The ROYAL COLLEGE of OPHTHALMOLOGISTS

Clinical Guidelines

Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on Monitoring

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Executive Summary

Recent data have highlighted that hydroxychloroquine retinopathy is more common than previously reported. The prevalence following long-term use appears to be around 7.5% and depending on dose and duration of therapy can increase to 20-50% after 20 years of therapy. Risk increases for patients taking more than 5mg/kg/day[1]. The retinopathy is manifest as damage to the photoreceptors and subsequent degeneration of the retinal pigment epithelium (RPE). This may produce a "Bull's eye maculopathy" and central visual loss. This is important as the only intervention to prevent further damage is stopping the drug. The risk is increased for patients taking more than 5mg/kg/day, those also taking Tamoxifen, and those with renal impairment. Whilst most affected patients demonstrate parafoveal toxicity (2-6 degrees from the fovea), some patients may exhibit pericentral toxicity (greater than 7 degrees from the fovea) which necessitates monitoring outside the macula. Chloroquine retinopathy appears to follow a similar, but more rapid course when compared to hydroxychloroquine retinopathy.

Following the publication of the RCOphth recommendations for monitoring in hydroxychloroquine and chloroquine users in 2018,[2] additional high-quality published evidence has prompted a review of the guideline. A systematic review of the literature was undertaken to identify studies of high-quality relating specifically to the timing of monitoring and the tests that should be performed. The selected studies included two recent large, high-quality audits of U.K. hydroxychloroquine monitoring services which were undertaken in accordance with the 2018 recommendations.[3, 4]

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 imaging with both spectral-domain optical coherence tomography (SD-OCT) and widefield fundus autofluorescence imaging (FAF). If widefield FAF is not available, FAF can be acquired in several photographic fields to encompass the macula and extra-macular areas.

Patients with abnormalities on either SD-OCT or widefield FAF should undergo central, static, automated visual field testing appropriate to the location of the abnormality seen on SD-OCT or FAF; patients with paracentral defects may benefit from 10-2 visual field testing, and those with pericentral disease may benefit from 30-2 visual field testing. Patients with structural abnormalities consistent with hydroxychloroquine retinopathy, but with no abnormality identified on repeated visual field testing should undergo multifocal electroretinography.

Monitoring may be started one year after therapy is initiated if additional risk factors exist e.g. very high dose of drug therapy, concomitant Tamoxifen therapy or renal insufficiency. Chloroquine appears to be more retinotoxic than hydroxychloroquine and so we recommend that monitoring begins after one 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. This amendment is supported by recent evidence of a low rate of drug discontinuation as a result of baseline testing (less than 4%).[3, 4] Furthermore, it is recognised that a significant proportion of patients discontinue hydroxychloroquine in the first five years of therapy, either due to adverse effects or insufficient clinical response. 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 specific 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 their patients are adequately monitored and to act on the results of monitoring. A useful aide memoir for these guidelines for hydroxychloroquine is the 5 x 5 rule (ideally keep dosage < 5mg/kg/day and monitor after five years of drug use).

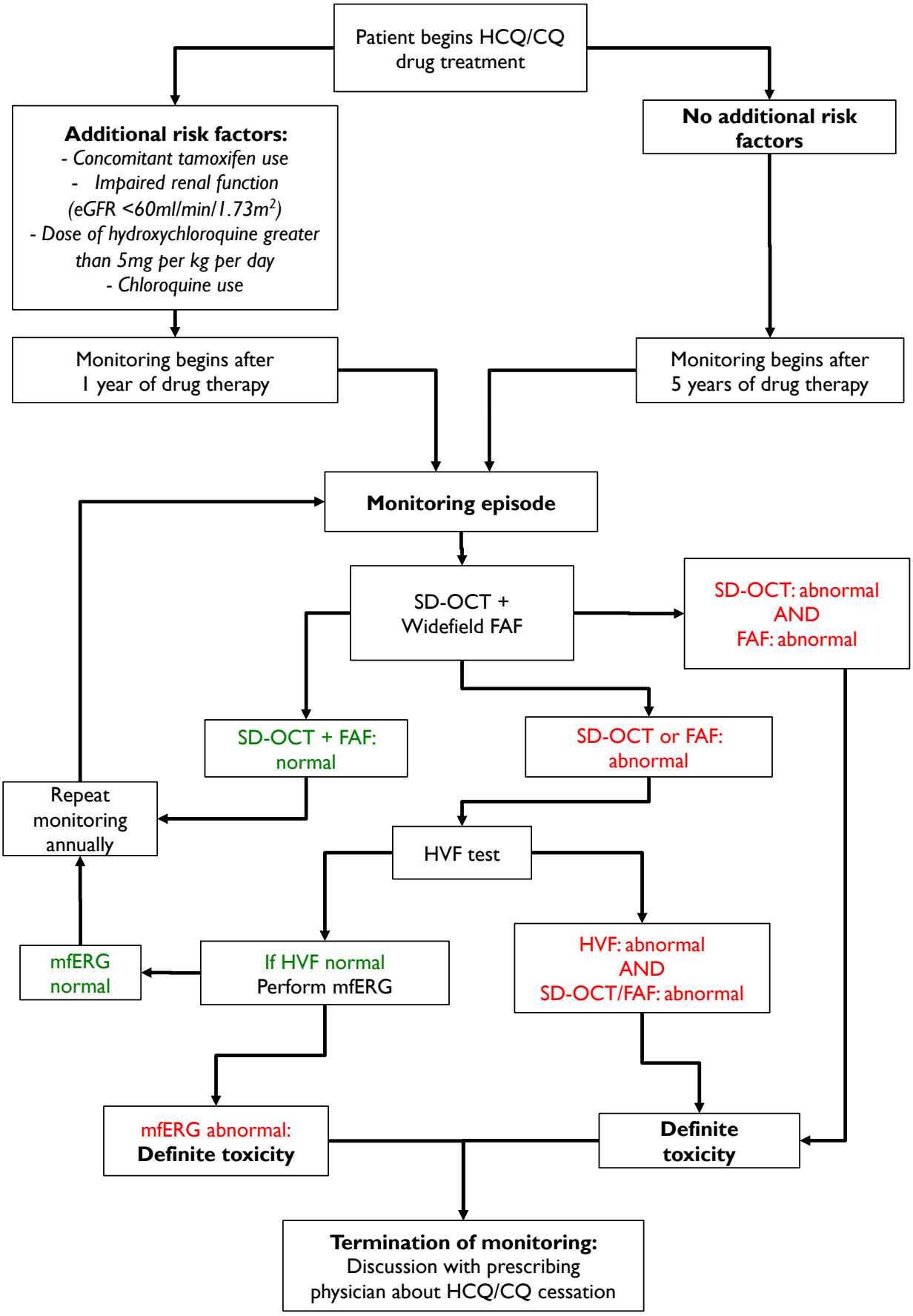
These recommendations (2020) replace the previously published recommendations for monitoring for hydroxychloroquine and chloroquine users (2018).[2]

1. Key Recommendations and Good Practice Points (GPP) for Implementation

The criteria used for the summary of grades of recommendations are found in Table 1 below.

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 did not support an A-C grading.

1.1 Monitoring Algorithm



1.2 Monitoring Criteria

Recommendation	Grade of evidence
All individuals who have taken hydroxychloroquine for greater than five years should receive annual monitoring for retinopathy.	B
All individuals who have taken chloroquine for greater than one 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.	GPP
It is the responsibility of the prescribing physician (as per GMC 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 toxicity and interpretation of test results.	GPP

1.3 Monitoring Protocol: Tests

The following is a standardised protocol for all patients.

Recommendation	Grade of evidence
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

Some patients at risk of hydroxychloroquine retinopathy may not be able to undertake the required monitoring tests, and in some there may be ocular co-pathology that prevents interpretable imaging. This may be identified at the first monitoring episode.

Recommendation	Grade of evidence
Where a patient taking hydroxychloroquine or chloroquine cannot undergo monitoring, or in whom retinal imaging cannot be performed or images interpreted, a discussion between the patient and the prescribing physician is recommended to determine whether hydroxychloroquine treatment should be continued without retinal monitoring.	GPP

1.4 Interpretation of Monitoring Results

Recommendation	Grade of evidence
No toxicity: No abnormalities suggestive of toxicity detected on OCT or FAF.	B
Possible toxicity: OCT or FAF result typical of hydroxychloroquine retinopathy, but neither visual fields or mERG 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

1.5 Management of Patients with Possible Retinopathy

Recommendation	Grade of evidence
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 or 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

1.6 Management of Patients with Definite Toxicity

Recommendation	Grade of evidence
A recommendation to stop hydroxychloroquine should be made to the prescribing physician to facilitate further discussion between specialist (for the treatment indication) and patient about the risk of stopping hydroxychloroquine and the options for alternative drug therapy.	B
Some description by the ophthalmology 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
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, certification of vision impairment, and referral to local and/or national charities.	GPP
Patients who are drivers should be advised not to drive until an Estermann visual field test confirms it is legal to do so. The patient should inform the Driver and Vehicle Licensing Agency (DVLA).	GPP

1.7 Termination of Monitoring

Recommendation	Grade of evidence
Monitoring for hydroxychloroquine retinopathy should be discontinued if patients stop taking hydroxychloroquine (due to retinal toxicity or for other reasons).	C

1.8 Organisation of Services

Recommendation	Grade of evidence
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

1.9 Work Commitment

Recommendation	Grade of evidence
Ophthalmologists who regularly complete the interpretation of hydroxychloroquine retinopathy monitoring test results should have sessional commitments allocated within their work plan.	GPP

2. References

1. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA ophthalmology*. 2014;**132(12)**:1453-60.
2. Yusuf IH, Foot B, Galloway J, Ardern-Jones MR, Watson SL, Yelf C, et al. The Royal College of Ophthalmologists recommendations on screening for hydroxychloroquine and chloroquine users in the United Kingdom: executive summary. Eye *(London, England)*. 2018;**32(7)**:1168-73.
3. Marshall E, Robertson M, Kam S, Penwarden A, Riga P, Davies N. Prevalence of hydroxychloroquine retinopathy using 2018 Royal College of Ophthalmologists diagnostic criteria. Eye *(London, England)*. 2020:1-6.
4. Gobbett A, Kotagiri A, Bracewell C, Smith J. Two years' experience of screening for hydroxychloroquine retinopathy. Eye *(London, England)*. 2020.
5. Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. Eye *(London, England)*. 2017;**31(6)**:828-45.

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