Retinal Complications in Patients with Systemic Lupus Erythematosus Treated with Antimalarial Drugs

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ABSTRACT. ***Objective.*** Hydroxychloroquine (HCQ) and chloroquine (CQ) are key drugs in systemic lupus (SLE) and related diseases. Retinal toxicity remains the most worrisome complication. We studied factors potentially associated with retinal toxicity, using case-control analyses.

Methods. Within our SLE clinic cohort, we identified patients with retinal changes using the Systemic Lupus International Collaborating Clinics Damage Index. We confirmed HCQ/CQ retinopathy with chart review, and selected up to 3 SLE controls for each case, matched by age at SLE diagnosis and SLE duration.

Results. Over an average 12.8 years of followup, within 326 patients exposed to antimalarial drugs, 18 (5.5%) developed retinal toxicity. The minimum number of years of HCQ/CQ exposure before retinopathy developed was 8 years (maximum 33 yrs). Median HCQ/CQ duration was statistically similar in cases [19 yrs, interquartile range (IQR) 14–20] and controls (16 yrs, IQR 11–22), likely due to our matching on SLE duration. Versus controls, cases tended to have more renal disease (cases 22.2%, controls 14.8%) and were slightly less likely to be white (cases 61.1%, controls 74.1%), but neither variable reached statistical significance. Among patients with retinal toxicity, the number previously exposed to CQ was more than 3 times that in controls.

Conclusion. Just over 5% of patients developed antimalarial retinal complications, over an average of 12.8 years. No cases were detected in the first 5 years of therapy. Past CQ use was more common in cases versus controls. Future studies using larger cohorts are under way to better define the roles of therapy duration, race/ethnicity, and other factors. (First Release February 1 2020; J Rheumatol 2020;47:553–6; doi:10.3899/jrheum.181102)

Key Indexing Terms:
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Hydroxychloroquine (HCQ) and chloroquine (CQ) are widely used to treat autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE). In addition, several promising clinical trials that are under way indicate that these quinolones could be used to treat diabetes mellitus, cancer, and cardiovascular diseases[1]. This growing list of clinical indications implies that a better understanding of the complications associated with their use will become invaluable. Retinopathy remains the most important complication, being uncommon but irreversible[2]. Little is known about the pathophysiology underlying the retinal toxicity observed in patients taking these compounds over several years. Our objective was to study HCQ/CQ retinopathy occurring in patients followed at the SLE clinic of Montreal General Hospital and to determine factors associated with retinal complications. Conformity to ophthalmologic assessments as per recent American Academy of Ophthalmology (AAO) recommendations was also evaluated[1].

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MATERIALS AND METHODS

Data were extracted from the McGill University Health Centre (MUHC) Lupus Clinic registry. Patients with a clinical diagnosis of SLE according to American College of Rheumatology (ACR) criteria[3] have been consecutively enrolled in the cohort. Patients are followed with annual research visits, during which data are systematically collected on demographics, drugs, disease activity, and organ damage. Upon enrollment, each patient's written informed consent to publish the data is obtained. We identified all patients who were ever exposed to HCQ and/or CQ and determined those who had scored positive for retinal change as assessed by the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI). The assessment was systematically updated at each visit[4]. The SDI item describes retinal change as that "documented by ophthalmologic examination, may result in field defect, legal blindness," which has been present for at least 6 months. It does not specify the cause of the pathology. Thus these cases were reviewed to confirm HCQ/CQ-related retinopathy as determined by an ophthalmologist's evaluation (which generally included assess-

ments of visual fields, color vision, optical coherence tomography, and other tests). For each case, we selected 3 SLE HCQ/CQ-exposed controls without retinopathy, matched on age at SLE diagnosis (within 5 yrs) and SLE duration (to give the controls an equal amount of time over which to develop retinopathy). At annual clinic visits, a record was made of whether a patient taking HCQ/CQ had seen an ophthalmologist in the preceding year; this allowed assessment of whether patients were adherent to ophthalmology screening for retinal toxicity.

We compared the cases and controls regarding potential demographic (distribution of race/ethnicity) and potential clinical predictors (duration of HCQ/CQ, average dose over time, and number with renal damage) of retinal toxicity. Renal damage was evaluated using the SDI[4]. The 3 items assessed for kidney function were abnormal glomerular filtration rate (GFR), proteinuria, and endstage renal disease. Only the presence of subnormal GFR and/or endstage renal disease were considered potential correlates of toxicity in our analyses, because they corresponded to how the recent AAO guidelines define renal disease (which is believed to increase the risks of retinopathy). HCQ/CQ doses per kilogram were calculated by dividing the HCQ or CQ dose at each annual visit by the actual body weight of the patient for that year. This was then averaged over the entire course of treatment to give an estimate of the average antimalarial dose that each patient was exposed to daily. In addition, we determined the number of patients who had ever been exposed to doses above 6.5 mg/kg for HCQ and 3.0 mg/kg for CQ (which were the previously recommended upper limits) or the current recommendations of 5.0 mg per kg for HCQ or 2.3 mg per kg for CQ[5]. One case and 1 control were missing information on dose, so those individuals were not used for those calculations. The new guidelines are based on actual weight but prior guidelines were based on ideal body weight. For simplicity, we used actual weight for both (this would lead to a conservative estimate for the no. patients exposed to doses above 6.5 mg/kg for HCQ or 3.0 mg/kg for CQ).

Descriptive statistics for the 2 groups included calculation of means, SD proportions, and differences in proportions, with 95% CI.

The ethics board approval was received through the MUHC by means of the SLE Annual registry (IRB number 96-060 REC).

RESULTS

As of 2016, there were 362 patients in current followup and of them, 326 (90%) have had at least 1 full year of antimalarial exposure. Of these 326, the majority (295, 90%) had only HCQ exposure while 31 had been exposed to both CQ and HCQ. Out of the 326, 18 had confirmed retinal toxicity associated with HCQ/CQ, representing 5.5% of the patients in our cohort who had been exposed to antimalarial drugs (Table 1). No retinal toxicity occurred within the first 5 years of exposure. The minimum number of years of HCQ/CQ exposure before retinopathy developed was 8 years and the maximum number was 33 years. Median SLE duration was 24 years [interquartile range (IQR) 18–39] for the cases and 23 years (IQR 17–33) for the controls (as indicated, this was a matching variable). Patients with retinal toxicity had taken 19 years of HCQ/CQ therapy on median (IQR 14–20), which was statistically similar to the 16 years for the control group (IQR 11–22). The similarity is likely because the patients were matched for SLE duration, which would be closely linked to duration of HCQ/CQ therapy. Average body mass index was 24 in cases and 25 in controls (up to 25 is considered healthy, above that is overweight/obese).

Many of the patients with retinopathy were older than 40 years (n = 15, 83.3%). Sex distribution was similar for the cases and controls. There were fewer whites in the group with retinal toxicity, although the difference in proportions was not statistically significant: 61.1% compared to controls (74.1%). The non-white patients with retinopathy were black (n = 3), Asian (n = 3), and of other origins[1]. The level of renal damage (according to the SDI) among patients who developed toxicity (n = 4, 22.2%) was slightly higher than that observed in the control group (n = 8, 14.8%), but the 95% CI for the difference in proportions included the null value.

Of the 18 retinal toxicity cases, 11 (61.1%), according to our calculations, had been exposed to average doses above 6.5 mg/kg of HCQ or 3.0 mg/kg of CQ (the accepted maximum doses prior to the more recent AAO guidelines[5]). This percentage was numerically greater than the controls (n = 24, 44.4%), although the 95% CI for the difference included the null value.

In 12 of those 18 patients with retinopathy (66.7%), average doses over the interval were higher than current recommendations[1,6]. This included 8 subjects with past average daily dose above 5 mg/kg and 4 subjects with a past daily dose of CQ above 2.3 mg/kg. In the controls, 26 (48.2%) had an average dose over time that was higher than current recommendations. This included 25 with past daily dose of HCQ above 5 mg/kg and 1 subject with a past daily dose of CQ above 2.3 mg/kg.

All patients with retinopathy, and 44 controls (81.5%), had been exposed to HCQ/CQ doses above the current recommendations on at least 1 annual assessment. Among patients with retinal toxicity, a higher percentage was exposed to CQ (7 patients, 38.9%) versus controls (7 patients, 13.0%); the 95% CI for this difference in percent (1.78–51.9) excludes the null value.

Regarding adherence to annual ophthalmologic assessments to screen for retinal damage, 9 (50.0%) of the cases had missed at least 1 year of assessment in the 5 years preceding discontinuation of antimalarial agents for toxicity and 35 (64.8%) of the controls had missed at least 1 year of assessment over their last 5 years of taking HCQ/CQ therapy. All patients who missed 1 ophthalmology assessment did have subsequent retinal evaluations.

DISCUSSION

The prevalence of retinopathy associated with longterm use of antimalarial drugs in our sample of 326 patients with SLE was 5.5%. This is slightly lower than the 7.5% reported in the study by Melles and Marmor[7] but is within the range reported in other publications[8]. Melles and Marmor suggested that the frequency of retinal complications varies significantly with duration of use as well as dosage[7]. In our study, because controls were matched for age and SLE duration (to give the controls the same opportunity over time to develop retinopathy), it was expected that the average number of years of treatment would be similar for cases and

Table 1. McGill University Health Centre SLE patients with retinal toxicity (cases) versus matched SLE controls without retinal toxicity[a].

Variable	Cases, n = 18	Controls[b], n = 54	95% CI for Difference
Females, n (%)	16 (88.9)	50 (92.6)	–10.9 to 29.2[f]
White, n (%)	11 (61.1)	40 (74.1)	–12.0 to 40.1[f]
Abnormal GFR or endstage renal disease, n (%)	4 (22.2)	8 (14.8)	–12.2 to 34.4[f]
Mean daily dose > 5 mg/kg HCQ or > 2.3 mg/kg CQ[c], n (%)	12 (66.7)	26 (48.2)	–10.5 to 41.9[f]
Ever exposed to > 5 mg/kg HCQ or > 2.3 mg/kg CQ, n (%)	17 (94.4)	44 (81.5)	–12.4 to 27.3[f]
Ever exposed to > 6.5 mg/kg HCQ or > 3 mg/kg CQ, n (%)	11 (61.1)	24 (44.4)	–12.0 to 41.2[f]
Missing ≥ 1 ophthalmology assessment, n (%)[d]	9 (50.0)	35 (64.8)	–12.4 to 41.0[f]
Median age at SLE diagnosis (IQR)[e]	29 (23–35)	29 (24–38)	–4.2 to 6.7[g]
Median HCQ/CQ use, yrs (IQR)[e]	19 (14–20)	16 (11–22)	–6.0 to 2.0[g]

[a] Based on the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index recorded at yearly SLE assessments. [b] Controls were matched 3:1 on age at SLE diagnosis (within 5 yrs), and SLE duration. [c] Daily dose of antimalarial agents per actual body weight averaged for the entire course of treatment. [d] Adherence to annual ophthalmology assessments recorded over the last 5 years preceding discontinuation of antimalarial therapy for patients with retinal toxicity (cases) and recorded over the last 5 years of antimalarial therapy for patients without retinal complications (controls). [e] IQR: interquartile range. [f] 95% CI for difference in percentage. [g] 95% CI for difference in mean. SLE: systemic lupus erythematosus; GFR: glomerular filtration rate; HCQ: hydroxychloroquine; CQ: chloroquine.

controls. We did not see any cases of retinopathy within the first 5 years, which is reassuring given that recent ophthalmology guidelines downplay the importance of retinal screening in this early window. At our center, we encourage yearly ophthalmology visits from the time of initiation of HCQ and especially CQ, because this establishes a baseline, reinforces for patients the importance of ophthalmology in their care routine, and provides a means of monitoring for other ocular complications seen in SLE, such as cataracts.

Among patients with retinal toxicity, the number previously exposed to CQ was more than 3 times that in the controls. This is consistent with the belief that CQ has greater potential for retinal toxicity than HCQ. However it must be noted that all of the patients exposed to CQ were also exposed to lengthy periods of HCQ. This made it impossible to determine the risk of retinopathy due to CQ alone. The presence of concomitant renal damage, which is considered a risk factor for toxicity[6,8,9], was numerically greater in subjects with retinopathy, although the 95% CI for the difference included the null value, possibly because of power issues[10].

Several studies have demonstrated a correlation between antimalarial dosage and retinopathy[6]. In our sample, all patients with retinopathy had at least once been exposed to doses above the current recommendations, as had the majority of controls. This finding was not surprising given that these recommendations were issued in 2016, and most of our patients had been taking HCQ for longer. There are several potential reasons why many patients received HCQ/CQ doses in excess of the ophthalmology guideline. First, we recorded HCQ/CQ dose and weight concurrently and only once a year; initiation of the drug may have been started by a non-clinic physician or at a time when the patient's weight was higher, or patients may have increased the dose themselves. Normally, the dose was lowered once a discordance between actual dose and guidelines was apparent. Interestingly, in verbal communication with other North American SLE specialists, it appears that some do not emphasize the importance of dosing by weight for HCQ, but simply use a maximum dose of 400 mg at initiation, and reduce the dose when clinical activity allows. At our center, we continue to aim for recommended dosing by weight.

Our study demonstrates that there is incomplete adherence to ophthalmology screening (as prescribed in the 2016 guidelines of the AAO concerning HCQ use[1]) in our sample. Indeed, in both cases and controls, over 50% of patients were incompletely adherent to annual ophthalmology assessments. In fact, the higher prevalence of nonadherence in controls does offer the possibility that some of them, who had not had ophthalmology assessments regularly, might have undetected retinal problems. This is unlikely because all patients who missed 1 ophthalmology assessment did have subsequent evaluations prior to the end of their observation interval. Still, ascertaining retinal toxicity from the SDI may lead to underdiagnosis. Recently available tests (e.g., spectral domain optical coherence tomography in combination with 10-2 Humphrey's visual fields) will be more sensitive in detection of retinopathy than were older tests (such as relying on fundus examination, visual acuity, or color vision assessments), which might miss early/mild retinopathy. This may be a potential limitation; however, we studied patients who were still in followup as of 2016. Thus the majority of patients who were non-cases would have had the newer tests done, once they became available. In the coming years, we might expect earlier detection of retinal damage.

Regarding the demographics, almost all patients who developed retinal complications were aged above 40 years, which is compatible with previous studies[11,12]. Interestingly, only 1 of our cases had pediatric-onset SLE. One study suggested that retinal toxicity is seen more often after the age of 40 because of the significant loss of retinal neurons between the ages of 20 and 40 years[12]. On the other hand,

patients with the longest SLE duration will also likely have the longest HCQ/CQ duration.

The race/ethnicity distribution showed a trend toward fewer whites among those with retinopathy versus controls. This could represent a real difference, but was not statistically significant, and the finding could be due to chance alone. Alternatively, this difference could be explained by physiological differences between racial/ethnic groups. It is known that the mechanism of retinal toxicity involves the binding and accumulation of HCQ/CQ molecules onto melanin pigments[13,14,15,16]. The melanin content is twice as high in the choroid of blacks compared to that of whites[17,18]. In addition, the quantity of uveal melanin in eyes with dark-colored irides (e.g., dark brown eyes) is significantly greater than that of light-colored irides (e.g., light blue or gray eyes)[19,20,21]. Whether patients with dark-colored eyes are more at risk of accumulating HCQ/CQ (which might in turn increase the incidence of retinopathy) is unknown. Further study is needed to fully elucidate this possibility.

We found that 5.5% of patients developed antimalarial-induced retinal complications, over an average of 12.8 years of followup. Among patients with retinal toxicity, the number previously exposed to CQ was more than 3 times that in the controls. No cases of retinal toxicity developed within 5 years; however, in our clinic we continue to endorse yearly screening from the time of HCQ and particularly CQ initiation. We observed incomplete adherence to ophthalmology screening in many patients. Future studies using larger cohorts are under way to more definitively examine the roles of therapy duration, race/ethnicity, and other factors.

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