

Adherence to Ophthalmologic Monitoring for Antimalarial Toxicity in a Lupus Cohort

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ABSTRACT. *Objective.* Antimalarial agents (hydroxychloroquine and chloroquine) are important in the treatment of various rheumatic diseases, including systemic lupus erythematosus (SLE). Although these agents may lead to ocular complications, little is known about adherence to policies for ophthalmologic monitoring. We investigated adherence to the 1996 American College of Rheumatology (ACR) guidelines (recommending yearly ophthalmologic assessments) at our clinic, and determined the factors associated with nonadherence.

Methods. Chart review of the Montreal General Hospital lupus clinic cohort.

Results. Of 195 subjects with at least one full year of antimalarial exposure during 1996–2001, 5 refused participation and data on ophthalmology monitoring was incomplete for 42. Of the remaining 148 patients, 47 (32%) had missed at least one annual ophthalmology assessment (were nonadherent) during the interval; almost half of these had missed ≥ 2 assessments. Nonadherence was present in 50% of the 52 patients who had been taking an antimalarial agent for ≥ 5 years. In adjusted logistic regression models, cumulative damage (measured by the Systemic Lupus International Collaborating Clinics/ACR Damage Index) and antimalarial exposure ≥ 5 years were predictive of nonadherence. Adjusted estimates indicated a 1.2-fold increase (95% CI 1.0, 1.5) in the odds of nonadherence for every point increase in the total Damage Index score. The adjusted OR for individuals exposed to an antimalarial for ≥ 5 years was 5.2 (95% CI 2.1, 13.8).

Conclusion. Our results indicate incomplete adherence to ACR guidelines at our center. Because patients with higher Damage Index scores were more likely to have missed ophthalmology appointments, even after adjusting for pertinent covariates, it suggests that sicker patients may be more at risk of nonadherence. The association of nonadherence with duration of antimalarial exposure, while not surprising, is still an important reminder that adherence to ophthalmologic monitoring may decrease as risk for retinal toxicity is increasing. (J Rheumatol 2003;30:1756–60)

Key Indexing Terms:

OPHTHALMOLOGIC MONITORING ANTIMALARIAL TOXICITY LUPUS

Antimalarial agents [hydroxychloroquine (HCQ) and chloroquine] are widely used in the treatment of various rheumatic diseases, including systemic lupus erythematosus (SLE). It is recognized that the use of these agents may lead to ocular complications, but little is known about adherence to standard policies regarding ophthalmologic monitoring. Recently, Blomquist and Chundru¹ examined current practices for screening for HCQ toxicity. They determined that most ophthalmologists report that they follow patients taking HCQ semiannually for the development of retinal complications, and that the majority perform slit lamp, color vision, and visual field evaluations. The authors acknowl-

edge that self-report data may be “suspect.” In a 1997 survey of current practices among British specialists prescribing HCQ for their patients, the majority reported that their patients were followed by an ophthalmologist for baseline and followup examinations². Similar findings were noted in another recent North American survey of rheumatologists³. Although these attempts to assess the practice of ophthalmologic monitoring are of interest, no one, to our knowledge, has determined to what extent the guidelines are actually employed in practice. We compared the current practice (in our cohort of patients with SLE) with standards suggested in 1996 by the American College of Rheumatology (ACR), recommending ophthalmologic assessments at least yearly, with the performance of visual field testing, for all patients taking an antimalarial agent⁴.

MATERIALS AND METHODS

The setting for this study was the Montreal General Hospital (MGH) Lupus Clinic, a university affiliated specialty clinic, where care for the period 1996–2001 was jointly provided by 2 subspecialists (a rheumatologist and an immunologist). The patients studied were members of the MGH lupus clinic cohort, begun in 1977. Each member has a clinical diagnosis of SLE according to ACR criteria^{5,6}. Consecutive patients are enrolled in the cohort at the time of presentation, and for this study we considered all individuals

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that had entered the cohort up to and including 2001. As of this time, the cohort numbered 399 individuals. We identified all patients who had been exposed to HCQ or chloroquine, using data from the cohort database and clinic chart. Subjects were asked for the name of the ophthalmologists who provided their care and permission to review their records. The clinic charts at our institution were examined. In cases where patients had been seen at an ophthalmology clinic outside our institution, ophthalmologists were contacted for information about the dates that the patients were seen and the assessments performed. The study was approved by the MGH ethics review board, with approval to review the MGH charts of patients who were deceased or lost to followup.

For patients with at least one full year of exposure during 1996–2001, we determined if ophthalmology monitoring occurred according to ACR guidelines. Data were obtained from the cohort database and medical records regarding stop and start dates and dosage of antimalarials, as well as relevant demographic and clinical data including SLE duration and damage, as assessed by the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index⁷. We determined frequency of ophthalmologic visits and whether visual field tests were done. During the observation interval, the routine procedure when beginning an antimalarial agent was as follows: patients were instructed (by the treating lupus clinic specialist) about the possible adverse effects and the need for annual ophthalmology examinations. If a patient was not already followed by an ophthalmologist, a referral was made with requests for a baseline evaluation and followup to monitor for retinal toxicity. If the patient had no ocular complaints, the clinic providers did not await the baseline ophthalmology assessment before beginning the antimalarial agent.

Statistical analysis. Descriptive statistics for the subjects included calculation of means (or proportions, as applicable) with 95% confidence intervals (CI), using the exact method for proportions. The number of patients who missed at least one annual ophthalmology assessment (allowing for a 3 month “grace period”) during 1996–2001 was used to calculate a simple proportion of nonadherence, as well as the number and proportion who had missed 2 or more annual assessments. Logistic regression (using SAS software) was performed to determine the factors associated with missing at least one ophthalmology visit. We considered duration of antimalarial exposure, patient age, sex, race, chloroquine exposure, and SLE duration and damage, in models that adjusted concurrently for each of the other factors. (History of ever-exposure to chloroquine was included, as this agent confers a greater risk of retinal toxicity than HCQ.) In this model, we also included dummy variables indicating whether the patient was followed by a retinal specialist versus a general ophthalmologist, and whether the ophthalmology practice was located at an academic center or in the community.

RESULTS

Out of 399 patients in the cohort, data on antimalarial use were available on 359 (90%); 305 of the 359 patients (85%) were or had been taking an antimalarial agent. Of these 305, 278 (91%) were or had been taking HCQ alone, 2 chloroquine alone, and 25 had been exposed to both at some time during their disease course. A total of 195 patients had at least one full year of exposure during 1996–2001. Of these, 5 did not wish to participate in this study. Eight patients were deceased, but information was available from the clinic records regarding their ophthalmology care. For 17 patients lost to followup, it could not be determined who the treating ophthalmologist had been, and for 25 patients, data on ophthalmologic monitoring were incomplete. Thus data on ophthalmologic monitoring were complete on 148 patients. Mean SLE duration and years of exposure to anti-

malarial medications for these 148 patients [average SLE duration 13.5 yrs (standard deviation 9.4) and average yrs of exposure 4.1 (SD 3.9)] were similar to those of the patients with missing data on ophthalmology monitoring [12.9 yrs (SD 6.3) and 4.2 yrs (SD 1.8)]. Age, sex, and race were also similar between the 2 groups (Table 1), as was the average level of education (13 yrs, SD 3). Of the 190 subjects with at least one full year of exposure during 1996–2001, 117 (62%) were followed by an ophthalmologist within our center (86 of these by the same ophthalmologist, a retinal specialist), 3 were followed by an ophthalmologist affiliated with another academic center, 51 were followed by an ophthalmologist in the community, and 2 did not recall being referred to an ophthalmologist (both patients were beginning their second year of HCQ use). In most cases ophthalmology assessments included, at a minimum, visual acuity, visual field testing, and funduscopy, and all but one ophthalmologist also regularly employed color vision testing.

Of the 148 patients for whom data were complete, 47 (32%) had missed at least one annual ophthalmology assessment during the interval 1996–2001; 45% of these had missed 2 or more. Of 52 patients who had been taking an antimalarial agent for 5 years or more, half had missed at least one annual ophthalmology assessment during the interval 1996–2001. Assuming that the 42 subjects for whom we did not have complete data also missed at least one annual ophthalmology assessment, the figure for nonadherence in the total group of 190 patients would be 42%. Of the patients studied, 2 (both with a history of prior exposure to chloroquine) developed symptomatic retinal changes consistent with antimalarial toxicity. These events occurred after 15 years of antimalarial exposure in one individual, and after 33 years of exposure in the other. Both patients appeared to have been dosed appropriately. One of these patients had not attended the prescribed schedule for ophthalmology monitoring.

In the logistic regression models (which concurrently adjusted for patient age, sex, race, SLE duration, cumulative damage, ever-use of chloroquine, duration of antimalarial exposure, and characteristics of the ophthalmology practice), cumulative damage score and antimalarial exposure ≥ 5 years were associated with missing one or more annual ophthalmology assessment. The adjusted odds ratio (OR) for SLE cumulative damage indicated a 1.2-fold increase (95% confidence interval 1.0, 1.5) in the odds of nonadherence for every point increase in the total SLICC/ACR Damage Index score. The adjusted OR for individuals who had taken an antimalarial for more than 5 years was 5.2 (95% CI 2.1, 13.8). Type of ophthalmology practice (university affiliated vs community) did not predict nonadherence, and rates of nonadherence were similar across all the ophthalmologists providing care to patients in this sample.

Table 1. Description of patients in the Montreal General Hospital lupus clinic cohort who were exposed to an antimalarial agent for at least one year during the interval 1996–2001.

	Mean	95% CI
Patients without data available from ophthalmologist (n = 42)		
SLICC/ACR total score*	2.2	0, 7.6
Age**	43.5	20.3, 66.7
Proportion		
Female	0.98	0.88, 1.0
Caucasian	0.74	0.58, 0.87
Deceased	0	0, 0.08
Ever exposed to chloroquine	0	0, 0.08
Patients with data available from ophthalmologist (n = 148)		
SLICC/ACR total score	2	0, 5.7
Age	46.7	16.2, 77.2
Proportion		
Female	0.90	0.84, 0.94
Caucasian	0.76	0.68, 0.83
Deceased	0.05	0.02, 0.10
Ever exposed to chloroquine	0.07	0.04, 0.13

* Score reflects damage as assessed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index, accumulated from the time of SLE onset to the last recorded assessment in the Montreal General Hospital Lupus Clinic. ** Age as recorded at last assessment in the Montreal General Hospital Lupus Clinic.

DISCUSSION

Our results indicate there is incomplete adherence to ACR guidelines in current practice at our center, and we suspect that this may be quite a universal phenomenon. Of course, it is unclear to what extent our results reflect incomplete adherence by the physicians to the guidelines, versus incomplete adherence by the patients to the physicians' recommendations. However, the level of adherence observed in our study is actually rather high compared to other examples of studies on guideline adherence, such as a recent Canadian study where adherence to preventive care guidelines in general practice was only 41%⁸. The relatively high adherence observed in our study is perhaps not surprising, since the MGH Lupus Clinic is a university based clinic run by specialists, and it has been suggested that specialists (vs primary care physicians) and university based clinics (vs non-university settings) adhere more closely to guidelines^{9–12}. Indeed, physician and clinic characteristics have been identified as more important than patient related characteristics¹¹.

We note that patients with higher SLICC/ACR Damage Index scores were more likely to have missed ophthalmology appointments, even when patient age and duration of SLE and of antimalarial exposure were controlled for. One hypothesis might be that sicker patients may be more at risk of missing ophthalmology assessments, perhaps because more life-threatening issues are being attended to. We acknowledge that the SLICC/ACR Damage Index does not itself measure SLE disease activity or severity (there is no accepted tool to measure SLE "severity," and instruments

to assess SLE activity^{13,14} apply only to a single point in time). However, SLICC scores are a well validated outcome measure that capture total damage accumulated from the time of SLE onset to the time of assessment⁷, and have been shown to reflect the effects of *cumulative* disease activity^{15,16} and to correlate with clinical severity¹⁶.

We point out that the American Academy of Ophthalmology has very recently recommended that young patients properly dosed (based on ideal body weight) need only be examined once in the first 5 years, with increased focus on closer monitoring as the cumulative exposure increases¹⁷. A case of relatively early (i.e., after less than 8 years of therapy) maculopathy developing despite regular monitoring has been recently reported¹⁸. We continue to advocate ophthalmology assessments at least yearly for patients under our care who are receiving antimalarial agents.

Thus, our results indicate incomplete adherence to ACR guidelines in current practice at our center, which we suspect may be quite a universal phenomenon; adherence to ophthalmology monitoring may be somewhat less in other clinics (since the literature suggests that, for example, guideline adherence is generally better within university settings). An association of nonadherence with duration of antimalarial exposure is, one may suggest, to be expected, but it is still an important reminder that adherence to ophthalmologic monitoring may fall off just as risk for retinal toxicity may begin to increase¹⁷. We also suggest that, at least at our center, nonadherence may be higher in sicker patients. We have thus begun to endorse the use of simple reminder sheets placed prominently within patient

charts, to indicate whether the patient exposed to an anti-malarial has recently been seen by his or her ophthalmologist. A sample template for this is appended.

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APPENDIX

A reminder sheet placed within patient charts to indicate whether the patient exposed to an antimalarial has recently been seen by the ophthalmologist.

Record of Ophthalmology Assessments for Patients on an Antimalarial Agent (Hydroxychloroquine or Chloroquine)

Patients with abnormal renal function or those who have received an antimalarial agent for more than 10 years require more frequent ophthalmologic evaluation. Hydroxychloroquine dose should not exceed 6.5 mg/kg ideal body weight in patients with normal renal function (lower doses are advocated for patients with significant hepatic or renal impairment).

Patient Name: _____

Date first exposed to an antimalarial agent: _____

Check if abnormal renal function Patient's Ideal Body Weight * _____

Date of Review	Agent & Current Dose	Date of Last Ophthalmology Visit	Visual Fields Test
			<input type="checkbox"/> Y <input type="checkbox"/> N
			<input type="checkbox"/> Y <input type="checkbox"/> N
			<input type="checkbox"/> Y <input type="checkbox"/> N
			<input type="checkbox"/> Y <input type="checkbox"/> N
			<input type="checkbox"/> Y <input type="checkbox"/> N
			<input type="checkbox"/> Y <input type="checkbox"/> N
			<input type="checkbox"/> Y <input type="checkbox"/> N
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			<input type="checkbox"/> Y <input type="checkbox"/> N
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			<input type="checkbox"/> Y <input type="checkbox"/> N

*Ex. Men: Ideal Body Weight (in kilograms) = 52 kg + 1.9 kg for each inch over 5 feet. Women: Ideal Body Weight (in kilograms) = 49 kg + 1.7 kg for each inch over 5 feet (Am J Hosp Pharm 1983;40:1016-9).

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