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The ROYAL COLLEGE of OPHTHALMOLOGISTS

EDITORIAL

The Royal College of Ophthalmologists recommendations on monitoring for hydroxychloroquine and chloroquine users in the United Kingdom (2020 revision): executive summary

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Introduction

The Royal College of Ophthalmologists (RCOphth) published recommendations for monitoring in users of hydroxychloroquine and chloroquine in the United Kingdom in 2018 in order to reduce the risk of irreversible sight loss from toxic retinopathy in this group [1]. The 2018 recommendations have been replaced by the recently published clinical guideline: "Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on Monitoring" (RCOphth, 14 Dec 2020)" [2]. This executive summary describes the new recommendations, and highlights the key changes from the previous clinical guideline with their justification. A review of the previous recommendations was prompted by the availability of high-quality published audit data based on the real-world outcomes of monitoring according to the 2018 recommendations [3, 4], feedback from UK retinal specialists and other key stakeholders, and the availability of supporting data from new clinical research studies judged to be of sufficient quality and relevance.

The case for monitoring was originally supported by the finding of an overall prevalence of retinopathy of 7.5% in long-term (>5 years) hydroxychloroquine users using modern retinal imaging techniques in the USA [5]. A real-world, UK-based audit identified a prevalence of retinopathy of 6.3% according to the same diagnostic criteria, validating the case for monitoring services in the UK for patients at risk [3].

The full guideline can be found online at: https://www.rcophth.ac.uk/standards-publications-research/clinical-guidelines/. An updated patient information leaflet written by the authors in collaboration with the Macular Society is available and should be distributed to patients. The criteria used for grading evidence is specified in Table 1. The recommendations and grade of evidence supporting them are detailed in Table 2a–h. Figure 1 presents a flow diagram summarising the monitoring algorithm—the recommended order of diagnostic tests for all patients.

Executive summary

After careful review of the existing peer-reviewed literature, we recommend that all patients be referred for annual monitoring after five years of therapy and be reviewed annually thereafter whilst on therapy. At each monitoring visit, patients should undergo retinal imaging with both spectral-domain optical coherence tomography (SD-OCT) and widefield fundus autofluorescence (FAF) imaging . If widefield FAF is not available, FAF can be acquired in several photographic fields to encompass the macula and extra-macular areas following pupil dilation.

Patients with abnormalities on either SD-OCT or widefield FAF should undergo central, static, automated visual field testing appropriate to the location of the anatomical defect seen on SD-OCT or FAF (i.e., 10-2 visual field testing in those with parafoveal defects and 30-2 in those with pericentral defects). Patients with structural abnormalities consistent with hydroxychloroquine retinopathy, but with no

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Table 1 Summary of recommendation grade.

Grade	Explanation
A	At least one meta-analysis, systematic review, or RCT rated as 1+ +, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results A body of evidence including studies rated as 2+ +, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1+ + or 1+
B	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2+ +
C	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
GPP	Good practice points based upon consensual expert opinion where the evidence base does not support A–C grading

abnormality identified on repeated visual field testing should undergo multifocal electroretinography.

Monitoring may be started 1 year after therapy is initiated if additional risk factors exist e.g. a very high dose of drug therapy (>5 mg/kg/day), concomitant Tamoxifen therapy or renal insufficiency (eGFR < 60 ml/min/1.73 m^2). Chloroquine appears to be more retinotoxic than hydroxychloroquine; we recommend that monitoring begins after 1 year of therapy for all patients on chloroquine using the same tests.

Baseline testing for new initiators of hydroxychloroquine or chloroquine is no longer recommended. Adequate monitoring may not be possible with retinal co-pathology. This may be identified at the first monitoring episode, and a discussion with the patient and prescribing physician about the suitability of continued hydroxychloroquine therapy may be arranged. There is no specific recommendation for patients to arrange annual community optometry assessments, or any particular form of self-assessment, before monitoring commences.

Monitoring may be best incorporated into the hospital eye service via virtual clinics. Alternatively, they may be commissioned in the community similar to a diabetic retinopathy service. The results of monitoring should be communicated back to the prescribing doctor, patient and GP as normal, possible or definite hydroxychloroquine retinopathy. It is the prescribing doctor's responsibility to ensure that their patients are adequately monitored and to act on the results of monitoring.

Key changes to the 2018 recommendations

Humphrey visual field testing is no longer recommended as a first-line monitoring test

Visual field testing can be demanding and time-consuming for patients and clinical care pathways, and is often unreliable. A large UK audit of hydroxychloroquine monitoring services identified that 33.1% of tests were unreliable (fixation losses, false-positives and/or false-negatives) with 24.9% of poor quality [3]. A further study identified 17% of visual field tests to be unreliable [4]. Some of these non-contributory visual field tests necessitate further appointment(s) to repeat them. New data regarding the early natural history of hydroxychloroquine retinopathy identified that structural changes on spectral-domain optical coherence tomography (OCT) may precede visual field deficits detectable on Humphrey visual field testing [6]. The new recommendations are that monitoring for hydroxychloroquine retinopathy should involve spectral-domain OCT imaging and widefield FAF imaging for all patients. Most will have normal structural imaging results on SD-OCT and FAF imaging and no further testing is required until the following year.

It should be noted that the definitions of "possible toxicity" (one abnormal test result) and "definite toxicity" (two abnormal test results) remain unchanged. However, the new monitoring algorithm (Fig. 1) modifies the way in which these criteria may be fulfilled; the requirement for abnormalities on one subjective test and one objective test is no longer relevant (Table 2c).

Those with a structural abnormality consistent with hydroxychloroquine retinopathy (i.e., on OCT imaging) should then undergo Humphrey visual field testing with a test protocol appropriate to the anatomical defect (i.e., 10-2 for parafoveal defects and 30-2 for pericentral defects). Those with visual field defects congruous to the anatomical defect on SD-OCT or FAF fulfil the criteria for "definite toxicity". Patients with a normal, reliable visual field test in this context should undergo multifocal electroretinography, which if abnormal would fulfil the criteria for "definite toxicity" [6]. Patients with structural abnormalities on both SD-OCT and FAF consistent with hydroxychloroquine retinopathy have "definite toxicity" and do not require further functional testing.

The new recommended monitoring algorithm is outlined in Fig. 1; it is expected that the efficiency, cost-effectiveness and acceptability of monitoring services should improve without any effect on the overall diagnostic

Table 2 (a) Monitoring criteria. (b) Monitoring protocol: monitoring tests. (c) Interpretation of monitoring results. (d) Management of patients with possible retinopathy. (e) Management of patients with definite toxicity. (f) Termination of monitoring. (g) Organisation of services. (h) Work commitment.

Recommendation	Grade
(a)	
All individuals who have taken hydroxychloroquine for greater than 5 years should receive annual monitoring for retinopathy	B
All individuals who have taken chloroquine for greater than 1 year should receive annual monitoring for retinopathy	B
All individuals taking hydroxychloroquine who have additional risk factors for retinal toxicity may be monitored annually after the initiation of therapy. This is to be decided by the prescribing physician should additional risk factors be present. *Additional risk factors: Concomitant tamoxifen use, impaired renal function (estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2), dose of hydroxychloroquine greater than 5 mg/kg/day.*	GPP
It is the responsibility of the prescribing physician (as per General Medical Council guidelines) to refer patients eligible for monitoring to the local hospital eye service.	GPP
The referring clinician should be encouraged to complete a standardised referral proforma specifying the key clinical details relevant to monitoring for retinal toxicity. This will allow a determination of risk of toxicity and interpretation of test results.	GPP
(b) The following is a standardized monitoring protocol that applies to all patients.	
In addition to oral communication, written information about hydroxychloroquine retinopathy and monitoring for hydroxychloroquine retinopathy should be given to all patients.	GPP
All patients should undergo both spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF), widefield if available.	B
Patients with abnormalities on either SD-OCT or fundus autofluorescence imaging should undergo automated visual field testing using either a 10-2 or 30-2 protocol depending on the location of the structural abnormality. Visual field testing is likely to be undertaken at a separate visit if dilating eye drops are used for imaging, or in the setting of virtual clinics when images are reviewed after the patient visit.	C
Patients with confirmed structural abnormalities on SD-OCT or FAF who do not demonstrate an anatomically consistent visual field defect on repeated testing should undergo multifocal electroretinography.	C
(c)	
No toxicity: no abnormalities suggestive of retinal toxicity detected on OCT or FAF	B
Possible toxicity: OCT or FAF result typical of hydroxychloroquine retinopathy, but neither visual fields or multifocal ERG are abnormal.	GPP
Definite toxicity: two tests with corresponding abnormalities consistent with hydroxychloroquine retinopathy. This definition can be satisfied in the following scenarios: – OCT *and* FAF typical of hydroxychloroquine retinopathy – Either OCT *or* FAF typical of hydroxychloroquine retinopathy, supported by either visual field testing or mfERG findings corresponding to the anatomical defect.	B
(d)	
Patients with possible hydroxychloroquine retinopathy should continue drug treatment. This will reduce the risk of inappropriate treatment cessation.	GPP
Patients with one abnormal test result on retinal imaging (SD-OCT & widefield FAF) but normal visual fields on repeated testing should be referred for multifocal electroretinography. Treatment should continue until the outcome of electrophysiology is known. This will reduce the risk of inappropriate treatment cessation.	GPP
(e)	
A recommendation to stop hydroxychloroquine should be made to the prescribing physician to facilitate further discussion between the specialist (for the treatment indication) and patient about the risks of stopping hydroxychloroquine and the options for alternative drug therapy.	B
Some description by the ophthalmologist of disease severity (mild, moderate, or severe) may be helpful to facilitate this discussion between patient and prescribing physician.	GPP
It would be inappropriate for ophthalmologists to stop hydroxychloroquine treatment.	GPP

Table 2 (continued)

Recommendation	Grade
Patients should be referred for appropriate support at the point of detection of hydroxychloroquine retinopathy. This may involve low vision or eye clinic liaison officer (ECLO) services, registration of visual impairment, and referral to local and/or national charities.	GPP
Patients who are drivers should be advised not to drive until an Esterman visual field test confirms it is legal to do so. The patient should inform the Driver Vehicle Licensing Agency (DVLA).	GPP
(f)	
Monitoring for hydroxychloroquine retinopathy should be discontinued if patients stop taking hydroxychloroquine (due to retinal toxicity or for other reasons).	C
(g)	
Monitoring for hydroxychloroquine retinopathy may most effectively take place in virtual clinics where visual field testing and dilated retinal imaging is undertaken before later being interpreted by either an ophthalmologist or an allied health professional under the supervision of a consultant ophthalmologist.	GPP
Written communication from the ophthalmologist indicating the outcome of a monitoring episode should be sent to the patient, prescribing physician and general practitioner.	GPP
In the event of failure to attend monitoring, patients should not be automatically discharged. Patients should be reminded of the purpose of monitoring and the approximate interval to the next monitoring appointment stated.	GPP
(h)	
Ophthalmologists who regularly complete the interpretation of hydroxychloroquine retinopathy monitoring test results should have sessional commitments allocated within their work plan.	GPP

yield. These recommendations may be considered in other healthcare settings in which resources are limited.

Baseline testing is no longer recommended for initiators of hydroxychloroquine or chloroquine

A large UK audit of 782 individuals who had taken hydroxychloroquine for less than 5 years found that none had an abnormality on baseline testing that precluded continuation of treatment [3]. A further audit identified that only 26 of 345 individuals (3.6%) undergoing baseline assessment were unsuitable for monitoring due to co-existing pathologies [4] (pooled frequency: 2.3% [3, 4]). Furthermore, it is recognised that a significant proportion of new initiators of hydroxychloroquine are no longer taking the medication at 5 years due to insufficient clinical response or adverse effects. Baseline assessments were found to constitute more than half of all hydroxychloroquine monitoring appointments in one UK audit [4], consuming significant resources. On consideration of these new data, the significant healthcare resources required were not justified by the limited clinical benefit offered by baseline testing.

Methods

The methods used in developing this guideline followed those specified in the RCOphth Clinical Guidelines Process manual and are outlined in full in the published guideline. The guideline development group considered how new evidence impacted upon the recommendations in the guideline and agreed that the guideline should undergo a partial revision.

Key research questions

Two specific research questions that formed part of the original 2018 guideline were systematically re-evaluated as to the quality of the evidence and relevance to the research questions according to the methodology described in the full guideline [2];

(1) When should patients be monitored for hydroxychloroquine retinopathy?
(2) What tests should be performed on patients as part of the monitoring schedule?

Grading the level of evidence

A pre-determined method for searching for evidence was followed, which involved Cochrane. The levels of evidence for each individual study were evaluated and graded by the guideline development group according to its strength using the Scottish Intercollegiate Guidelines Network framework (SIGN 50). The grade of each recommendation has been based upon the quality of the

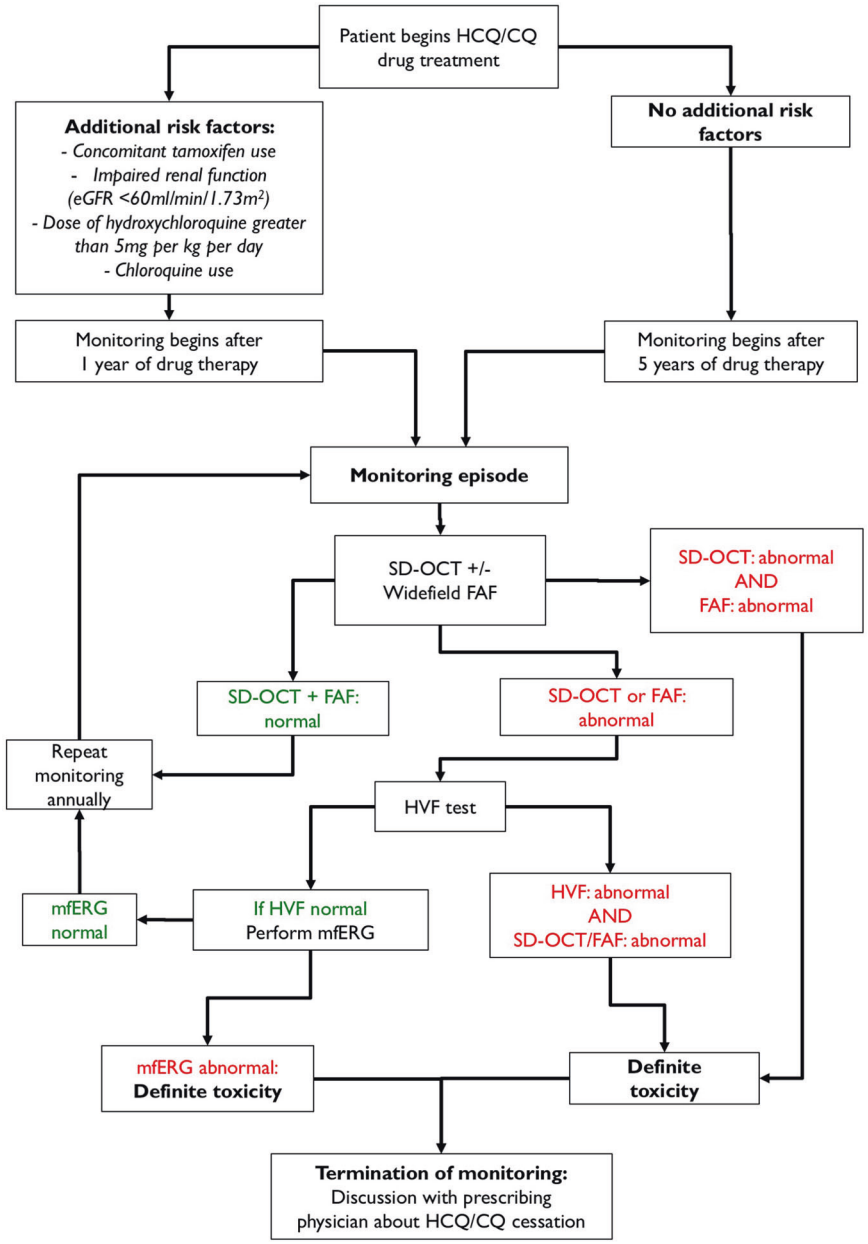

Fig. 1 Monitoring algorithm for hydroxychloroquine and chloroquine users.

evidence and the potential for patient benefit (Table 1), rather than the clinical importance of the recommendation. This evidence was then evaluated in the context of the defined research questions to develop the recommendations and grade their strength. Using the evidence identified, the Guideline Development Group determined the guideline recommendations.

Key recommendations and good practice points (GPP) for implementation

Table 2a–h specify the key components of the recommendations.

Safe dosing

Safe dosing by general practitioners and hospital specialists is likely to reduce the incidence of hydroxychloroquine retinopathy in patients at risk [5]. Current evidence suggests the highest risk of hydroxychloroquine retinopathy in patients taking a dose greater than 5 mg/kg per day [5]. Many patients take 400 mg of hydroxychloroquine per day, which is a higher than recommended dose for any patient who weighs less than 80 kg [7]. All prescribers should be aware of the good practice recommendation that a dose of less than 5 mg/kg per day will reduce the risk of hydroxychloroquine retinopathy, although no absolutely safe daily dose has been identified [5]. A useful aide memoir for these

guidelines for hydroxychloroquine is the 5 × 5 rule: ideally keep dosage <5 mg/kg/day and begin monitoring after 5 years of drug use.

Considerations for patients

Education of patients at risk of hydroxychloroquine retinopathy is vital to ensure that the risks of treatment are understood in the context of the significant benefits, the nature of monitoring tests, the monitoring schedule and how the outcome of monitoring is communicated and acted on. This will minimise any anxiety that may occur in patients at risk of retinopathy. In order to support the ongoing education of this patient group, the Macular Society has produced an updated patient information leaflet with input from the RCOphth guideline development group, which is available online and should be distributed to all patients taking hydroxychloroquine and chloroquine. Prescribing physicians should be aware of the updated monitoring recommendations so that appropriate referral to the hospital eye service can be made and that information given to patients about monitoring remains consistent.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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