Hydroxychloroquine-related retinal toxicity

Hui Jen Ding1,2,a, Alastair K. Denniston3,4, Vijay K. Rao2 and Caroline Gordon2,5

Abstract
HCQ is widely used for the treatment of rheumatic diseases, particularly lupus and RA. It is generally well tolerated, but retinopathy is a concern. Retinopathy is rare, but is sight threatening, generally irreversible and may progress even after cessation of therapy. Damage may be subclinical. Although a number of risk factors have been proposed (such as duration of therapy and cumulative dose), the many exceptions (e.g. retinopathy on low-dose HCQ, or no retinopathy after a very large cumulative dose of HCQ) highlight our limited understanding of the disease process. Novel technologies such as optical coherence tomography (OCT), fundus autofluorescence (FAF) and multifocal electroretinogram (mfERG) may provide the earliest structural and functional evidence of toxicity in these stages. Along with the well-established technique of central visual field testing (10-2 visual fields), these modalities are increasingly being used as part of screening programmes. The ideal single test with high sensitivity and high specificity for HCQ retinopathy has still not been achieved. Screening for HCQ retinopathy remains an area of considerable debate, including issues of when, who and how to screen. Commonly accepted risk factors include receiving >6.5 mg/kg/day or a cumulative dose of >1000 g of HCQ, being on treatment for >5 years, having renal or liver dysfunction, having pre-existing retinopathy and being elderly. HCQ continues to be a valuable drug in treating rheumatic disease, but clinicians need to be aware of the associated risks and to have arrangements in place that would enable early detection of toxicity.

Key words: hydroxychloroquine, retinal toxicity, ocular safety, risks, screening modalities, systemic lupus erythematosus.

Introduction
Antimalarials are an important and long-established part of the armamentarium for treating rheumatic diseases.

There have been several early descriptions of antimalarial use in rheumatic diseases, starting from 1894 till the 1950s [1-5]. Chloroquine (CQ) was introduced in 1953, followed by HCQ in 1955, but over the years HCQ has superseded the use of CQ because of its better ocular safety profile [4]. The adverse effects of HCQ have also been well documented and include neuromyotoxicity, cardiotoxicity and ocular toxicity. Ocular toxicity of HCQ ranges from a non-significant keratopathy to a potentially blinding retinopathy [6, 7]. There has been uncertainty concerning the risk factors for ocular toxicity and the appropriate methodology for assessing whether or not it is present. This review provides an update of our current understanding of these issues.

Mechanism of action of HCQ
HCQ is a lipophilic base that passes easily across cell membranes and into acidic intracellular vesicles, altering...
lysocome stability and leading to suppression of antigen presentation, inhibition of prostaglandin and cytokine production and influencing toll-like receptor signalling and leucocyte activation [8] which translates into immunosuppressive, antiproliferative, antithrombotic and photoprotective effects. HCQ is used mainly in RA and SLE. Most of its benefits have been well described elsewhere, mainly in the context of lupus: reduction of flares and damage, enhancement of MMF response, improvement of survival, and reduced risk of seizures and thromboses [9–15].

**Mechanism of toxicity**

HCQ has 70–80% bioavailability after oral administration and a half-life of 50 (16) days [16]. HCQ is melanotropic and is deposited in tissue with high melanin content like skin, ciliary bodies and the retinal pigment epithelium (RPE). It is excreted by the kidney and liver, and is minimally removed during dialysis; therefore, persistent liver and renal dysfunction potentiates its toxicity.

It has been postulated that the lower toxicity of HCQ compared with CQ may be due to the hydroxyl group limiting the ability of HCQ to cross the blood–retinal barrier [17]. The actual mechanism of retinal toxicity is not well established. Primate studies suggest that the earliest detectable changes are in the neural retina (specifically ganglion cells and photoreceptors), with RPE changes occurring later [18]. In vitro studies on cultured RPE cells suggest that HCQ alters RPE lysosome pH, resulting in higher levels of lipofuscin, a type of pigment that commonly accumulates with age and is associated with photoreceptor degeneration [19].

**Corneal verticillata**

Like a number of other drugs, HCQ and CQ can cause corneal verticillata (also known as vortex keratopathy). These epithelial changes arise due to precipitation of the drug, typically forming a whorl-like pattern that is reversible with drug cessation [7]. These changes are generally regarded as being of no visual significance [20], although some patients do report haloes. The presence of corneal verticillata does not correlate with retinal toxicity. Corneal verticillata is less common with HCQ than CQ [7, 21, 22].

**Retinopathy**

Although rare, retinopathy is the major concern expressed by most patients and clinicians using HCQ. Fear of side effects has been cited as one of the reasons for non-adherence [23, 24] and has led to estimated adherence to HCQ regimens to be as low as 49% [25]. Blood monitoring showed that undetectable HCQ levels (suggesting severe non-adherence) were present in 29–64% [23, 26].

In its advanced form, it may lead to profound irreversible loss of central vision, associated with clinically obvious changes in the macula. The challenge is that it can be very difficult to identify in its early stages, when it may be asymptomatic with no obvious clinical changes on fundoscopy. It is this early asymptomatic stage that justifies the argument for screening. Although the best way of doing this is still a matter of debate, the various methods all provide useful insights into the structural and functional consequences of early toxicity. The pattern of retinopathy caused by both HCQ and CQ is similar, but is much less common with HCQ.

The earliest clinical changes in HCQ retinopathy are subtle changes at the macula, with pigmentary stippling and loss of the foveal reflex (the typical light reflection seen on fundoscopy). Patients are usually asymptomatic, because the earliest functional changes occur peripherally, that is, in a ring around central fixation. Since central visual acuity is preserved, the patient may not notice any problem until much later in the disease process. In passing, it should be noted that standard visual acuity tests (such as Snellen distance acuity) are similarly unlikely to detect early changes, although formal central visual field testing (such as the use of a 10-2 Humphrey visual field) may detect the paracentral reduction in sensitivity at an early stage.

Newer imaging modalities have revealed some of the structural changes that occur at these early stages. Spectral Domain Optical Coherence Tomography (SD-OCT) shows that there is early thinning of outer retinal layers [27], typically with loss of the paravascular photoreceptor inner segment/outer segment (IS/OS) junction and central foveal sparing [28–30]. There is preservation of the RPE and external limiting membrane. These perifoveal changes explain the unusual paracentral pattern of visual loss seen in early HCQ toxicity. Significant early ocular findings, as detected by the different screening modalities, are summarized in Table 1 and Fig. 1.

In its advanced stage, HCQ retinopathy progresses to a symptomatic paracentral and eventually central scotoma with a characteristic bull’s eye maculopathy (BEM), a clear zone of depigmentation around the fovea [20]. Although HCQ retinopathy is bilateral, asymmetric changes may be seen. Sometimes prominent choroidal patterns and fine granularity of the retina can be seen peripherally [20]. Less commonly, with severe damage, there may be attenuation and segmental constriction of retinal arterioles with disc pallor [20]. With continued treatment, these pigmentary changes may become generalized, with resultant loss of visual acuity and peripheral vision [34].

Progression of disease is associated with evolving symptomatic loss of vision. Difficulties with reading may be noted earlier than any worsening in distance vision. Although the paracentral visual field is asymptomatic in its early stages, it becomes noticed due to its increasing severity and central extension of this scotoma [35]. Photopsia (perception of flashes or flickering light), metamorphopsia (distortion e.g. of straight lines) and, in its later stages, reduced colour vision [36] and peripheral field loss [7] are also reported.

Early toxicity may be reversible, with resolution of symptoms and objective recovery in functional [visual field and multifocal electroretinogram (mERG)] and morphologic (SD-OCT) abnormalities [37–46]. Cessation of therapy usually results in stabilization of disease [7, 47], although damage has been reported to continue for up to
HCQ-related retinal toxicity

Table 1 Early ocular changes of HCQ toxicity

<table>
<thead>
<tr>
<th>Screening modality</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Fundoscopy</td>
<td>Macular pigmented changes/fine pigmented stippling of the macula [20]</td>
</tr>
<tr>
<td>Visual fields</td>
<td>Paracentral scotoma [31]</td>
</tr>
<tr>
<td>FAF</td>
<td>Pericentral ring of increased FAF, mottled pericentral loss of FAF with adjacent increased FAF [32] Reduced FAF or areas of early photoreceptor damage (increased autofluorescence from accumulation of outer segment debris) [32]</td>
</tr>
<tr>
<td>SD-OCT</td>
<td>Moth-eaten photoreceptor IS/OS appearance [28] Loss of perifoveal photoreceptor IS/OS junction, perifoveal thinning of outer nuclear layer, apparent posterior displacement of inner retinal structures towards RPE, creating a flying saucer sign [29]</td>
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<tr>
<td>MIERG</td>
<td>Increased R1/R2 ring ratio [33]</td>
</tr>
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IS/OS: inner segment/outer segment; MIERG: multifocal electoretinogram; RPE: retinal pigment epithelium; FAF: fundus autofluorescence.

7 years after cessation of therapy [35, 48–51], including frank progression to BEM [52]. There has also been a report of a delayed onset of toxicity that occurred 1 year after discontinuation of treatment [53]. It should be noted, however, that progression of disease after cessation of therapy should prompt the clinician to consider alternative aetiologies for the retinopathy.

Ocular safety

Since the first cases of HCQ retinopathy were reported in the 1960s, there have been over 180 cases reported in the world literature. Increased sensitivity of screening tools and greater awareness of the condition has accelerated the rate of reporting of HCQ cases. Yam’s review of HCQ cases from the 1960s to 2003 noted 47 cases of HCQ retinopathy [7], whereas since 2003 there have been nearly 160 cases. These reports are summarized in supplementary Table S1, available at Rheumatology Online.

A number of retrospective and prospective studies have attempted to assess the risk of developing HCQ retinopathy and to identify risk factors for toxicity [54, 55]. In the largest such study to date, Wolfe and Marmor screened 3995 patients who had received HCQ for SLE or RA for self-reported toxicity, followed by specialist confirmation of these cases. In this study definite or probable HCQ toxicity was noted in 0.65% (95% CI: 0.31, 0.93%). They reported a clear increased risk with duration of exposure: <0.3% for those with HCQ exposure of <5 years but up to 2% for those with exposure of 10–15 years. Interestingly, they found no association with daily dosage, but they note that their data regarding this was incomplete [55]. Levy’s retrospective chart review of 1207 patients receiving HCQ found no cases of definite toxicity in patients on HCQ <6.5 mg/kg/day, but one patient with definite toxicity and five with indeterminate but probable toxicity in those who received >6.5 mg/kg/day HCQ [54]; the patient with definite toxicity had taken HCQ for 7.3 years at a dose of 6.98 mg/kg/day. Overall definite or probable toxicity occurred in 0.5% of patients in the Levy series, a similar proportion to the Wolfe study. Smaller studies include those of Mackenzie, who found no cases of HCQ retinopathy in a cohort of >900 patients with HCQ toxicity. Mavrikakis et al. [58] reported on their prospective series of 526 patients who received HCQ, of which 400 patients had received at least 6 years of treatment. Prior to 6 years of treatment, no patients had developed retinopathy. Two patients subsequently developed retinopathy (one at 6.5 years and one at 8 years), equating to a rate of 0.5% for those patients with over 6 years of treatment. The mean duration of treatment in this group was 8.7 years, indicating a relative paucity of patients with longer follow-up.

Prospective studies have also suggested a low rate of HCQ toxicity. Mavrikakis et al. [58] reported on their prospective series of 526 patients who received HCQ, of which 400 patients had received at least 6 years of treatment. Prior to 6 years of treatment, no patients had developed retinopathy. Two patients subsequently developed retinopathy (one at 6.5 years and one at 8 years), equating to a rate of 0.5% for those patients with over 6 years of treatment. The mean duration of treatment in this group was 8.7 years, indicating a relative paucity of patients with longer follow-up.

Accurately estimating the incidence of HCQ retinopathy is difficult. Most studies are case series or retrospective cohorts, and the relatively few prospective studies are limited in size and duration of follow-up. Definitions of retinopathy vary between studies, in part reflecting the increasing sensitivity offered by novel screening modalities. The data available does, however, suggest that HCQ retinopathy remains rare (~0.1–0.7% overall, but increasing with duration of treatment), and HCQ-associated BEM is very rare (~0.1%) [54, 55].

Risk factors for toxicity

Reported risk factors for toxicity include: daily dose >400 mg, or >6.5 mg/kg ideal/lean body weight for short individuals; cumulative dose >1000 g; duration of use >5 years; renal or hepatic dysfunction; obesity; age >60 years; and pre-existing retinal disease or maculopathy [31]. It is recognized, however, that retinal toxicity is occasionally seen in apparently low-risk individuals, inviting the possibility that there may be genetic [59] or other as yet unrecognized risk factors or alternative causes of retinopathy, as these can be hard to distinguish clinically, especially in early stages.
The relationship between daily and/or cumulative dose and toxicity is still unclear. The concept of 6.5 mg/kg/day as a safe threshold arises from studies such as Mackenzie’s series, in which the author reports that there were no cases of toxicity in >900 patients taking <6.5 mg/kg/day (mean follow-up of 7 years) [56]. This threshold has been adopted by national bodies such as the Royal College of Ophthalmologists (RCOpht) UK.

A female patient was diagnosed with HCQ retinal toxicity at the age of 53 years, having taken HCQ for 12 years at 400 mg/day. She was not obese and had no additional risk factors for toxicity. Classic bilateral BEM was visible clinically, as seen on fundal photographs (A and B). FAF demonstrates typical symmetrical high signal haloes in the right eye (C) and left eye (D), which are also visible on the Infrared reflectance image (E). SD-OCT shows typical thinning of the inner retinal layers with loss of the parafoveal photoreceptor ellipsoid zone and relative central foveal sparing (F).

SD-OCT: spectral domain optical coherence tomography; FAF: fundus autofluorescence; BEM: bull’s eye maculopathy.

**Fig. 1** Ocular findings of HCQ retinal toxicity as detected by various screening modalities
(endorsed by the British Society for Rheumatology and the British Association of Dermatologists), and was present in the 2002 American Academy of Ophthalmology (AAO) guidelines (endorsed by the ACR). It should be noted, however, that there are many reports of toxicity in patients taking <6.5 mg/kg/day) [37, 47, 58, 60–62], with Rüther reporting a case of retinopathy on only 2 mg/kg/day HCQ [63]. Furthermore a number of key studies, such as that of Wolfe and Marmor [55] and that of Lyons [43], have not found an association between daily dose and toxicity. Bergholz et al. [64] reported two cases of retinopathy while on HCQ <6.5 mg/kg/day. An additional issue is that although it is recommended that HCQ dosage should be calculated based on lean or ideal body weight, this is often not specified in reports of toxicity in the HCQ literature, making comparison between studies more difficult. The more recent guidelines from the AAO (published 2011) have advised that a maximum dose of 400 mg/day is recommended but that lower doses (not >6.5 mg/kg) be used in individuals of short stature [35].

Recently there has been an increasing emphasis on the risk associated with a cumulative dose >1000 g. In their retrospective study of 3995 patients receiving HCQ (discussed earlier), Wolfe and Marmor [55] reported an odds ratio of toxicity of 4.5 in those taking a cumulative dose >1000 g compared with <1000 g. MIERG studies by Lai et al. [45] and Lyons and Severns [33, 43] suggest that cumulative dose is associated with mfERG abnormalities. In the Lyons and Severns [43] study, 41% of patients on cumulative doses >1250 g showed mfERG changes compared with 10% of those on <1250 g (P < 0.001). It should be noted, however, that some patients seem to tolerate very high doses of HCQ (up to 3923 g) without toxicity [54, 65], whereas other patients develop toxicity to lower doses [62, 63]. A French study showed that whole-blood HCQ concentration >1000 ng/ml reduced risk of lupus flares [66]. Measurement of HCQ blood levels may suggest that some patients require >6.5 mg/kg/day to achieve the recommended level. These patients should not be at increased risk of toxicity, providing levels are monitored, but it may be important to monitor cumulative dose as well when assessing risk of ocular toxicity. Although there are no published data on using HCQ blood levels to assist in monitoring for ocular toxicity, there is evidence that levels increase with impaired renal function [67] and that zero levels can reveal patients that are non-compliant. Further studies are required to determine the value of monitoring levels in routine practice.

A number of studies have identified increasing risk with duration of treatment, with many identifying a significant increase in risk at around 5–7 years of therapy [55, 59]. In the study discussed earlier by Wolfe and Marmor [55], they provided point estimates of toxicity: 0.29% at 5 years, 0.33% at 7 years, 1.0% at 10 years, 2.1% at 15 years and 3.1% at 20 years. It should be recognized that the estimates of toxicity risk become more uncertain for longer durations of therapy due to the small proportion of such patients included in these studies. Once again, however, it should be recognized that there is no absolute safe zone. Moschos et al. [44] showed that mfERG abnormalities were seen in patients who had been exposed for ≤5 years, while Michaelides et al. [48] and Farrell [22] have reported cases of toxicity developing by 2 and 3 years of use. These patients had received a cumulative dose of 365–476 g of HCQ [44, 48], a high daily dose of 11.7 mg/kg/day [48] and were older when started on antimalarial therapy [22].

As HCQ is cleared by the liver and kidney, dysfunction in these systems could potentiate toxicity. Although a number of cases of retinopathy in renal impairment have been reported [46, 53, 68–72], this is seldom seen in the larger series, possibly because clinicians have been appropriately cautious of using HCQ in patients with renal or liver dysfunction.

As HCQ does not distribute in fatty tissue, there is a danger of overdosage if obese patients are dosed based on weight alone. As noted earlier, the most recent AAO recommendations advise that the daily dose should not exceed 400 mg/day in any individual, but that lower doses should be used in individuals of short stature [35].

Age >60 years has been postulated as a risk factor [7, 65]; however, Wolfe and Marmor [55] found no such association, with 30% of patients with definite or probable toxicity being <60 years of age. The main issue with elderly patients is the higher risk of age-related macular changes that may be difficult to distinguish from early HCQ retinopathy [35]. Additionally, there may be some age-related reduction in function, with Martinez-Costa demonstrating that those >60 years old had worse retinal sensitivities on microperimetry [73].

Screening practices

Screening practices (USA) exist to guide monitoring for HCQ maculopathy and are outlined below. The main difference between them is that the UK recommendation focuses on what should be done at baseline, while the USA recommendation focuses on identifying risks for toxicity and advises on what should be done in those at risk and those who have been on >5 years of treatment. The UK recommendation does not address what should be done in those patients who have been on treatment for >5 years, and we understand that this recommendation is currently under review.

United Kingdom

Recommendations for screening practice in the UK were produced by RCOphth in 2009 (Table 2). These were developed in collaboration with the British Society of Rheumatologists and the British Association of Dermatologists [74].

United States of America

The AAO has published an update on recommendations for screening for CQ and HCQ toxicity in the USA in 2011 [35].
TABLE 2 Summary of Royal College of Ophthalmologists 2009 recommendations [74]

| Recommendations for good practice in rheumatology and dermatology clinics |
| Maximum dosage if HCQ should not exceed 6.5 mg/kg lean body weight (typically 200–400 mg/day); if overweight, check lean body weight with BMI calculator |
| Establish renal and liver function at baseline assessment |
| Enquire about any visual impairment which is not corrected with spectacles at baseline and at annual review |
| Record reading performance with each eye with a reading spectacle correction if worn, using a near-vision test type, at baseline and at annual review |
| If the patient can read a small print size such as N8 or N6 at baseline assessment, treatment with HCQ can be commenced |
| If visual impairment is suspected, the patient should be advised to consult with an optometrist first. If any apparent impairment is correctable with refraction, treatment may commence. Any relevant abnormality detected by the optometrist would be referred to an ophthalmologist in the usual way. |

Referral to an ophthalmologist if:
- Patient has visual impairment or eye disease detected at baseline assessment as confirmed by optometrist
- Notices reduced vision, patchy central vision or distorted central vision while on treatment. Patients are warned to seek advice from the prescriber and to have vision checked by an optometrist.

Examination by the ophthalmologist should include:
- Enquiry about disturbances of central vision
- Visual and reading acuity
- Central visual field, using Amsler chart (preferably red on black) or automated perimetry
- Slit-lamp examination of cornea
- Stereoscopic slit lamp examination of the retina
- Subsequent evaluations done at the discretion of the ophthalmologist
- Patients who have received five continuous years of HCQ may have further evaluations arranged on an individual basis as agreed locally

Adapted from The Royal College of Ophthalmologists Hydroxychloroquine and Ocular Toxicity Recommendations on Screening 2009, with permission from the Royal College of Ophthalmologists.

The AAO guidelines recommend that patients get a baseline examination within the first year of use and annual screening after 5 years of use, or earlier in higher-risk patients, that is, those on higher than recommended doses of HCQ, those taking HCQ >5 years, those with persistent renal or hepatic dysfunction, those who are obese, the elderly and those with pre-existing retinal and macular disease that may make it harder to screen for early changes. It is also important to counsel patients at every visit about the risk of HCQ, the importance of regular screening and the need to inform the physician or ophthalmologist of any visual changes suggestive of toxicity or development of systemic disease that would put them at higher risk of toxicity.

The AAO recommend that screening visits should include subjective tests and at least one objective test, where such tests are available. Subjective tests include detailed ophthalmologic examination (visual acuity, corneal examination, retinal exam through a dilated pupil) and an automated visual field test (Humphrey 10-2 test). The objective tests recommended by the AAO are one or more of SD-OCT, mFERG and fundus autofluorescence (FAF). Any abnormalities picked up on the automated visual field test should be followed by more detailed objective tests.

The primary value of fundoscopy is not for screening for toxicity but for documentation of other retinal pathology. Tests which are no longer recommended are the Amsler grid test, colour vision tests, fundus photograph, time-domain OCT, fluorescein angiography and full-field ERG as they are not sensitive enough to detect early signs of toxicity. The AAO also provides recommendations on how to manage toxicity categorized according to: suggestive findings, possible toxicity and probable toxicity [35].

**Screening modalities**

Screening tests can be divided into those looking at morphological abnormalities (FAF and SD-OCT) and those looking at functional abnormalities [mFERG and Humphrey visual field (HVF)]. Although each of these have value in identifying early HCQ retinopathy before clinically evident structural changes are seen [33, 48, 72, 75], none are 100% sensitive [22] and are generally used in a complementary manner [72]. There are limited studies comparing the sensitivity and specificity of these tests with the automated 10-2 visual field test [42, 76, 77]. Studies investigating HCQ retinopathy based on the screening modality used are summarized in supplementary Table S2, available at Rheumatology Online. Microperimetry is a novel modality that is still being evaluated for its potential as a screening tool. A brief description is provided in the supplementary data in the section on microperimetry, available at Rheumatology Online.

**Humphrey visual field test**

Automated perimeter of the central 10° (e.g. 10-2 HVF) is the commonest additional test performed for HCQ retinopathy screening. In a study of 262 patients undergoing screening, Elder et al. reported four patients who showed reproducible evidence of toxicity on HVF 10-2 testing before changes in visual acuity, colour vision or
fundoscopy [77]. The classic finding is of a partial or complete ring defect between 2° and 6°, with central sparing [31]. The 10-2 white protocol is recommended (as per AAO guidelines), although the red protocol may be more sensitive [78]. Although perimetry is very dependent on patient engagement with the test, it may in some patients be the first modality to detect toxicity, even before mfERG [22, 42, 72] or SD-OCT [74].

**SD-OCT**

OCT is a non-invasive interferometric optical imaging modality that provides detailed cross-sectional imaging of tissue morphology [79]. HCQ toxicity is first manifested by thinning of inner retinal layers [80], followed by loss of the parafoveal photoreceptor inner segment/outer segment junction with central foveal sparing [27–29]. There is preservation of the RPE and external limiting membrane, and downward displacement of overlying inner retinal layers, sometimes described as the flying saucer sign [29]. In most cases, the SD-OCT findings correspond to HVF 10-2 and fundoscopic examination abnormalities [28], although in some cases SD-OCT changes may preceede any other abnormality [80, 81]. Interestingly, Mittelut et al. [46] showed that preservation of the external limiting membrane on OCT is a positive prognostic sign, with a higher probability of photoreceptor layer regeneration and functional visual improvement on perimetry after discontinuation of therapy.

**Fundus autofluorescence**

Autofluorescence imaging—commonly using a 488-nm Scanning Laser Ophthalmoscope to detect lipofuscin autofluorescence—may detect early photoreceptor damage (high signal due to accumulated lipofuscin) [32, 82–84] or RPE loss (low signal) [85]. Abnormalities start as a fine pericentral ring of increased autofluorescence, progressing to mottling and generalized loss of pigment epithelium (manifested as absent autofluorescence) [32]. It is not as widely available as SD-OCT. Although it may pick up early retinopathy and may predate mfERG abnormalities [32], the changes may be more subtle than those seen with SD-OCT and may be missed [46]. (We would recommend that it is used as an adjunct to SD-OCT examination, and not in isolation.)

**MfERG**

MfERG measures local electroretinogram responses across the macular and perimacular regions of the retina (central 40°) [22, 86]. MfERG has been shown to be a sensitive test for toxicity [33, 42, 45, 68, 87, 88]. MfERG changes correlate with both structural (SD-OCT) and functional (HVF 10-2) findings in detecting HCQ retinopathy [89, 90]. Maturi et al. [42] noted that mfERG changes were associated with a cumulative dose of >500 g and >5 years use and could be classified into four patterns: paracentral loss, foveal loss, peripheral loss and generalized loss. Paracentral loss, especially with prolonged implicit times, is the most specific pattern for HCQ toxicity [42, 45]; foveal loss appeared to be an early feature and generalized loss a late pattern [42]. Lyons and Severns [33] showed that ring ratio analysis (increased R1/R2 ratio) was useful in detecting early toxicity; Lyons suggested that these changes were detectable from a lower cumulative dose of >400 g (i.e., after 2–3 years of standard dosing). In another series, Kellner et al. [32] reported that all patients with abnormal FAF were found to have abnormal mfERG. In some cases, cessation of HCQ is associated with some recovery of mfERG response [33, 42, 45]. The paracentral changes seen in mfERG do appear to be fairly specific, and may be used as supportive evidence both that any reported visual loss is retinal in origin and that it is likely to be due to HCQ (rather than e.g. early changes of age-related macular degeneration) [33]. It should be noted, however, that most studies investigating the use of mfERG in HCQ toxicity have compared with SLE patients not taking HCQ or healthy controls and not with patients with other causes of macular pathology.

**Adherence to guidelines**

An effective screening programme for HCQ toxicity requires engagement from rheumatologists and ophthalmologists. In a survey of rheumatologists in the USA, Fraenkel found that 94% of the respondents screen their patients annually, and most would continue to screen because they would not risk visual loss (75%) or litigation (74%); interestingly 44% said they would continue to screen even if the ACR advised that it was unnecessary [91]. A study of UK rheumatologists by Samanta et al. [92] found that the national guidelines (RCoPhth 2004 Guidelines) were not consistently followed with regard to baseline assessment (47% did not assess baseline visual symptoms), referral to ophthalmology (28% referred all patients on HCQ routinely for screening) and frequency of monitoring (highly variable).

It is also important that healthcare professionals involved in the care of these patients are familiar with the guidelines. Semmer surveyed the knowledge and familiarity of ophthalmologists in Minnesota, USA, with the 2002 AAO guidelines and found that most were unable to identify the risk factors for toxicity and that screening for low-risk patients was done more frequently than recommended. This translated to an excess cost of screening in the first 5 years of therapy [93].

Browning studied the impact of the 2011 AAO recommendations on the practices of ophthalmologists and optometrists in North Carolina, USA, and concluded that the revised recommendations, emphasizing mfERG, SD-OCT or FAF, raised screening costs without improving case detection [94]. The recommended 5-year screening-free interval for low-risk patients after baseline examination was ignored for reasons that were unclear. Browning also pointed out that interpretation of SDOCT and mfERG reports can be difficult, and only those familiar with them should be interpreting them. In his response to Browning, Marmor [78] argues that this series highlights the limitations of perimetry and underlines the need for
additional tests such as SD-OCT, FAF and mfERG. Interestingly, Marmor [78] also suggests that it might be possible to institute a non-physician screening programme in which undilated SD-OCT and 10-2 HVF are sent to a central reading centre.

**Conclusion**

HCQ retinopathy is a rare but serious complication of a valuable therapy. Marmor and Hu [95] recently published a case series of assessment of progression of retinopathy of various stages after discontinuation of therapy. Those with severe retinopathy, as defined by SD-OCT and FAF changes, continued to progress for at least 3 years after cessation of therapy. These changes were not reflected in visual acuity until very late. In contrast, the prognosis of those with early retinopathy, that is, without RPE changes, was better; the changes stabilized and the risk of progression to visual loss was minimal. Even those with moderate disease appeared to have some stabilization of disease. Those with severe changes had received higher doses of HCQ (8–11 mg/kg/day).

The evidence strongly supports the need to keep dose ≤6.5 mg/kg/day and to ensure screening for ocular toxicity in those treated for >5 years. There is no single definitive test for early retinopathy, but a number of modalities may detect structural or functional changes prior to symptoms. The rationale for screening is based on the possibility that these changes can be detected early, avoiding progression. Guidelines for screening, such as from the AAO, are increasingly emphasizing the use of newer objective tests annually to supplement clinical examination and perimetry. This has important implications for service provision, and there needs to be agreed protocols with local health care providers in order to reduce the risk of visual loss with long-term therapy, given the association with increasing duration of exposure.

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**Supplementary data**

Supplementary data are available at *Rheumatology* Online.

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