RHEUMATOLOGY ADVANCES IN PRACTICE

Concise Report

Incidence of blindness in a population of rheumatic patients treated with hydroxychloroquine

Dilpreet K. Singh (iD) [1], **Leila Muhieddine**[1], **Douglas Einstadter**[1] and **Stanley Ballou**[1]

Abstract

Objective Long-term HCQ use for the treatment of rheumatic diseases has been associated with retinopathy in a daily and cumulative dose-dependent manner by weight. We examined the incidence of ocular toxicity in a large population of patients treated with HCQ for inflammatory arthritis and SLE and followed long term in a tertiary centre.

Methods Our retrospective longitudinal review identified 2867 rheumatic patients from 1999 to August 2017 who had a prescription written for HCQ. Thirty-one patients were identified as having a diagnosis of blindness or toxic maculopathy in their electronic medical record, and we carried out an extensive chart review.

Results Of our 31 patients with a diagnosis of blindness or toxic maculopathy, 11 had documented blindness, in all cases attributed to a cause other than HCQ-related ocular toxicity: stroke (27%), pre-existing macular disease (18%), diabetic retinopathy (18%), hypertensive retinopathy (9%) and cataracts (9%). Seventeen of 31 patients had visual impairment that was multifactorial and unrelated to HCQ. We identified two patients with bull's eye maculopathy [person-time incidence rate, 0.12 cases per 1000 person-years (95% CI: 0.01, 0.43)] and one with early HCQ toxic maculopathy [person-time incidence rate, 0.06 cases per 1000 person-years (95% CI: 0.002, 0.33)]. All three patients received HCQ for >18 years, and none had functional vision loss at diagnosis.

Conclusion HCQ-induced macular toxicity is rare in routine clinical practice, seems to require prolonged HCQ therapy (>18 years) and is not necessarily associated with functional visual loss. Our findings suggest that co-morbid conditions that are common in RA and SLE contribute substantially to vision loss and should not be ignored.

Key words: hydroxychloroquine, blindness, retinal maculopathy, vision impairment, co-morbidity

CLINICAL SCIENCE

Key Messages
- The incidence of retinal toxicity in long-term HCQ users in a large US population is low.
- HCQ-induced macular toxicity is not necessarily associated with functional visual loss or blindness at diagnosis.
- Co-morbid conditions that are common in RA and SLE contribute substantially to vision loss.

Introduction

HCQ is widely used in the treatment of articular and skin manifestations of chronic rheumatic diseases. Its long-term use has been associated with retinopathy in a daily and cumulative dose-dependent manner by body weight, potentially augmented by several risk factors described in the literature (age >60 years, renal or liver disease, pre-existing retinal disease and concurrent tamoxifen use). Maculopathy can present insidiously and range from a

[1]Case Western Reserve University, MetroHealth Medical Center, Cleveland, OH, USA

Submitted 21 December 2018; accepted 20 March 2019

Correspondence to: Dilpreet Kaur Singh, Case Western Reserve University, MetroHealth Medical Center, Division of Rheumatology, 2500 Metrohealth Drive, Cleveland, OH 44109, USA. E-mail: dilpreet70@hotmail.com

subtle change of the retinal pigment epithelium to the less frequent advanced retinopathy, bull's eye maculopathy (characterized by concentric, parafoveal retinal pigment epithelial loss), which has been associated with severe and irreversible visual loss. HCQ-related retinopathy can be symptomatic, characterized by central visual loss, including reading difficulties, reduced colour vision, central scotomata, flashing lights and visual field defects. However, even after withdrawal of HCQ, owing to its long half-life (50 days) and delayed systemic clearance, progressive and irreversible retinal damage can occur and, rarely, can result in blindness [1–4].

The American Academy of Ophthalmology (2016) recommends HCQ use of $\leq$5.0 mg/kg/day actual body weight compared with the previous recommendations of <6.5 mg/kg ideal body weight to reduce the risk of retinopathy and emphasizes regular screening for early detection of retinal toxicity [5]. These recommendations are based primarily on one retrospective cohort study that reported a much higher prevalence of HCQ retinopathy (7.5%, $n = 2361$) than previously observed (0.5–2.0%) among patients taking HCQ for >5 years [6–8]. Marmor *et al.* [5] reported that retinal toxicity markedly increases with concurrent kidney disease, in a cumulative manner as previously described, with duration of use >20 years and dose >5.0 mg/kg actual body weight. They excluded patients with certain retinal co-morbidities (such as macular degeneration or diabetic retinopathy) and, importantly, did not mention the degree of vision loss in those with HCQ-related retinopathy, nor did they specify the possible contribution of other co-morbidities to vision loss or retinopathy.

Interestingly, observations from clinical practice, supported by earlier studies, suggest that the occurrence of blindness during long-term HCQ use is thought to be rare. The actual frequency of blindness in a defined population has not been reported. Nor have previous studies commented on the effect of co-morbidities on ocular toxicity in patients treated long term with HCQ. In addition, literature reports of cases with HCQ-related retinopathy have reported variable effects on vision loss, if described at all [3, 7–12].

To provide a more accurate estimate of the incidence of HCQ-related retinopathy and visual loss in clinical practice, we examined cases of ocular toxicity in patients treated with long-term HCQ for inflammatory arthritis and SLE in a tertiary medical centre in the USA and report the outcomes as a person-time incidence rate.

Methods

Our retrospective longitudinal study initially identified 2867 patients from 1999 to August 2017 with a diagnosis of RA, inflammatory polyarthritis, SLE, subacute cutaneous lupus or discoid lupus erythematosus who had a prescription written for HCQ using an institutional database. Further stratification of the search criteria identified 31 patients with inclusion criteria of a diagnosis of blindness or toxic maculopathy. Their electronic medical records were extensively reviewed for: demographics; rheumatological diagnosis; duration of HCQ use; dose of HCQ at initiation, discontinuation and at onset of any ocular symptoms; actual body weight at initiation and discontinuation; co-morbidities known to affect vision, including diabetes, hypertension, glaucoma, cataracts and pre-existing macular disease; risk factors for retinal toxicity, such as kidney disease, liver disease, pre-existing retinopathy and tamoxifen use; and the reason for vision impairment or blindness, as recorded by the attending ophthalmologist. Use of HCQ has replaced chloroquine at our institution owing to its favourable side-effect profile. Therefore, patients with chloroquine use were not included in the search criteria and were excluded from the study. Before 2006, yearly screening included fundus examination, colour vision testing and visual field testing, according to American Academy of Ophthalmology guidelines (2002, 2011, 2016). When the second-generation spectral domain optical coherence tomography (SD-OCT) examination became available in 2006, it became standard of care at our institution, along with an annual examination and visual field testing. A baseline SD-OCT assessment was obtained, and subsequent screening results were compared with the baseline. Data were recorded as the mean (S.D.) for continuous variables and the number (percentage) for categorical variables. Institutional review board approval was obtained from Metrohealth Medical Center institutional review board. Given that existing information was used from our institutional database and patients were not contacted, patient informed consent was not deemed necessary by the institutional review board.

The total time of follow-up for each person was evaluated, starting with the first HCQ prescription date and ending with the end date of the last prescription or the last visit date, whichever was greater. Likewise, the total time on HCQ for all patients was calculated based on the time from the start date of the first HCQ prescription until the end date of the last prescription. If there was no end date on the last prescription, 1 year was added to the start date of the last prescription, and that was used as the date of last HCQ use.

Results

We identified 31 patients with a diagnosis of either blindness or toxic maculopathy. Eleven of these had documented blindness of one or both eyes. In all cases, a diagnosis other than HCQ ocular toxicity was confirmed as the cause of blindness: stroke (18% or 2/11), pre-existing macular disease (18% or 2/11), diabetic retinopathy (18% or 2/11), hypertensive retinopathy (9% or 1/11), cataracts (9% or 1/11) and other problems (Table 1). Seventeen of the 31 patients had vision impairment, which in each patient was thought to be multifactorial in origin, related to refractive error and medical co-morbidities; none was thought to be related directly to HCQ toxicity (refer to Table 1). There was no association of a specific rheumatic disease diagnosis with vision loss.

TABLE 1 Incidence of blindness in a population of rheumatic patients treated with HCQ

	Percentage (n)
Cohort (n = 31)	
Female	77 (24)
Age, mean [S.D. (range)], years	61 [12 (23–76)]
Race	
White	45.2 (14)
African American	48.4 (15)
Hispanic	6.5 (2)
Rheumatological diagnosis[a]	
RA	48.4 (15)
SLE and subacute and discoid lupus	38.7 (12)
Other	19.4 (6)
HCQ treatment	
Duration of use, mean [S.D. (range)], months	72.2 [75.5 (0–300)]
Cumulative dose, mean [S.D. (range)], g	833.2 [902.0 (0–3600)]
Dose at initiation by actual body weight, mean [S.D. (range)], mg/kg	4.49 [1.8 (1.69–7.34)]
Co-morbidities[a]	
Hypertension	67.7 (21)
Chronic kidney disease (stage 1–5)	58.1 (18)
Cataracts	35.5 (11)
Diabetes mellitus (types 1 and 2)	19.4 (6)
Glaucoma	6.5 (2)
Chronic hepatitis C virus	3.2 (1)
Liver disease [fatty liver (1), liver cirrhosis (1)]	6.4 (2)
Other ocular disease [retinal holes, retinal tear, chronic posterior vitreous detachment (2), macular degeneration, coloboma of retina, optic neuropathy secondary to alcohol/poor nutrition, episcleritis, malignancy, iron line]	22.6 (7)
Tamoxifen use	0.0 (0)
Blindness	
None (incorrect diagnosis on problem list)	9.4 (3)
Blindness of one or both eyes	35.5 (11)
Reason for blindness (n = 11)[a]	
Bull's eye maculopathy or retinopathy related to HCQ use	0.0 (0)
Stroke	18.2 (2)
Pre-existing macular disease	18.2 (2)
Diabetic retinopathy	18.2 (2)
Hypertensive retinopathy	9.1 (1)
Cataract	9.1 (1)
Other [congenital (2), tuberculosis (1), malignancy (1), pseudotumour cerebri (1), amblyopia since childhood (1), unknown (1)]	63.6 (7)
Vision impairment	51.6 (17)
Reasons for vision impairment (n = 17)[a]	
Refractive error [Myopia (5)/hyperopia (4)/presbyopia (7)/amblyopia (1)]	88.2 (15)
Diabetic retinopathy	7.1 (1)
Hypertensive retinopathy	7.1 (1)
Retinal detachment	7.1 (1)
Optic neuropathy attributable to alcohol consumption/poor nutrition	7.1 (1)
Cataract	7.1 (1)

The mean follow-up time at our institution was 5.9 years for all patients, 7.3 years for those with eye disease defined as toxic maculopathy or blindness, and 5.9 years for those without eye disease. Accounting for the total number of treated patients of 2867, the mean total time on HCQ was 4.6 years for all patients, 5.4 years for those with eye disease, and 4.6 for those without eye disease.

Three of the 31 patents in this retrospective longitudinal study were diagnosed by ophthalmology as having HCQ-related retinal toxicity, each without blindness or functional vision loss. Two of these cases were

determined to have bull's eye maculopathy attributed to HCQ, diagnosed by fundus and SD-OCT examination. Case one was a 51-year-old female who had been treated for SLE with HCQ 400 mg daily for >20 years at a dosage of 7.1–8.2 mg/kg/day based on documented weight over 15 years; cumulative dose was 2880 g. Visual acuity was 20/20 in both eyes. Case two was a 66-year-old female who had been treated for SLE with HCQ 400 mg daily for ≥18 years at a dosage 7.3–8.2 mg/kg/day based on documented weight over 13 years; cumulative dose was 2592 g. Visual acuity was 20/40 in the right eye and 20/30 in the left eye. Co-morbidity in case one was chronic kidney disease stage 2 (glomerular filtration rate 80 ml/min/1.73 m^2), whereas case two had hypertension, myopia corrected with prescription glasses, and cataracts (not visually significant); both without prior use of tamoxifen. Case three had HCQ retinal toxicity without bull's eye maculopathy but with pigmentary changes on fundus examination, and loss of photoreceptor inner segment and outer segment junction with thinning of the retina on SD-OCT examination. She was 57 years old, with 25 years use of HCQ 400 mg daily at a dosage of 6.3 mg/kg/day based on documented weight over 11 years; cumulative dose was 3600 g. Visual acuity was 20/40 in both eyes. She had underlying myopia corrected by prescription glasses, without visual complaints.

Follow-up ophthalmology examination for case one is pending, because she was recently diagnosed. Case two and case three have had stable functional and structural examinations without changes in visual acuity since discontinuation of HCQ for 1 and 4 years, respectively.

Discussion

We found no cases of blindness directly attributable to toxic maculopathy from HCQ use in 2867 patients followed up at our institution for up to 25 years [mean (s.d.) of 6.0 (6.3) years]. We identified two patients with bull's eye maculopathy [person-time incidence rate 0.12 cases per 1000 person-years (95% CI: 0.01, 0.43)] and one with early HCQ toxic maculopathy [person-time incidence rate 0.06 cases per 1000 person-years (95% CI: 0.002, 0.33)]; all three patients (person-time incidence rate 0.18 cases per 1000 person-years) received HCQ for >18 years, and none had functional vision loss at diagnosis. Our findings suggest that HCQ retinal toxicity is rare. This is reassuring for clinicians and patients, because the fear of ocular side effects has been a common reason for non-adherence. To our knowledge, no other studies have assessed the impact on vision loss or blindness of co-morbid conditions that are common in RA and SLE. We suggest that these co-morbidities should not be ignored.

Over the years, research has shown that HCQ is safer than chloroquine with respect to ocular toxicity, and thus has largely replaced it in the treatment of rheumatic and dermatological diseases in the USA [5]. A strength of our study is that we limited our focus to determining the incidence of HCQ retinal toxicity in a large population, which is more relevant to contemporary clinical practice, whereas previous studies have reported both chloroquine and HCQ retinal toxicity [1, 3, 9, 12].

The more sensitive objective diagnostic tests for structural and functional imaging used by ophthalmologists for routine screening at our institution can detect subclinical retinal toxicity. SD-OCT was not available in earlier studies as a routine clinical test before 1993 [13]. One case of early retinal changes on SD-OCT examination from 2867 HCQ-treated patients was detected. Thus, in accordance with older studies, the incidence of HCQ retinopathy, including early maculopathy, in our retrospective longitudinal study is infrequent.

Two of our three patients with retinal toxicity had advanced maculopathy, and all three of them had the major significant risk factors of increased age, long duration of HCQ use and excessive dose above the current recommended daily dose (>5 mg/kg actual body weight) [5]. Interestingly, the smaller body habitus of these patients (weight range: 52–64 kg) renders even the common daily dose of 400 mg of HCQ an overdose. Periodic risk stratification with respect to co-morbid conditions and re-examination of daily HCQ dosage to avoid prolonged use of >5 mg/kg/day actual body weight [6], should guide the ocular screening regimen and might further reduce the rate of retinal toxicity in long-term HCQ users, as suggested by the data of Marmor *et al.* [2].

Given the large population, duration and nature of the present study, it was difficult to assess how many patients might have been lost to follow-up for various reasons (e.g. relocation, passed away, re-established care with another provider). However, we tried to mitigate this by accounting for those with consistent long-term follow-up in our institution. Even with the limitation of this study being a retrospective review of records from a single ambulatory centre, our findings have the potential to improve the care of rheumatic disease patients. HCQ remains a cornerstone of SLE management in reducing risk of disease flare, mortality, morbidity and end-organ renal damage [14, 15]. It helps to maintain disease control in SLE, APS, CTD and inflammatory arthritis. HCQ is an effective CS-sparing agent and an adjunct DMARD in the treatment of RA. It is well tolerated, and its side-effect profile confers significant advantages over many other immunosuppressive agents. Educational efforts should focus on the importance of identifying and managing co-morbidities that are common in rheumatic patients to reduce ocular sequela using a multidisciplinary approach involving primary care and appropriate subspecialists, concurrent with routine ophthalmic examination and surveillance for early detection of retinal toxicity.

None of the 2867 HCQ-treated patients at our institution had blindness attributable to toxic maculopathy from HCQ use. HCQ-induced macular toxicity is rare in routine clinical practice (person-time incidence rate 0.18 per 1000 cases in our practice), was identified in three patients with >18 years of treatment and was not associated with functional visual loss. Co-morbid conditions that are common in RA and SLE might contribute substantially to vision loss and blindness and should not be ignored.

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