

# Screening for hydroxychloroquine maculopathy

## Abstract

**Introduction:** Hydroxychloroquine (HCQ) is an immunosuppressant widely used by rheumatologists in treatment of Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE) and other conditions.

**Methods:** Literature review on reasons why HCQ is commonly prescribed, its side effects and when it is practical to screen for them and what happen if those side effects develop.

**Conclusion:** Hydroxychloroquine is a disease modified medicine used in rheumatologic diseases. Since retinal toxicity is normally irreversible and progressive even after cessation of medicine, it essential to screen for early feature of retinal toxicity.

**Keywords:** chloroquine, hydroxychloroquine, maculopathy, rheumatoid arthritis, systemic lupus erythematosus, DMARDs

Volume 9 Issue 6 - 2019

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**Received:** September 23, 2019 | **Published:** November 15, 2019

## Introduction

Disease-modifying antirheumatic drugs (DMARDs) are a groups of medicines used to alter the course of rheumatological conditions. Chloroquine was first introduced as an antimalarial drug in the Second World War. In countries outside the United States, it is still primarily used as a prophylactic agent against malaria. It is also used, along with its derivatives, as DMARDs in the treatment of Amebiasis, RA and SLE. Chloroquine and its derivatives have an affinity for melanin pigment. Therefore is found is highest levels in uveal tract in the eye and skin. That is where side effect of this Chloroquine and its derivatives are highest.<sup>1</sup> Chloroquine and its derivatives are usually administered orally. Bioavailability of HCQ is well around 74% with linear kinetics. It reaches its highest concentration in plasma in about 3 to 4 hours. Patients with rheumatoid arthritis show inverse correlation between disease activity and plasma concentration and hence absorption of HCQ. Higher absorption and concentration is found is patients with less disease activity.<sup>2-4</sup>

## Retinal toxicity

The toxic retinopathies form a diverse group of conditions that result from retinal damage caused by systemically administered drugs. Although they are relatively rare, these conditions should be considered whenever an “unusual” retinopathy is evaluated, particularly when features of bilateral pigmentary disturbance or retinal crystal deposition are present. Adequate knowledge of systemic medication use in a patient with an unusual retinopathy can lead to prompt recognition of a toxic retinopathy. This may minimize an otherwise extensive workup and spare the patient from future exposure to the noxious agent. A variety of medications are associated with retinal abnormalities. These medicines could be introduced systemically, topically or intravitreally. If use of such medication is needed it is usually recommended that ocular toxicity signed are screened for since in many cases the toxicity happens while patient is asymptomatic. The majority of toxicities are reversible following cessation of the offending medicine. However there are some occasions where permanent or progressive visual loss occur even after cessation of the inciting agent.

Retinal toxicity caused by Chloroquine (CQ) and its derivatives is mainly caused by the medicines’ affinity towards melanin pigment

being highest in the eye in the uveal tract and retinal pigment epithelium. Therefore retinal is the first part of the eye to suffer from such toxicity. Such toxicity will be related to the dose of medicine used over a certain period of time reaching a certain cumulative dose and hence a certain level of concentration in the melanin pigments rich tissues. Chloroquine is normally in doses around 3 mg/kg/day lean body weight. A dose higher than this usual does will be accompanied by increased incidence of complications/toxicity feature. For an average lean body weight of 65 kg the daily dose would be around 200 mg of Chloroquine. A dose exceeding 250 mg per day although is slightly higher than the average does increase the chance of toxicities as it add up to reach the total cumulative does of 100-300 gm faster which is the cumulative dose normally needed to develop features of toxicity. One studies showed that lower daily doses are accompanied with lower incidence of toxicity even with cumulative doses of up to 1000g. CQ normally takes a very long time to clear from the body. Therefore toxic effects can still manifest up to 7 years following the medicine’s withdrawal.<sup>5</sup> Given the incidence of toxicity with chloroquine, most rheumatologists prefer hydroxychloroquine for the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Although it can produce a retinopathy identical to chloroquine, its occurrence is much less common.

## HCQ toxicity

HCQ retinal toxicity can be severe and irreversible. With continued use of the drug or even cessation in case of toxicity, progressive pigmentary changes continue. Advanced maculopathy can be in the form of bullseye maculopathy, peripheral pigment irregularity and bone spicule formation, vascular attenuation and optic disc pallor.<sup>6</sup> When retinal toxicity occurs, patients start to complain of night vision difficulties as well as reading problems. A central or paracentral scotomas can be also manifested which may enlarge, multiply and/or ultimately reduce visual acuity.

As patients are normally asymptomatic at the beginning of retinal toxicity Fundus examination is necessary to rule out any abnormality. Dullness of foveal reflex is the earliest sign of fundus abnormality. This foveal dullness is a result of irregularity in the macular pigmentation. This may later become surrounded by a concentric zone of hypopigmentation usually horizontally oval and more prominent inferior to the foveal, hence the paracentral scotoma

is usually superior to fixation. The appearance of alteration hyper and hypo pigmentation gives the appearance of Bullseye and hence the maculopathy is normally referred to as Bullseye maculopathy as a classic feature of advanced HCQ toxicity.<sup>7</sup>

Risk factors for HCQ retinal toxicity:

- a. Preexisting maculopathy is a contraindication to HCQ use as it masks the toxicity features.
- b. Duration longer than 5 years of use
- c. Doses above 5 mg/kg lean body weight/day
- d. Existing renal and/or hepatic disease
- e. Age greater than 60 years
- f. Concomitant use of tamoxifen.<sup>7</sup>

### Screening for maculopathy

A baseline ocular exam should be performed within the first year of hydroxychloroquine treatment. This baseline exam should include best corrected distance visual acuity (BCVA), an automated threshold visual field (VF) of the central 10 degrees (with retesting if an abnormality is noted), and spectral domain ocular coherence tomography (SD-OCT). Annual exams are recommended for patients with significant risk factors for retinal damage. For patients without significant risk factors, annual exams may be deferred until 5 years of treatment. In Asian patients, retinal toxicity may first be noticed outside the macula; therefore, visual field testing should be performed in the central 24 degrees instead of the central 10 degrees. Discontinue hydroxychloroquine if ocular toxicity is suspected and monitor the patient closely for ocular disease (i.e., retinal changes) and visual disturbance which may progress even after discontinuation of therapy.<sup>8–10</sup>

In early 2016, the American Academy of Ophthalmology task force on screening recommendations for hydroxychloroquine retinopathy published new updated guidelines in the journal *Ophthalmology*. The 2016 guidelines have lowered the recommended safe dosage to <5.0 mg/kg per day of real body weight. Additionally, it is important to recognize that patients of Asian descent tend to have perifoveal retinopathy, rather than central macular involvement. Annual screening, especially after 5 years of hydroxychloroquine usage, should be performed with Humphrey VF 10–2 and SD-OCT.<sup>11</sup>

### Discussion

HCQ is a DMARD with lower incidence of retinal toxic features than its predecessor, CQ. Patients should be screened for maculopathy prior to starting HCQ. Those with maculopathy before starting HCQ should be considered for alternative treatments as the preexisting maculopathy with make it harder to spot toxic changes due to medicine as they develop. Patients with no maculopathy and no other risk factor for retinal toxicity should be discharged by ophthalmologist back to their rheumatologists as ophthalmic examination can be deferred to five year following commencement of HCQ especially on doses less than 5 mg/kg lean body weight.

Monitoring earlier than five years can certainly be justified, and would often be recommended, if there are other risk factors such as: concomitant renal or liver disease, concomitant use of tamoxifen,

age greater than 60 years, daily dose greater than 400 mg (or in persons of short stature, a daily dose over 6.5 mg/kg of their ideal body weight), or some combination of these factors. Patient should see an ophthalmologist as soon as they develop visual symptoms in particular superior paracentral scotomas. These scotomas can be an early feature of retinal toxicity even on absence of fundal abnormality. The scotomas appear on the central 10 degrees visual field testing in majority of patients except those of Asian descent where a slightly larger visual field plot involving the central 24 degrees would be more beneficial in spotting the paracentral early changes. With Spectral domain Optical Coherence SD-OCT being widely available now, screening for HCQ toxicity has become an easy task to spot the earliest signs of maculopathy. Rheumatologist should weigh the risks against the benefits of stopping HCQ and decide whether an alternative DMARD would be safer for a patient instead of exposing patient to the irreversible retinal side effects of HCQ use.

### Conclusion

HCQ is a medicine to treat a wide array of rheumatologic disease. Ophthalmologists should be involved in the care of patient receiving HCQ. Ongoing monitoring by ophthalmologists and rheumatologists should continue to prevent the development of irreversible macular damage as long as patient is using HCQ and perhaps even longer.

### Financial disclosure

Authors have no financial interest to disclose.

### Acknowledgments

None.

### Conflicts of interest

Author declares that there is no conflict of interest.

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