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 in long term use patients 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. 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. In some patients, toxicity may first present as pericentral retinopathy and thus requires monitoring outside the macula. We assume chloroquine retinopathy follows a similar course as hydroxychloroquine retinopathy and so these guidelines also apply to patients taking chloroquine therapy.

After careful review of the existing peer reviewed literature, we recommend that all patients planning to take hydroxychloroquine long term i.e. over five years have a baseline examination in a hospital eye department ideally within six months, but definitely within 12 months, of starting therapy with a colour retinal photograph and spectral domain optical coherence tomography (SD-OCT) scans of the macula.

Patients should 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 10-2 Humphrey visual field testing, followed by pupillary dilation and imaging with both 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 widefield FAF with normal 10-2 visual field test results should undergo 30-2 visual field testing on another date. Patients with persistent and significant visual field defects consistent with hydroxychloroquine retinopathy, but without evidence of structural defects on SD-OCT or FAF may be considered for multifocal electroretinography. Monitoring may be commenced before five years of therapy if additional risk factors exist e.g. very high dose of drug therapy, concomitant Tamoxifen therapy or renal insufficiency. Adequate monitoring may not be possible with retinal co-pathology.

Chloroquine appears to be more retinotoxic than hydroxychloroquine and so we recommend identical baseline and monitoring tests, but that monitoring begins after one year of therapy for all patients on chloroquine.

Monitoring may be best incorporated into the hospital eye service via virtual clinics. 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).

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.

Monitoring Criteria

Criteria	Level 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 from the baseline visit or annual monitoring commenced before five years of treatment completed. This is to be decided by a consultant ophthalmologist following the baseline visit. *Additional risk factors: Concomitant Tamoxifen use, impaired renal function (estimated glomerular filtration rate of less than 60ml/min/1.73m^2), does of hydroxychloroquine greater than 5mg/kg/day.*	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

Monitoring Protocol: Baseline Examination

Criteria	Level of evidence
All patients planning to be on therapy long term (≥ five years for hydroxychloroquine and >one year for chloroquine) should receive baseline examination ideally within six months of starting hydroxychloroquine or chloroquine and definitely within 12 months.	C
Baseline examination should include a fundus photography and spectral domain optical coherence tomography.	GPP
If the baseline examination demonstrates macular pathology, a baseline Humphrey 10-2 visual field test may be undertaken.	GPP

Monitoring Protocol: Monitoring Tests

The following is a standardised protocol for all patients.

Criteria	Level 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 10-2 Humphrey visual fields testing (using a white stimulus), followed by pupillary dilation and imaging with both spectral domain optical coherence tomography (SD-OCT) and widefield fundus autofluorescence (FAF).	B
Patients with abnormalities on widefield fundus autofluorescence with normal 10-2 visual field test results should undergo 30-2 visual field testing on another date.	C
Patients with persistent and significant visual field defects consistent with hydroxychloroquine retinopathy, but without evidence of structural defects on SD-OCT or FAF may be considered for multifocal electronicretinography.	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.

Criteria	Level of evidence
Where a patient taking hydroxychloroquine or chloroquine cannot undergo monitoring (i.e. cannot perform visual field testing), 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

Interpretation of Monitoring Results

Criteria	Level of evidence
No toxicity: No abnormalities suggestive of toxicity detected on any test.	B
Possible toxicity: One test result (which in the case of visual fields should be reproducible) typical of hydroxychloroquine retinopathy, but typical abnormalities not present in other tests.	GPP
Definite toxicity: Two test results (one subjective test and one objective test) with abnormalities typical of hydroxychloroquine retinopathy.	B

Management of Patients with Possible Retinopathy

Criteria	Level 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 & widefield FAF) but normal visual fields (including 30-2 protocol (if appropriate) should return for annual review as per the monitoring schedule. This will reduce the risk of inappropriate treatment cessation.	GPP
Patients with persistent visual field abnormalities in the context of normal structural imaging (SD-OCT and widefield FAF) may be referred for multifocal electroretinography. Treatment should continue until the outcome of electrophysiology is known.	GPP

Management of Patients with Definite Toxicity

Criteria	Level 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

Termination of Monitoring

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

Organisation of Services

Criteria	Level of evidence
Monitoring for hydroxychloroquine retinopathy should take place in the hospital eye service.	GPP
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

Work Commitment

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

The Royal College of Ophthalmologists

18 Stephenson Way
London, NW1 2HD

T. 020 7935 0702
contact@rcophth.ac.uk