The quinolines, hydroxychloroquine (Plaquenil) and chloroquine are used primarily for their anti-inflammatory effects in the treatment of auto-immune conditions such as rheumatoid arthritis.

Another common use of these drugs is the prophylaxis and suppression of malaria. The use of quinolines may cause several ocular side-effects. The most significant complication is irreversible macular damage resulting in both visual acuity and visual field loss. However, the Royal College of Ophthalmologists (RCO) recently recommended against the monitoring of patients receiving quinoline therapy as it was deemed to be too costly, given the low incidence of retinal complications. In this article, we present a case of hydroxychloroquine retinopathy, describe the ocular changes associated with quinoline therapy, and recommend a review schedule for optometric patients who are currently taking these drugs. Furthermore, we recommend a proactive approach toward medical practitioners prescribing these drugs for optometric-based monitoring of these patients.

The quinolines, chloroquine and hydroxychloroquine (Plaquenil), are most commonly used in the treatment of rheumatoid arthritis, systemic lupus erythematosus and cutaneous lupus, with recent studies establishing the efficacy of hydroxychloroquine in reducing the severity of pain, inflammation and disability in these conditions1-2. However, both drugs are associated with ocular side-effects.

Both chloroquine and hydroxychloroquine also act as effective anti-malarial agents, though current practice guidelines recommend the use of either low-dose hydroxychloroquine (less than 6.5mg/kg/day)3 or mepacrine, as reports of ocular toxicity with these drugs are rare3,4. Chloroquine, however, is associated with a far greater incidence of irreversible ocular toxicity and is generally only considered when other treatment options have failed4.

Case report
A 54-year-old female presented with reduced visual acuity in the right eye (RE), which had been noted for several weeks. The left eye (LE) was reported as normal. The patient was being treated for rheumatoid arthritis and had been taking 1 tablet (200 mg) of hydroxychloroquine daily for 3 years. This dose is well below the maximum safe daily dosage, as recommended by the RCO3.

Corrected visual acuities were 6/9 RE with no improvement with pinhole and 6/4.8 LE. Pelli-Robson contrast sensitivities were 1.60 and 1.70 log CS, respectively. Assessment of colour vision, using the D15 panel, revealed a blue-yellow defect in the right eye only (Figure 1). Fundus examination revealed stippling of the RPE and several regions of both hyperpigmentation and depigmentation in the right eye (Figure 2). The left fundus was free of any pigmentary changes. Neither cornea showed any sign of corneal epithelial changes. Neither fundus showed peripheral pigmentary change.

The patient was referred back to her rheumatologist and use of the drug was discontinued. The observed RPE disturbances and associated visual loss remained at follow-up, 6 months later.

Clinical features of quinoline-related ocular toxicity
The toxic ocular effects of quinoline therapy were first reported in 19585 by Hobbs and reviewed by Collin4 in 1962. They may be either reversible and asymptomatic, requiring no change in management, or irreversible and symptomatic, usually resulting in...
cessation of the therapy with these drugs. As with chloroquine, the most severe ocular complication of hydroxychloroquine treatment is maculopathy1. However, hydroxychloroquine appears to be less toxic than chloroquine. Early stippling of the RPE is typically followed by the occurrence of fine granular macular pigmentation and loss of the normal foveal reflex. These changes which tend to form a circular pattern (Figure 3) may progress to the classical bull’s eye maculopathy (Figures 4 and 5). This condition involves the formation of concentric zones of hyperpigmentation and depigmentation (with a hyperpigmented zone beneath the fovea). Advanced retinopathy may follow, including widespread pigmentary changes, optic atrophy and arteriolar attenuation5.

Generalised visual disturbances, difficulty with fixation and, rarely, a scotoma to white targets may develop in association with, and possibly even prior to, the early fundus changes6,12. Visual field defects correlate with the severity of the above-mentioned fundus changes13,14. However, prior to any retinal changes, a small paracentral (between 4 and 9 degrees from fixation) scotoma to a red target may develop20. Following the onset of bull’s eye maculopathy, central scotomata to white light and peripheral field constriction can occur21. It is yet to be seen whether more sensitive methods of perimetry (such as flicker or blue-yellow protocols), which have proven useful for other conditions, would identify field defects any earlier than standard methods permit.

Advanced maculopathy is accompanied by diminished visual acuity15 and colour vision defects16. In the early stages, even in a patient with significant pigmentary change, the full-field electroretinogram may have normal photopic voltages and latency17. As the retinopathy progresses peripherally, dark adaptation is affected and a subnormal ERG indicates a greater loss of cones than rods18. The usual field loss is central19 but an often overlooked finding is a peripheral pigmentary retinopathy (Figure 6) with an associated peripheral visual field loss, occasionally leading to a mistaken diagnosis of retinitis pigmentosa or cone-rod dystrophy20.

Conical verticillata or “vortex keratopathy” in which greyish or golden conical epithelial deposits appear in a vortex pattern is the other common side-effect of quinoline therapy. These deposits begin as individual white deposits but later become pigmented and yellowish21. Later, there are yellowish curved lines in the typical vortex pattern22. These deposits are not the drug itself, but rather lipid inclusions which are also seen with amidone and chlorpromazine use, and in the lysosomal storage diseases such as Fabry’s disease22. They all have a common pathophysiology of causing binding of anionic phospholipids of lysosomal membranes and the promotion of intracellular inclusions19. The appearance of the keratopathy is not dose-related and usually is not correlated with the development of subsequent retinopathy23. Remission usually follows cessation of therapy, although spontaneous resolution is possible24. These deposits are asymptomatic, except in rare cases when they become dense enough to cause haloes and impaired vision25.

Disturbances of accommodation and extra-ocular muscle palsies have been associated with quinoline therapy, but are rare and transient26. In addition, adverse reactions involving the skin and gastro-intestinal tract may coincide with the use of hydroxychloroquine and chloroquine. Non-specific complaints such as headache, vertigo and muscle weakness may also occur27. Following chloroquine therapy, marked bleaching of hair28, 29 may occur. Eyebrows, eyelashes and axillary and pubic hair may be affected30. In some cases, the hair may fluoresce with ultraviolet light31.

The progression of quinoline retinopathy is variable and unpredictable, but development of retinal lesions is typically progressive – especially where treatment is continued – and often up to three years after cessation of drug use32, 33. Progression of retinopathy after cessation of treatment is more likely if the retinopathy is advanced, conversely retinopathy is more likely to resolve if treatment ceases during the early stages of retinopathy34. Interestingly, the onset of retinopathy has been observed up to 5 years after quinoline therapy has concluded16. Nevertheless, the prognosis is strongly dependent on detection of early changes, particularly macular pigment disturbance. Therefore, it is important for optometrists as primary eye care practitioners and, when screening patients for rheumatologists, to recognise these changes in order for modifications to therapy to be made, if appropriate, and the extent of visual loss minimised.

Pathophysiology
While the precise mechanism of their anti-inflammatory effect is not understood, quinolines are known to interact with cellular components, such as nucleic acids and melanin12, 35. Thus, the quinolines become concentrated in the melanin-containing structures of the eye such as the iris and retinal pigment epithelium.

Quinolines exert their toxic effect upon both the RPE and directly on the photoreceptors36. The earliest histopathological change, even before the RPE damage, appears to be membranous cytoplasmic bodies in ganglion cells and degenerative changes in photoreceptor outer segments37. Chloroquine has been shown to cause swelling in the pigmented cells, reduction in melanin concentration and a decrease in the activity of several dehydrogenase enzymes38. Other studies indicate that chloroquine destroys or inhibits oxidative enzymes within the ellipsoids of...
the inner segment. Loss of both rods and cones is followed by pigment migration into the outer retinal layers, though the inner retina remains intact. Hence, it is likely that quinolines diminish the effectiveness of both the regulatory mechanisms of the retina and RPE, and the photo-protective melanin-containing RPE cells.

A factor that adds to the toxicity of chloroquine and hydroxychloroquine is their very slow excretion rate. Small amounts of chloroquine are detectable in blood and urine as long as five years after the drug is discontinued. This prolonged retention may account for reports of progressive and delayed-onset retinopathy despite discontinuation of therapy.

**Discussion**

Ocular toxicity subsequent to hydroxychloroquine treatment is uncommon. As an indication of the rarity of this condition, we are aware of only 29 published incidences since 1968. Furthermore, several prospective studies have addressed the issue of prevalence, with a total of 2 cases of retinopathy observed in 2707 patients receiving the drug. Most of the reported cases were observed in patients receiving doses higher than the current recommended maximum (6.5mg/kg/day). Importantly, in those patients exhibiting toxic effects and taking less than the recommended safe dosage, the overwhelming majority had cumulative doses of greater than 200g.

This is consistent with the proposal of Mills, Beck and Power who suggested that maculopathy is unlikely to develop in patients with normal fundi prior to treatment, provided a cumulative dose of approximately 200g is not exceeded. In support of this suggestion that patients with normal fundi may have a greater tolerance of hydroxychloroquine, Johnson and Vine reported that no retinopathy was found in nine patients with cumulative doses ranging from 1,054g to 3923g. In the case reported here, the cumulative dose was 200g – serving as some justification for the suggestion of Mills et al (1981) that eye examinations should be conducted at each 100g of cumulative treatment.

Despite the infrequency of complications, the manufacturer of hydroxychloroquine recommends an initial ophthalmic examination prior to therapy and subsequent 6-monthly monitoring. Temporary cessation of treatment is suggested at the appearance of any corneal changes and complete withdrawal of the drug following the detection of any fundus signs or visual field defects.

Mills, Beck and Power doubted whether routine visual field screening was justified, and suggested that careful opthalmoscopy appeared to be the most effective test, but, Bernstein included in his definition of hydroxychloroquine retinopathy the presence and persistence of paracentral or central visual field scotomata to supra-threshold white stimuli.

Given the low incidence of quinoline-related ocular toxicity, the Royal College of Ophthalmologists (RCO) found there was no evidence-based justification for an ophthalmic screening programme. Furthermore, they described any such screening programmes as costly and as generating needless anxiety for patients and unnecessary work for clinicians. Despite this, the RCO have suggested an annual evaluation (by the prescribing medical practitioner) of visual acuity and referral for ophthalmic examination in the presence of any loss.

According to RCO, the ocular examination should include:

- Distance and near acuity measurement
- Colour vision assessment
- Visual field assessment (automated perimetry)
- Corneal biomicroscopy
- Mydriatic fundus examination

As these may all be components of a routine ophthalmic examination, optometrists are ideally suited to monitor patients receiving hydroxychloroquine therapy in a thorough and cost-effective manner. The advent of automated perimeters with rapid testing paradigms facilitates the inclusion of visual field testing in a routine examination protocol for patients receiving hydroxychloroquine treatment.

The authors concur with the advice of Mills, Beck and Power that patients receiving hydroxychloroquine therapy should be monitored every 100g of cumulative dose. Table 1 gives the suggested examination frequency according to dosage.

Finally, the authors recommend a proactive awareness campaign directed at the prescribing medical practitioner. Optometrists possess the necessary skill and equipment to monitor these patients efficiently and cost-effectively. To reduce the risk of irreversible visual loss, prescribing practitioners should be encouraged to refer patients to optometrists for review at 100g cumulative dose intervals.

**References**


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