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Retinal Complications in Systemic Lupus Erythematosus Patients Treated with Antimalarial Drugs

Elvis-Raymond Mukwikwi (Université de Montreal), **Christian A Pineau** (McGill University Health Centre, McGill University), **Evelyne Vinet** (McGill University Health Centre, McGill University) , **Ann E Clarke** (University of Calgary), **Emil Nashi** (McGill University), **Fares Kalache** (McGill University Health Centre), **Louis-Pierre Grenier** (McGill University Health Centre), **Sasha Bernatsky** (McGill University Health Centre, McGill University)

Objectives: Hydroxychloroquine (HCQ) and chloroquine (CQ) are key drugs in systemic lupus (SLE) and related diseases. Retinal toxicity remains the most concerning complication. We studied factors potentially associated with retinal toxicity, using case-control analyses.
Methods: Within our lupus clinic cohort, we identified patients with retinal changes using the SLICC Damage Index. We confirmed HCQ/CQ retinopathy with chart review, and selected up to three SLE controls for each case, matched on age at SLE diagnosis and SLE duration.
Results: Over an average 12.8 years of follow-up, 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 years). Mean HCQ/CQ duration was similar in cases (18.5 years, 95% CI 15.2, 21.7) and controls (16.7 years, 95% CI 14.3, 19.0) 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 Caucasian (cases 61.1%, controls 74.1%), but neither variables reached statistical significance. Among patients with retinal toxicity, the number previously exposed to CQ was more than three times that in controls.
Conclusion: Just over 5% of patients developed anti-malarial 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 underway to better define the roles of therapy duration, race/ethnicity, and other factors.

Key words: systemic lupus erythematosus, anti-malarial drugs, hydroxychloroquine, chloroquine, retinal toxicity

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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 underway 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 as to 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 the 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).

Materials and Methods

Data was extracted from the McGill University Health Center (MUHC) Lupus Clinic registry. Patients with a clinical diagnosis of SLE according to ACR criteria (3) have been consecutively enrolled in the cohort. Patients are followed with annual research visits where data are systematically collected on demographics, drugs, disease activity, and organ damage. Upon enrollment, patient's written informed consent to publish the data is obtained. We identified all patients who were ever exposed to HCQ and/or CQ exposure and determined those who had scored positive for retinal change as assessed by the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index, SDI, which is 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 evaluation (which generally included assessments of visual fields, color vision, optical coherence tomography, and other tests). For each case, we selected three SLE HCQ/CQ-exposed controls without retinopathy, matched on age of SLE diagnosis (within 5 years), and SLE duration (in order to give the controls an equal amount of time over which to develop retinopathy). At annual clinic visits, a record is made of whether a patient taking HCQ/CQ has 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 in terms of 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 SLICC/ACR

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damage index (4). The three items assessed for kidney function are abnormal glomerular filtration rate (GFR), proteinuria and end-stage renal disease. Only the presence of subnormal GFR and/or end-stage renal disease were considered as potential correlates of toxicity in our analyses, as this corresponds 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 one control were missing information on dose so these 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 number of patients exposed to doses above 6.5 mg/kg for HCQ or 3.0 mg/kg for CQ).

Descriptive statistics for the two groups included calculation of means, standard deviations (SD) proportions, and differences in proportions, with 95% confidence intervals (CI).

The ethics' board approval was received through the MUHC via the SLE Annual registry. The IRB number is 96-060 REC.

Results

As of 2016, there were 362 patients in current follow-up and of them, 326 (90%) have had at least one 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 five 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. Mean SLE duration was 26.4 years for the cases and 24.5 years for the controls (as indicated in the methods, this was a matching variable). Patients with retinal toxicity had taken 18.5 years of HCQ/CQ therapy on average (95% CI 15.2, 21.7), which was similar to the 16.7 years for the control group (95% CI 14.3, 19.0). 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).

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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 Caucasians in the group with retinal toxicity, though the difference in proportions was not statistically significant; (61.1%) compared to controls (74.1%). The non-Caucasian patients with retinopathy were black (N=3), Asian (N=3) and of other origins (1). The level of renal damage (according to the SLICC/ACR damage index) 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 17 retinal toxicity cases with known HCQ dosing, eleven (64.7%), according to our calculations, had been exposed to average doses over the interval above 6.5 mg/kg of HCQ or 3.0 mg/kg of CQ (the accepted maximum doses prior to the recent AAO guidelines (5)). This percent was numerically greater than the controls (N=24, 45.3%) although the 95% CI for the difference included the null value.

In 12 of those 17 patients with retinopathy, 12 (70.6%) had average doses over the interval that was higher than current recommendations (1) (6). This included eight subjects with past average daily dose above 5 mg/kg and four subjects with a past daily dose of CQ above 2.3 mg/kg. In the controls, 26 (49.1%) 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 one subject with a past daily dose of CQ above 2.3 mg/kg.

All patients with retinopathy, and 44 (83.0%) of controls had been exposed to HCQ/CQ doses above the current recommendations on at least one annual assessment. Among patients with retinal toxicity, a higher percent 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, nine (52.9%) of the cases had missed at least one year of assessment in the 5 years preceding discontinuation of antimalarial agents for toxicity and 35 (74.5%) of the controls had missed at least one year of assessment over their last 5 years on HCQ/CQ therapy. All patients who missed one ophthalmology assessment did have subsequent retinal evaluations.

Discussion

The prevalence of retinopathy associated with long term use of antimalarial drugs in our sample of 326 lupus patients was 5.5%. This is slightly lower than the 7.5% reported in the study published 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 dosing (7). In our study, since controls were matched for age and SLE duration (in

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order to give the controls the same opportunity over time to develop retinopathy), it is expected that the average number of years of treatment would be similar for cases and 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 centre, we encourage yearly ophthalmology visits from the time of initiation of HCQ and especially CQ, as this establishes a baseline, reinforces for patients the importance of ophthalmology in their care routine, and also 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 three 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 due to power issues(10).

Several studies 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 (which is not surprising given that these were issued in 2016 and most of our patients had been taking HCQ for longer than this), as had the majority of controls. 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 occurred either by a non-clinic physician or at a time when the patients' 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 lupus 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 (verbal communication), and reduce the dose when clinical activity allows. At our center, we continue to aim at 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 non-adherence in controls does offer the possibility that some of the controls, who had not had ophthalmology assessments regularly, might have undetected retinal problems. We do not think this is the case, since all patients who missed one ophthalmology assessment did have subsequent evaluations prior to the end of their observation

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interval. Still, ascertaining retinal toxicity from the SLICC damage index may represent an under-ascertainment. It is known that recently available tests (e.g. SD-Optical coherence tomography in combination with 10-2 Humphrey's visual fields) will be more sensitive in terms of detecting retinopathy than older tests (such as relying on fundus exam, 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 follow-up as of 2016, thus the majority of patients who were non-cases would have had the newer tests done, once they became available. Thus in more recent years, we might expect earlier detection of retinal damage.

As for the demographics, almost all patients who developed retinal complications were aged above 40 years, which is compatible with previous studies (11, 12). Interestingly, only one of our cases had pediatric-onset SLE. One publication suggested that retinal toxicity is seen more often after the age of 40 because of the significant loss in retinal neurons between the ages of 20-40 years (12). On the other hand, patients with the longest SLE duration will also likely have the longest HCQ/CQ duration.

Interestingly, the race/ethnicity distribution showed a trend towards fewer Caucasians in those with retinopathy versus controls. This difference 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(13-15). (16). Interestingly, the melanin content is twice as high in the choroid of black people as opposed to that of Caucasians(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 grey eyes) (19-21). Whether or not 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.

In conclusion 5.5% of patients developed anti-malarial-induced retinal complications, over an average of 12.8 years of follow-up. Among patients with retinal toxicity, the number previously exposed to CQ was more than three times that in the controls. No cases of retinal toxicity developed within five 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 underway to more definitively explore the roles of therapy duration, race/ethnicity, and other factors.

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

Variable	Cases[b] (N=18)	Controls[b] (N=54)	95% CI for difference In percent
Females (N, %)	16 (88.9)	50 (92.6)	(-10.9, 29.2)
Caucasian (N, %)	11 (61.1)	40 (74.1)	(-12.0, 40.1)
Abnormal glomerular filtration rate or end-stage renal disease (N, %)	4 (22.2)	8 (14.8)	(-12.2, 34.4)
Mean daily dose >5 mg/kg HCQ or >2.3mg/kg CQ [c]	12 (70.6)	26 (49.1)	(-8.45, 44.2)
Ever exposed to >5 mg/kg HCQ or > 2.3mg/kg CQ (N, %)	17 (100)	44 (83.0)	(-7.45, 30.3)
Ever exposed to >6.5mg/kg HCQ or > 3 mg/kg CQ (N, %)	11 (64.7)	24 (45.3)	(-10.3, 43.6)
Missing ≥1 ophthalmology assessment (N, %)[d]	9 (52.9)	35 (74.5)	(-6.16, 48.3)
Mean age at SLE diagnosis (95% CI)	27.7 (23.9, 31.5)	30.9 (27.9, 34.0)	
Mean HCQ/CQ use, years (95% CI)	18.5 (15.2, 21.7)	16.7 (14.3, 19.0)	

[a]Based on the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index recorded at yearly lupus assessments. [b]Controls were matched 3:1 on age of SLE diagnosis (within 5 years), 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).

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