The Royal Australian and New Zealand College of Ophthalmologists

Guidelines for Screening for Hydroxychloroquine Retinopathy

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We acknowledge the Aboriginal and Torres Strait Islander Peoples, the Traditional Owners of Country throughout Australia and recognise their continuing connection to land, waters and community. We pay our respects to them and their cultures; and to their Elders past, present and emerging.
In recognition that we are a bi-national College, we also acknowledge the Rangatiratanga of Māori as Tangata Whenua and Treaty of Waitangi partners in Aotearoa New Zealand.

1. Purpose and scope

Retinal toxicity associated with antimalarial (hydroxychloroquine and chloroquine) drug use in inflammatory conditions is well described and may be more common than previously recognized. The long-term overall prevalence is 7.5% and is cumulative dose dependent. The risk is low in the first 5 years of usage but increases exponentially to almost 20% after 20 years of therapy.[1] Retinopathy involves damage to photoreceptors and retinal pigment epithelium (RPE). Patients may experience progressive central scotoma and diminished colour vision even after cessation of medication.

There is currently no treatment available. Best practice is therefore early detection. Possible/definite cases should be referred to an ophthalmologist with retinal expertise for confirmation of diagnosis. In cases of toxicity secondary to hydroxychloroquine (HCQ) or chloroquine (CQ) use, the findings should be communicated to the patient, prescribing doctor and general practitioner. The prescribing doctor, taking into account the opinion of the ophthalmologist, will then discuss cessation or alternative therapy with the patient as appropriate.

The purpose of these guidelines is to provide Australian and New Zealand ophthalmologists guidance on screening and improve awareness among health professionals.

2. Screening process

The following recommendations are based on the American Academy of Ophthalmology and the Royal College of Ophthalmologists' guidelines on screening for HCQ and CQ retinopathy.[2] [3]

RANZCO recommends:

- Baseline examination within first year of use; and
- Annual screening after 5 years of use for patients with no risk factors
- Consideration of earlier review for patients who are at increased risk ie. patients:
    - on chloroquine
    - on hydroxychloroquine dose >5mg/kg real weight/day
    - with renal impairment
    - with concomitant Tamoxifen use
    - Patients with concomitant retinal/macular disease
- Consideration of wider field testing for extra-macular changes in Asian patients

2.1. Baseline and follow-up screening

Examination on initiation of HCQ or CQ is optimal for education of the patient and referring healthcare professional, to look for concomitant retinal/macular disease and to establish a baseline status. Subsequent testing is aimed at identifying parafoveal and pericentral changes at the macula.

Minimum requirements include dilated fundus examination (insufficient for screening alone but required to exclude concomitant retinal pathology), automated visual field testing and spectral-domain optical coherence tomography (SD-OCT) of the macula. There is evidence to suggest wider testing to encompass the pericentral region to include the arcades is useful in detecting changes in Asian patients prior to central involvement.[4] Other modalities to consider include fundus autofluorescence (FAF) and multifocal electroretinogram (mfERG) in equivocal cases.

Minimum Requirements	
Ocular examination	Best corrected reading and distance vision. Whilst not sufficient for screening (low sensitivity), dilated fundus examination is important for detection of associated/other retinal and macular disorders.
Automated Visual Fields	10-2 threshold testing to detect complete/incomplete ring scotomas (often appear superonasally 3-8 degrees from fixation corresponding with inferotemporal retinal changes) Additional wider field testing (24-2 or 30-2) in Asian patients to detect pericentral changes along the arcades
SD-OCT of the macula	Spectral domain Optical coherence tomography (SD-OCT) testing is useful in detecting morphological changes at baseline and in subsequent tests. Changes detected may include: 1. *Concurrent macular changes* 2. *Changes in macular thickness, particularly inferior/inferotemporal retina initially* 3. *Outer retinal changes:* • *Disruption to photoreceptors* • *Disruption to the ellipsoid zone* • *Loss of space between ellipsoid zone and interdigitation zone (photoreceptor outer segment layer)* • *Loss of interdigitation zone* • *RPE loss and accumulation of debris* • *Increased choroidal reflectance secondary to RPE loss*
Extra Tests	
Fundus autofluorescence (FAF)	To diagnose/exclude concomitant pathology, changes detected may include: • *Early hyperfluorescence indicating RPE stress* • *Late hypofluorescence indicating RPE loss* *Extra-macular changes may be detected in Asian patients*
Multifocal Electroretinogram (mfERG)	Valuable for evaluation of suspicious or unreliable visual field loss; may show damage earlier than field loss. Changes detected include: • *Amplitude reduction* • *Prolonged implicit time* • *Ring response reduction and ring ratios greater than normal* • *Colour difference plots indicating decreased response*

2.2. Not recommended for screening

Colour fundus photography	Useful as adjunct test for documentation at baseline and subsequent comparison
Frequency doubling technology (FDT) automated visual field	Insufficient sensitivity for screening
Confrontation field testing	Insufficient sensitivity for screening
Time-domain OCT	Insufficient resolution for screening
Fluorescein angiography	Only necessary in evaluation and management of concurrent retinovascular pathology
Full-field ERG	Not able to detect maculopathy; May be useful in patients with very advanced toxicity who develop widespread retinal abnormalities
Amsler grid	Use only as adjunct test
Colour testing (e.g. Ishihara plates)	Use only as adjunct test

3. Patients who fail screening

Patients who fail screening or have equivocal findings should be referred promptly for specialist retinal assessment with an ophthalmologist, which may involve further objective testing including mfERG.

4 Diagnosis and treatment

Diagnosis requires the comprehensive assessment of an ophthalmologist. Further confirmation may sometimes be required by a retinal specialist, especially in the cases requiring interpretation of electrophysiology. The diagnosis is then communicated to the patient, the treating doctor, and the general practitioner. The treating doctor then makes the decision to stop/alter the treatment regime as appropriate.

5 High risk patients

5.1 Chloroquine

Chloroquine has a higher risk of retinal toxicity than hydroxychloroquine. Retinal toxicity may continue to progress after cessation.

5.2 Dose

High risk patients have been identified as those with a cumulative dose of 1000g or with a daily dose of HCQ > 5 mg/kg real weight/day (revised from 6.5mg/kg/day).[2] In most patients dosing at 400 mg HCQ will result in 1000g cumulative dose at 7 years. Patients treated on higher doses are recommended to have baseline screening followed by annual screening from treatment initiation.

5.3 Concomitant medications

Tamoxifen is known to increase risk of toxicity. Patients are recommended to have annual screening from treatment initiation.

5.4 Renal and liver disease

HCQ and CQ are metabolised by both the kidney and liver. Patients with significant renal and/or hepatic impairment are recommended to have baseline screening followed by annual screening from treatment initiation.

5.5 Macular disease

Patients with underlying macular or widespread retinal pathology may be at higher risk of toxicity, although there is no evidence for this. Moreover, screening for subtle new macular damage from HCQ in a patient with concurrent macular disease may be difficult.

6 Patient Counselling

The key to early recognition of toxicity (sometimes prior to onset of symptoms) is patient counselling to emphasize the risk of toxicity and need for periodic examinations. These recommendations should be noted carefully in the medical record. Patients should understand that screening can diagnose toxicity early and minimize visual loss but cannot necessarily prevent all toxicity or guarantee there will be no visual loss. Screening seeks to recognize the earliest hints of functional or anatomic change, before the toxic damage is well developed.

7 Contributors

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8. References

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2. Marmor MF, Kellener U, Lai TYY et al. American Academy of Ophthalmology Statement - Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology 2016; 123:1386-1394.
3. Lotery A, Ardern-Jones M, Bishop P et al. Clinical Guidelines Hydroxychloroquine and Chloroquine Retinopathy: Recommendations on Monitoring. The Royal College of Ophthalmologists, United Kingdom. January 2020.
4. Melles RB, Marmor MF. Pericentral Retinopathy and Racial Differences in Hydroxychloroquine Toxicity. Ophthalmology 2015; 122:110-116.

9. Record of amendments to this document

Page	Details of Amendment	Date amended
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