Hydroxychloroquine dosing and toxicity: A real-world experience in Saudi Arabia of 63 patients

Fadwa Al Adel, Samir S. Shoughy¹, Khalid F. Tabbara¹,²

Abstract:

PURPOSE: To assess the ocular toxicity in patients on high doses of hydroxychloroquine (HCQ) per weight, as per the latest American Academy of Ophthalmology (AAO) screening guidelines for HCQ toxicity.

METHODS: This is a multi-center study looking at consecutive patients attending the ophthalmology clinics at a tertiary hospital and a private clinic in Saudi Arabia. A data collection sheet was used to collect patient’s information regarding the dose per body weight, duration of HCQ use and any risk factors associated with the use of the medication as per the latest AAO guidelines for HCQ screening. Ancillary testing including fundus photography, automated visual field (10-2) and spectral domain ocular coherence tomography were done. Further testing with fundus auto-fluorescence and multifocal ERG were done when needed. The presence or absence of toxicity was recorded.

RESULTS: A total of 63 patients were included in the study, 58 females and 5 males. The average patient age was 45 years (range 18–72). The mean dosage of HCQ was 3.9 mg/kg. Fourteen (22%) patients were on doses higher than 5 mg/kg. The duration of treatment ranged from 1-30 years (average 8.3). Thirty six (57%) patients were on the drug for more than 5 years. We found only one (1.58%) patient with HCQ toxic retinopathy over a mean of 8 years treatment period.

CONCLUSION: A significant number of our patients were found to be on doses of >5 mg/kg of HCQ, which may put them at a higher risk for retinal toxicity. Low dose HCQ such as 100 mg tablets should be made available to help physicians in adjusting the dose as per the latest reported guidelines by the AAO.

Keywords: Chloroquine, cornea verticillata, hydroxychloroquine, screening, toxic retinopathy

INTRODUCTION

Hydroxychloroquine (HCQ) is an anti-malarial drug that is used to treat a variety of autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, juvenile idiopathic arthritis and Sjogren’s syndrome.¹,² Novel indications for HCQ are also emerging including its potential use in cancer therapy, diabetes mellitus, heart disease, and pediatric inflammatory disorders.¹,² Hydroxychloroquine is a less toxic metabolite of chloroquine.² Chloroquine has largely been replaced by HCQ. There is an ongoing increase in the number of patients who are using HCQ for prolonged duration because of the expanding indications and the relatively safe systemic profile.

Hydroxychloroquine can cause variable ocular adverse effects including corneal deposits, posterior sub-capsular cataract, ciliary body dysfunction and toxic retinopathy. Toxic retinopathy caused by HCQ has been recognized for many years. Patients with toxic retinopathy usually complain of blurry vision. The classical clinical picture of HCQ toxic retinopathy is a bilateral bull’s-eye maculopathy, which is caused by a ring of parafoveal RPE depigmentation that spares the fovea. The exact mechanism responsible for the development of this pattern is not fully understood, however, it is believed that the primary damage is in the photoreceptors and...
outer nuclear layer leading to secondary disruption of the RPE.[21]

Dark skinned individuals may bind and store HCQ in the melanin of the RPE and this may predispose them for retinal toxicity.

Certain risk factors have been found to increase the risk of HCQ toxic retinopathy. The American Academy of Ophthalmology (AAO) listed the major risk factors for HCQ toxic retinopathy in their 2016 recommendations.[22] The most significant risks are high dose (HCQ dose >5.0 mg/kg of real body weight) and long duration of use (>5 years). As well as other factors such as concomitant renal disease, use of Tamoxifen and macular disease.[22]

Proper screening for HCQ retinopathy may help in early detection of structural or functional changes in the macula prior to the development of irreversible visual loss and end stage maculopathy. The screening tests include automated visual fields, spectral-domain optical coherence tomography (SD OCT), multifocal electro-retino-gram (mf-ERG) and fundus auto-fluorescence (FAF).

The overall prevalence of toxicity was estimated to be 7.5% in a study that included 2361 patients[6], although it varies greatly with the daily dose and duration of use. Recent advances in imaging such as in SD-OCT and mf-ERG technologies has allowed for better and earlier detection of retinopathy.[5] Comparison of the incidence of HCQ toxic retinopathy among different populations may be challenging. This may be explained by variations in the definitions of HCQ toxic retinopathy, imaging techniques used to detect retinopathy and the study population characteristics.[6]

The aim of this study was to report the percentage of patients on high daily doses per weight (>5mg/kg) of HCQ, as per the latest American Academy of Ophthalmology (AAO) screening guidelines for HCQ toxicity and look at the percentage of retinal toxicity.

**Methods**

The institutional review board approval was obtained from King Khalid University Hospital and The Eye Center clinics. The study was adherent to the tenets of the declaration of Helsinki and was registered at clinicaltrials.gov (registration number is NCT04010110). This was a multi-center study looking at a consecutive sample of sixty-three consecutive patients attending the ophthalmology clinics at King Khalid University Hospital and The Eye Center in Riyadh, Saudi Arabia. Consent was obtained from each patient. The period of data collection was from June 2017 until June 2018. We included patients on HCQ therapy who came for their ophthalmology screening appointment irrespective of the duration of use of the medication. We excluded patients who have stopped their HCQ medication. A data collection sheet [Figure 1] was used to collect patient’s information. The following data were collected: demographic data (age, gender, race), dose of HCQ per body weight, duration of use, reason for use and risk factors associated with the use of HCQ such as renal disease (abnormal glomerular filtration rate), Tamoxifen use, and preexisting macular disease. All patients underwent a complete ophthalmic examination including assessment of visual acuity, anterior segment examination looking for corneal verticillata and a dilated fundus examination looking for retinal pigment epithelium (RPE) depigmentation either in a para-foveal or extra-macular distribution within the retina. Ancillary tests were done which included: fundus photography, automated visual field testing (10–2), spectral domain ocular coherence tomography (SDOCT). Fundus auto-fluorescence (FAF) and mf-ERG were done if further ancillary testing was needed in doubtful cases or to confirm findings. The diagnosis of toxic retinopathy was based on the positivity of at least two objective tests to confirm the subjective findings. The presence or absence of toxicity was recorded.

**Results**

A total of 63 patients were included in this study. There were 5 male and 58 female patients. All patients were from Saudi Arabia [Table 1]. The average age was 45 years (range 18–72). There were 43 patients with Systemic Lupus Erythematosus, 17 with Rheumatoid Arthritis, one with scleroderma, one with Sjogren syndrome and one with antiphospholipid syndrome. The dose of HCQ ranged from 1.7 to 8.9 mg/kg (average 3.9 mg/kg). Surprisingly fourteen patients (22%) were on doses of >5 mg/kg. The duration of treatment ranged from 1-30 years (average 8.3 years). Thirty-six patients (57%) were on the drug for more than 5 years. Seven patients (11%) had renal impairment (abnormal glomerular filtration rate) and one of them was on dialysis. 6 patients (9.5%) had preexisting macular pathology, i.e., drusens, retinal pigment epithelium (RPE) changes. None of the patients were ever on Tamoxifen. None of the patients had corneal verticillata on anterior segment examination. The dilated fundus examination of all patients was normal except for 6 patients who had drusens and RPE changes consistent with macular degeneration that was further confirmed by ancillary testing, i.e., SD OCT, FAF. One patient had para-foveal RPE depigmentation on funduscopic examination. On further testing with SD OCT, the patient had a para-foveal outer segment loss.

| Table 1: Demographic characteristics of participants, n=63 |
|-----------------------------------------------------------|
| **Variables**                                             | **n (%)** |
| Mean age±SD                                               | 45±13.5   |
| Females                                                   | 58 (92%) |
| Males                                                     | 5 (8%)    |
| Ethnicity                                                 |          |
| Arabs (Saudi Arabian)                                     | 63       |
| Duration of treatment                                     |          |
| <5 years                                                  | 27       |
| >5-10 years                                               | 16       |
| >10 years                                                 | 20       |
| Reason for HCQ therapy                                    |          |
| Systemic lupus erythematosus                              | 43       |
| Rheumatoid Arthritis                                      | 17       |
| Scleroderma                                               | 1        |
| Sjogren syndrome                                          | 1        |
| Antiphospholipid syndrome                                 | 1        |
and disruption of the inner segment-outer segment line [Figure 2]. Visual field testing was normal in 30 cases (48%) and had nonspecific changes in 31 cases (49%). One patient had a bitemporal hemianopia and was referred to neurology for further evaluation, and one patient (the patient with para-foveal RPE depigmentation) had a superonasal defect on visual field testing. Further testing with mf-ERG was done to the patient with para-foveal RPE depigmentation (suspicious of HCQ retinopathy) that had results of depressed retinal sensitivity and confirmed the diagnosis of HCQ toxicity. There was only one patient out of our cohort who was found to have HCQ toxicity.

**DISCUSSION**

HCQ is an excellent medication in controlling rheumatological diseases with much fewer side effects than other alternative
Among our 63 patients, one patient was found to have HCQ retinopathy. Of note, this patient had renal failure and was on dialysis. In this case, parafoveal inner segment-outer segment line loss was detected on SDOCT. The mf-ERG generated corresponding depression in the parafoveal area. The overall percentage of HCQ toxicity in our study was 1.6% for an 8 years average duration of treatment.

The low percentage of HCQ toxicity found in our study population, maybe due to screening patients irrespective of the duration of use of the medication. According to the most recent AAO recommendations, a baseline screening should be done initially followed by an annual screening after 5 years of starting the medication for patients on acceptable doses and without major risk factors.[2]

Our small sample size is a limitation in our study. However, there is a lack of studies about the percentage of HCQ toxic retinopathy in our region. Further studies with a larger sample size are needed.

In conclusion, a significant number of patients were found to be on doses of >5 mg/kg of HCQ which may put them at a higher risk for retinal toxicity as per the recent AAO guidelines. A better dosing should be suggested to rheumatologists to prevent retinal toxicity in the future. Regular annual screening should be emphasized for those at risk. We propose using a data sheet, similar to the one used in our study that has all risk factors for toxicity listed, which helps in proper assessment of the possibility for HCQ retinal toxicity. The lack of availability of low dose HCQ tablets makes it difficult for physicians and patients to adjust the dose as per the latest reported guidelines by the AAO. We suggest making low dose HCQ available in tablets such as 50 and 100 mg tablets.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: From malaria to autoimmunity. Clin Rev Allergy Immunol 2012;42:145-53.
2. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 Revision). Ophthalmology 2016;123:1386-94.
3. Marmor MF. Comparison of screening procedures in hydroxychloroquine toxicity. Arch Ophthalmol 2012;130:461-9.
4. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol 2014;132:1453-60.
5. Mavrakis I, Stikakis PP, Mavrakis E, et al. The incidence of irreversible retinal toxicity in patients treated with hydroxychloroquine: A reappraisal. Ophthalmology 2003 Jul;110(7):1321-6.
6. Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. Eye (Lond). 2017;31(6):828-45.
7. Lee JY, Luc S, Greenblatt DJ, et al. Factors associated with blood hydroxychloroquine level in lupus patients: Renal function could be important. Lupus 2013;22:541-2.
8. Carmichael SJ, Day RO, Tett SE. A cross-sectional study of
hydroxychloroquine concentrations and effects in people with systemic lupus erythematosus. Intern Med J 2013;43:547-53.
9. Costedoat-Chalumeau N, Dunogué B, Leroux G, et al. A critical review of the effects of hydroxychloroquine and chloroquine on the eye. Clin Rev Allergy Immunol 2015;49:317-26.
10. Jallouli M, Galicier L, Zahr N, et al. Determinants of hydroxychloroquine blood concentration variations in systemic lupus erythematosus. Arthritis Rheumatol 2015;67:2176-84.
11. Lee JY, Vinayagamoorthy N, Han K, et al. Association of polymorphisms of cytochrome P450 2D6 with blood hydroxychloroquine levels in patients with systemic lupus erythematosus. Arthritis Rheumatol 2016;68:184-90.
12. Yam JC, Kwok AK. Ocular toxicity of hydroxychloroquine. Hong Kong Med J 2006;12(4):294-304.
13. Leung LS, Neal JW, Wakelee HA, Sequist LV, Marmor MF. Rapid onset of retinal toxicity from high-dose hydroxychloroquine given for cancer therapy. Am J Ophthalmol 2015;160:799-805.
14. Navajas EV, Krema H, Hammoudi DS, et al. Retinal toxicity of high-dose hydroxychloroquine in patients with chronic graft-versus-host disease. Can J Ophthalmol 2015;50:442-50.