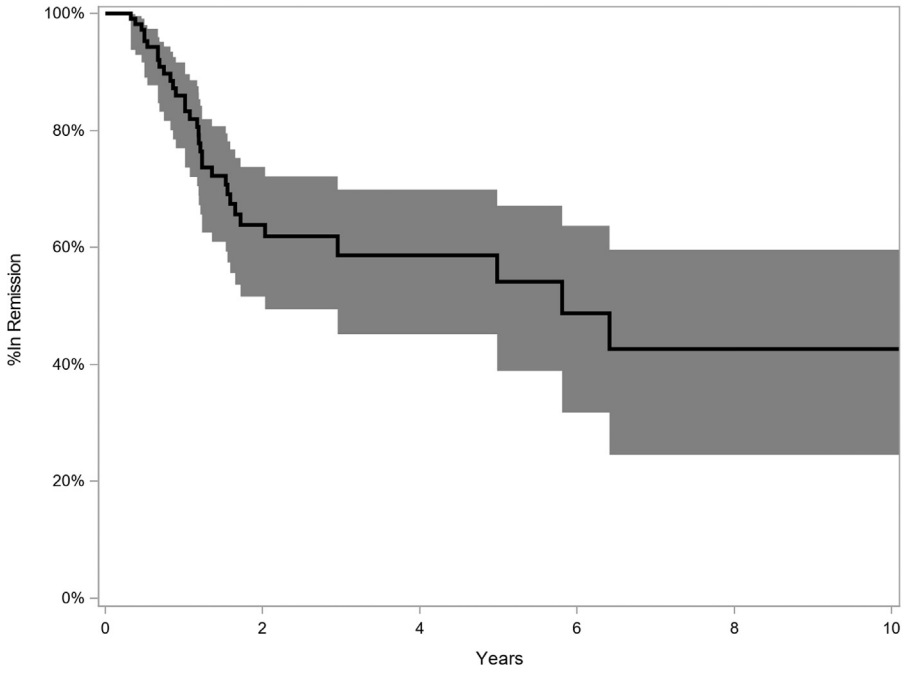

FIGURE 9. Relapse of Scleritis After Occurrence of Remission: Estimated overall time-to-relapse among eyes with non-infectious, non-necrotizing scleritis from the point at which remission of scleritis was observed. [Among participants in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study.] 95% confidence bands are indicated in gray. The median time-to-relapse was 5.8 years.

remission then no longer followed-up after scleritis became inactive off of suppressive medication), the estimated incidence of remission would be substantially less, but the general conclusion that remission occurs in a substantial proportion of cases given enough time still would be correct. The primary outcome definition of remission used in this study might slightly overestimate the number of remissions. However, given that patients are likely to cease long-distance travel for tertiary care once disease is inactive while not taking suppressive medication, it is likely that the true remission incidence in a tertiary ocular inflammation practice is close to that of our primary analysis, and higher than that in the more strict sensitivity analysis. This supposition is supported by the observation that large numbers of cases stopped follow-up before three months after obtaining inactivity off suppressive treatment, and many more had no further visits after three months of inactivity off suppressive medication. Given that cases managed at tertiary centers such as these tend to be more severe, it is likely that the incidence of remission for scleritis cases presenting to general ophthalmology practices is higher/more favorable.

The incidence of remission for scleritis tended to be less than with new onset cases of anterior uveitis,[60] but more favorable than among cases of intermediate uveitis,[34] each managed in the same ocular inflammation subspecialty centers with data collected as part of the same study. Thus far, data are not available to compare the incidence of remission with that for other forms of ocular inflammation.

Several potentially clinically important factors predictive of remission incidence were observed in this study. Our results supported the hypothesis that statins might improve remission of scleritis, with about a 50% more favorable incidence of remission observed among scleritis cases treated with statins within the last 90 days, whereas hyperlipidemia (the condition for which statin therapy is most often indicated) was not associated with a change in remission incidence—especially after adjusting for statin therapy. Given that statins are well-tolerated in most clinical scenarios, but that observational data have limitations (see below), this result suggests that such treatment should be assessed further to determine whether statins have a role as a treatment to induce remission in cases of scleritis. Further assessment is important because statins in particular have been observed to be associated with a "healthy user effect" (users of statins tend to be more healthy than non-users) which might produce false positive associations.[70] However, given relatively strong preliminary data and rationale to predict effect, further exploration of the relationship between scleritis remission and statins seems justified given that such treatment would provide a relatively safe means of inducing remission of a troublesome disease if future results support the approach.

Additional clinically relevant factors predictive of the incidence of scleritis remission also were identified, although the others were of a non-modifiable nature. Unilaterality of scleritis also was identified as a favorable prognostic factor for remission, as also has been reported for new onset anterior uveitis[60] but not for intermediate uveitis.[34] Bilaterality may indicate more severe disease. Also, given that eyes may be asymmetric in their severity or clinical course, it may be less likely that suppressive therapy will be stopped in bilateral cases, which may explain part of this association.

The presence of systemic inflammatory disease associated with scleritis was in general a predictor of an approximate 64% lower incidence of remission, consistent with the idea that more widespread disorder of immunity may indicate more severe disease that is less likely to remit. RA and GPA specifically were associated with substantially lower incidences of remission of scleritis (78% and 92% lower respectively). However, part of these associations may arise from a greater need of immunosuppressive drugs for treatment of the associated systemic disease, leading to misclassification of some cases as not in remission (regarding the eye manifestation of scleritis). However, the very strong associations observed for RA and especially GPA in contrast to other systemic inflammatory disorders which showed less association suggest that at least these may be real associations with lower scleritis remission. Despite our inability to sort out whether patients with scleritis and systemic inflammatory disease continue to get suppressive medications for the scleritis or the systemic inflammatory disease or both, the results are useful in predicting that the chances of a patient with scleritis and systemic inflammatory diseases experiencing prolonged quiescence of scleritis without a need to take suppressive medications are less than patients with scleritis without systemic inflammatory disease.

Some factors we expected to be associated with scleritis remission proved to be non-associated in our analysis. Smoking has been implicated as a factor associated with more incidence of anterior uveitis,[71] with more recurrence (although not with differences in remission) for ocular inflammatory diseases in general,[51] a greater likelihood of presenting for ophthalmic care with various kinds of uveitis,[72] and with occurrence of macular edema in intermediate uveitis,[72,73] However, our results provide little evidence that smoking is an important factor for remission of scleritis. Nodular vs. diffuse presentation of scleritis did not presage appreciable differences in the incidence of remission. Ocular surgery prior to presentation was infrequent, limiting power to test associations with scleritis remission, but no association was observed for cataract surgery.

Regarding the effect of immunosuppressive therapy on remission, our method had a number of limitations to address the issue. First, receiving the therapy itself leads to the case being classified as not in remission, and most cases are treated for a protracted period of time before tapering is attempted to see if remission has occurred; for this reason we only could compare drugs with each other. In general, the drugs were similar to each other regarding associations with scleritis remission.While rituximab has been noted to induce remission in reported cases of scleritis,[74,75] our results do not provide evidence one way or the other regarding whether rituximab is better than alternative immunosuppressants in inducing remission; our number of observations regarding rituximab was very small. We previously reported that for all forms of ocular inflammation in aggregate, cyclophosphamide resulted in remission of approximately 63% of patients who did not suffer toxicity requiring cessation of therapy within two years. However, 33.5% of patients starting cyclophosphamide stopped therapy within one year as a result of side effects.[33] Thus, cessation of therapy may have tended to cancel out any advantage of alkylating agents compared with the other immunosuppressants in this analysis. Comparing immunosuppressants' association with remission from two years onward (corresponding to the practice pattern used by some of our clinicians) did not find statistically significant differences either.

Relapse of scleritis after remission occurred in a large proportion of the patients who continued follow-up, but the large majority of these remained in remission for years. Furthermore, given that a large number of cases did not follow-up even for three months after apparent remission, the incidence of relapse may be substantially lower (more favorable) than our estimates suggest. It is likely that the cases which continued to be followed at the participating tertiary centers were at higher risk of relapse than those who did not return; in fact many may have returned precisely because a relapse of scleritis had occurred, whereas those without relapse for years would have not had a need to return for tertiary care, and often probably did not do so. Thus, the relapse incidence described here should be interpreted as an upper limit on the range of plausible incidence rates for relapse after remission, which still is relatively favorable. These results suggest that most remitted cases remain in remission for years, but not necessarily for the rest of their lives.

Limitations of this study include its retrospective, observational nature, including a limited duration of follow-up which requires us to generalize results from periods under follow-up vs. periods after patients have ceased coming for clinical care. Because patients may come for care less after improvement of their clinical condition, remission estimates may be somewhat low. Most likely, the true incidence is closer to that observed for the primary outcome than the strict analysis, as discussed above. As also noted above, this concern about differences between patients continuing to be followed and those lost to follow-up is probably even more important for our assessment of the incidence of relapse after remission. Another limitation is conduct of the study at tertiary centers, where cases are expected to be more severe than they would be if

they could be obtained from a general population sample. This limitation likely led to underestimation of the incidence of remission in non-tertiary settings, although our results likely are a reasonable estimate of the experience a tertiary ocular inflammation center is likely to have. These problems probably are less relevant to investigation of potential risk factors, as the limitations are likely to affect groups with and without a risk factor similarly. With the number of observations our ability to assess the relationship between several rare systemic inflammatory diseases and scleritis remission was limited. However, the power was more favorable for assessing association for more common systemic inflammatory disorders. As is typical for an epidemiological study, the assessment involves multiple comparisons without adjusting *P*-values for the multiple looks, so results should be confirmed by additional research.

The study had several strengths, including a very large study population, which improves precision to assess the incidence of scleritis remission, and to assess the relationship with a wide number of potentially predictive factors of interest, including the ability to address the hypotheses of interest. Potential risk factors were identified in advance of occurrence of the events of interest, avoiding recall bias problems. Also, sensitivity analyses generally came to the same conclusions about associations of predictive factors with remission. However, it would be valuable to confirm the predictive factors identified given that this was an observational study prior to embarking on treatment to induce remission of scleritis.

In summary, our results suggest that most cases of non-infectious anterior scleritis will remit given enough time. Clinicians should not assume perpetual suppression will be necessary for all cases, but should take into account the possibility of remission and should consider tapering off of suppressive therapy periodically. Perhaps such taper attempts should be after progressively longer intervals of suppression, given that remission occurred more frequently in the early years after presentation than in the later ones. Our results are less robust in addressing relapse after remission, but suggest that most remitted cases will be relapse-free after remission for well over a year; nevertheless remitted patients should be warned of the possibility of relapse. Systemic inflammatory diseases tend to be associated with a lower incidence of remission of scleritis, perhaps in part because they may in themselves serve as an indication for ongoing use of suppressive therapies. The non-modifiable predictive factors observed in this study should be relevant for counseling patients and making clinical decisions regarding the probability of remission over time. The study identified a promising association suggesting that statins might be useful to increase the incidence of remission. Because well-tolerated, low risk medications like statins would be desirable as treatments to induce remission of scleritis, further study to confirm this association is warranted. These observations provide a preliminary suggestion that ancillary treatments or adjustment of scleritis-suppressing treatment strategies to enhance the incidence of remission might be a valuable adjunct to primary treatment with NSAIDs, corticosteroids and/or immunosuppressants to control anterior scleritis.

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