Review

Guidelines on prescribing and monitoring antimalarials in rheumatic diseases: a systematic review

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ABSTRACT

Objective. *The purpose of this systematic review was to identify existing guidelines for antimalarial prescribing and monitoring, specifically for hydroxychloroquine, and how these guidelines compare and have evolved over time.*

Methods. *A literature search was conducted using Embase and Medline to identify guidelines published from 1946-2018. MeSH terms were used and alternative spelling and related words were entered as keywords to broaden results.*

Results. *243 results were reviewed to obtain 11 recommendations. Ophthalmology sources included the American Academy of Ophthalmology, Royal College of Ophthalmologists and Canadian editorials. The American College of Rheumatology and Canadian Rheumatology Association consensus statements summarised rheumatology recommendations. Recently, American and British guidelines changed from suggesting hydroxychloroquine doses ≤6.5 mg/kg/day to ≤5 mg/kg/day. American guidelines recommended baseline visual field (VF) testing and annual screening after five years. Visual field (VF) testing evolved from the Amsler grid to current recommendations of 10-2 automated VF and spectral-domain optical coherence tomography (SD-OCT). The 2012 Canadian recommendations suggested initial VF testing every two years, with SD-OCT after 10 years. Older British guidelines advocated for baseline and annual assessment with Amsler grids during rheumatology clinic visits. The 2018 British guidelines supported baseline and annual screening after five years with 10-2 VF, SD-OCT and fundus autofluorescence.*

Conclusion. *The newest recommendations are heterogeneous suggesting lower hydroxychloroquine dosing. Retinal toxicity is irreversible and the risk increases over time. Annual screening after five years with automated VF and SD-OCT may be warranted to detect early changes and discontinue therapy if necessary.*

Introduction

Hydroxychloroquine (HCQ) and chloroquine (CQ) are medications commonly prescribed for a variety of autoimmune disorders, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), for which HCQ has shown a survival benefit (1). The expectation is that many patients will remain on these medications for years; and possibly lifelong. These drugs, initially intended for the treatment of malaria, modulate immune responses through multiple mechanisms that impair antigen-antibody reactions. HCQ inhibits toll-like receptors 7 and 9 on plasmacytoid dendritic cells, thereby inhibiting interferon-alpha production (2). HCQ also increases lysosomal pH in antigen-presenting cells which interferes with the processing of antigenic peptides required to trigger autoimmune responses (3).

HCQ and CQ are associated with irreversible vision loss secondary to retinal toxicity. CQ has a higher risk of retinal toxicity than HCQ (4). Antimalarial induced retinopathy presents with bilateral damage to photoreceptors and loss of the retinal pigment epithelium (RPE) (4). The classic appearance is known as a "bull's eye maculopathy", with central, concentric, parafoveal damage (4). The mechanism by which this damage occurs is unclear, however one study has shown that CQ and HCQ inhibit the uptake of organic anion transporting polypeptide A12 which is expressed in RPE cells and is involved in the recycling of all-transretinol (5).

It is uncertain why photoreceptors in the parafovea are most affected as there are no clear predisposing anatomic features (4, 6). Other rare adverse effects of antimalarial medications include liver failure, hypoglycaemia, bone marrow suppression and cardiomyopathy (4, 7).

Prevalence of HCQ retinal toxicity varies in the literature, with rates of 0.1–0.97% in the first five to seven years of treatment, increasing to over 10% for longer treatment duration (8-12). A more recent meta-analysis with mean treatment duration of 1–14.1 years found a pooled incidence of toxicity of 6% (13). A large, retrospective study by Melles *et al*. reported an overall prevalence of hydroxychloroquine retinopathy of 7.5% in patients on therapy for more than 5 years and almost 20% after 20 years (6). Some risk factors for toxicity include HCQ dose greater than 5 mg/kg/day, CQ dose greater than 2.3 mg/kg/day, duration of therapy greater than 5 years, renal impairment, tamoxifen use, and underlying macular disease (4, 6, 14). Over time there has been a shift to utilise real body weight instead of ideal body weight when calculating the recommended safe HCQ dose since the medication distributes poorly in fat tissue (6). Real body weight is simply the patient's weight, while ideal body weight is usually measured by attributing 45 kg for women (50 kg for men) for the first 1.5 m of height, then adding 2.3 kg for each 2.5 cm over 1.5 m (6).

Screening for antimalarial retinal toxicity may detect changes in the macula prior to the development of clinical symptoms, which include decreased colour vision, impaired night vision and later central vision loss (4, 8, 14). Although the toxicity is irreversible, cessation of treatment upon diagnosis of HCQ/CQ retinopathy can limit the extent of damage. Screening methods include visual field testing, spectral domain optical coherence tomography (SD-OCT), fundus autofluorescence (FAF) and multifocal electroretinography (mfERG) (4, 12). Colour vision testing was previously performed as a screening method (15-22). Visual field testing is potentially more sensitive, however it is subjective and relies on the patient's ability to follow instructions (4, 6). In contrast, SD-OCT is a highly specific and objective test for damage that may be clinically significant. It provides high-resolution cross-sectional images of the retina; parafoveal thinning of the outer retina and loss of the photoreceptor outer segment with foveal cone sparing are suggestive of hydroxychloroquine-related retinal toxicity (4). FAF is another objective test, which uses a monochromatic light source to elicit autoreflectance within the RPE. In hydroxychloroquine retinopathy, hyperfluorescence may be present early on indicating RPE stress and later hypofluorescence indicates RPE loss (19). FAF may reveal earlier changes than those visible on SD-OCT (4). The availability of mfERG is currently limited, however it is a highly sensitive, objective test that is helpful in individuals who have visual field deficits but normal SD-OCT and FAF results (4). In mfERG, the retina is stimulated using hexagonal light sources and electrical responses are recorded; parafoveal or extramacular electroretinogram depression are suggestive of early retinopathy (13, 19).

The purpose of this systematic review was to identify existing guidelines for antimalarial prescribing and monitoring, specifically for HCQ, and to determine how these guidelines from different international associations compare and evolve over time. This information will assist physicians in managing patients on treatment with HCQ or CQ.

Methods

A literature search was conducted by two independent reviewers using Embase and Medline to identify ophthalmology and rheumatology guidelines on antimalarial use published from 1946 to September 2018. The search date was September 17th, 2018. MeSH terms were employed with alternative spelling and related words entered as keywords and separated by 'OR' to broaden results (Fig. 1). The Embase and Medline strategies both contained the same sub-searches for antimalarials and retinal disease, however they differed in the use of MeSH terms pertaining to guidelines. In addition to reviewing all English search results, the references of all articles were also reviewed to retrieve additional guidelines. Data on antimalarial dosing, screening and management of toxicity was extracted. Methodological quality of the results was evaluated by two independent reviewers, using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument (23).

Results

There were 218 results from the Embase search and 79 from Medline. A total of 243 articles were reviewed after de-duplication, to obtain 11 recommendations (Fig. 2). The sources included guidelines from ophthalmology and rheumatology associations. The American Academy of Ophthalmology published guidelines in 2002, 2011, and 2016 (14-16). The Royal College of Ophthalmologists in the United Kingdom published guidelines in 1998, 2009, and 2018 (17-19). Canadian ophthalmology recommendations included editorials by Dr Michael Easterbrook in 1998, 2002, and 2012 (20-22). The American College of Rheumatology (ACR) issued a position statement, first published in 2003 and last revised in 2016 (24). The Canadian Rheumatology Association (CRA) published a consensus conference in 1998 (25).

Antimalarial dosing

The international ophthalmology guidelines are summarised in Table I. American recommendations changed from suggesting HCQ doses <6.5 mg/kg/day using ideal body weight with a maximum of ≤400 mg daily to, most recently, ≤5 mg/kg/day using real weight (14-16). British guidelines initially recommended ≤6.5 mg/kg/day using lean body weight, however now recommend <5 mg/kg/day using weight (17-19). Recommended CQ doses have changed from <3 mg/kg/day using ideal body weight to ≤250 mg/day to ≤2.3 mg/kg/day using real weight as per the American guidelines (14-16). The older Canadian sources suggested HCQ doses of <6.5 mg/kg/day and CQ <3 mg/kg/day based on ideal body weight (22).

Rheumatology recommendations are

summarised in Table II. The ACR position statement from 2016 suggested ≤5 mg/kg/day from actual body weight (24). The CRA consensus conference in 1998 suggested HCQ doses of ≤6.5 mg/kg/day using either ideal or real body weight, whichever is less (25).

Screening for retinal toxicity

American guidelines recommend baseline fundus exam with visual field testing and annual screening after five years of therapy. Field testing evolved from use of the Amsler grid to current recommendations of 10-2 automated visual fields and spectral domain optical coherence tomography (SD-OCT) (14-16). Also, multifocal electroretinography (mfERG) or fundus autofluorescence (FAF) are included as optional imaging in the 2016 guidelines (14). The original British guidelines suggested baseline optometry assessment including visual fields with an Amsler grid or Humphrey 10-2 protocol and referral to ophthalmology for abnormalities, with no systematic recommendations (17-19). The 2018 British guidelines supported baseline and annual screening after five years of antimalarial therapy (19). Screening methods now include 10-2 Humphrey visual field testing using white stimuli and both SD-OCT and FAF imaging if available. If abnormalities are only detected with FAF, 30-2 visual field testing is warranted, and mfERG should be ordered if the patient has visual field deficits without abnormalities on other imaging tests (19).

Canadian recommendations originally suggested a baseline ophthalmology exam followed by annual screening, however the most recent 2012 editorial suggested screening every 2 years until 5 years of therapy, then annually if no risk factors exist (20-22). As these editorials are a bit older, they continue to suggest visual field testing using an Amsler grid. Humphrey 10-2 red and white testing are recommended after 5 years (unless Amsler testing is abnormal) and SD-OCT after 10 years of therapy. FAF and mfERG are considered optional imaging tests (22).

The most updated ACR statement recommended baseline exam and annual screening after 5 years with Humphrey 10-2 automated VF test and if available, SD-OCT, mfERG or FAF (24). The CRA recommended baseline ophthalmology exams with follow-up every 12-18 months with central 10-degree visual field testing using manual or automated methods (25).

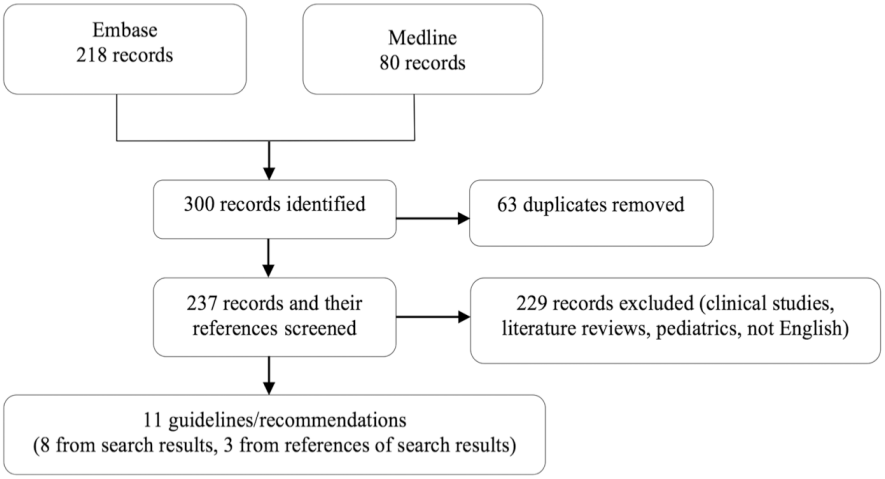

Fig. 1. Study selection

Both Databases:
Hydroxychloroquine OR (Hydroxychlorochin OR Hydroxychloroquine OR Oxychlorochin OR Oxychloroquine OR Plaquenil).mp
AND
Retinal diseases OR (Retinopath* OR maculopathy* OR retinal toxicit* OR macular toxicit*).mp
AND

Embase:
Practice guideline/ OR Gold Standard/ OR Consensus/ OR Consensus development/ OR Professional standard/ OR Algorithm/ OR (best practice* OR guideline* OR current practice* OR care standard* OR gold standard* OR recommendation* OR expert consensus OR expert panel OR consensus development OR professional standard* OR algorithm* OR critical path*).mp

Medline:
Guideline.pt. OR Guidelines as Topic/ OR Practice Guideline.pt. OR Practice Guidelines as Topic/ OR Standard of care/ OR Quality Indicators, Health Care/ OR Consensus/ OR Consensus Development Conference, NIH.pt. OR Consensus Development Conference.pt. OR Consensus Development Conferences, NIH as Topic/ OR Consensus Development Conferences as Topic/ OR Algorithms/ OR (best practice* OR guideline* OR current practice* OR care standard* OR gold standard* OR recommendation* OR expert consensus OR expert panel OR consensus development OR professional standard* OR algorithm* OR critical path*).mp

Fig. 2. Embase and Medline search strategies.
.mp: Multiple posting; * Truncation symbol; / Subject heading; .pt: Publication type.

Management of toxicity

The general consensus amongst recommendations suggests the decision whether to stop antimalarial therapy should be made jointly between the prescriber and patient. Patients with possible toxicity may choose to stop therapy or be followed at more frequent intervals until there is further evidence to confirm or disprove antimalarial-induced retinopathy. Cessation of therapy is recommended for patients with definite toxicity. In the 2018 British guidelines, definite toxicity was defined by retinopathy findings typical of antimalarial treatment with one subjective and one objective test. Possible retinopathy was considered as one abnormal test with findings typical of antimalarial retinopathy in the absence of typical abnormalities on other testing (19).

Discussion

The guidelines on antimalarial prescribing and monitoring have changed over time to consider newer clinical studies and advancements in imaging modalities. Prescribers should consider newer guidance for antimalarial prescribing and monitoring, as older recommendations are no longer the standard of care and did not always utilise rigorous methodologies, rendering their quality lower than the newer guidelines. The most recent recom-

Table I. International Ophthalmology guidelines on antimalarial use.

Guidelines / Recommendations	Maximum HCQ and CQ doses	Frequency of Screening	Method of Screening	Management of Toxicity	Quality of Guideline (Agree II Instrument)
American Academy of Ophthalmology (2002)	HCQ: <6.5 mg/kg/day CQ: <3 mg/kg/day	• Baseline ophthalmology exam • Screening q2-4 years, annually after 5 years • Annual screening in patients with risk factors	• Visual acuity • Dilated cornea and retina exam • Amsler grid or Humphrey 10-2 VF • Optional: colour testing, fundus photography, mfERG	• Cessation after discussion with prescriber and patient • Patients with "possible" early toxicity can be followed at 3 month intervals until disease evidence	Scope: 81% SI: 36% Rigor: 38% Clarity 83% Applicability: 33% EI: 0% Overall: 3/7
American Academy of Ophthalmology (2011)	HCQ: ≤400 mg/day or 6.5 mg/kg/day using IBW if short stature CQ: ≤250 mg/day or 3 mg/kg/day using IBW if short stature	• Baseline ophthalmology exam • Annual exam after 5 years • Annual screening in patients with risk factors	• Dilated retinal exam • VF with white 10-2 automated threshold testing • If available, one objective test: SD-OCT, mfERG or FAF	• Cessation after discussion with prescriber and patient • Patients with "possible" early toxicity may choose to stop therapy or be followed at 3-6 month intervals until further evidence to rule toxicity in or out	Scope: 100% SI: 36% Rigor: 41% Clarity 89% Applicability: 44% EI: 50% Overall: 4/7
American Academy of Ophthalmology (2016)	HCQ: ≤5.0 mg/kg/day using real weight CQ: ≤2.3 mg/kg/day using real weight	• Baseline ophthalmology exam • Annual exam after 5 years • Annual screening in patients with risk factors	• Fundus evaluation of macula • 10-2 automated VF • SD-OCT • Optional: mfERG and FAF	• Cessation after discussion with prescriber and patient if definitive signs of retinopathy evident	Scope: 100% SI: 36% Rigor: 43% Clarity 94% Applicability: 52% EI: 79% Overall: 5/7
Royal College of Ophthalmologists (1998)	HCQ: ≤6.5 mg/kg/day using lean body weight	• Baseline and annual assessment of vision during rheumatology clinic visit • Optometry and/or ophthalmology referral if concerns, with further visits at their discretion	• Visual acuity using a reading chart in rheumatology clinic • Colour vision • VF using red pin and red Amsler grid • Cornea and retina exam	N/A	Scope: 83% SI: 56% Rigor: 23% Clarity 69% Applicability: 35 EI: 0% Overall: 3/7
Royal College of Ophthalmologists (2009)	HCQ: ≤6.5 mg/kg/day using lean body weight	• Baseline and annual assessment of vision during rheumatology clinic visit • No systematic screening program recommended • Optometry and/or ophthalmology referral if concerns, with further visits at their discretion	• Visual acuity using a reading chart in rheumatology clinic • Colour vision • Central VF using Amsler Chart or Humphrey 10-2 protocol • Cornea and retina exam • Consider retinal photography, SD-OCT, FAF, and other imaging	• Patients should have vision checked by optometrist and seek advice of prescriber if visual changes noted	Scope: 83% SI: 56% Rigor: 27% Clarity 94% Applicability: 46 EI: 100% Overall: 4/7
Royal College of Ophthalmologists (2018)	HCQ: <5 mg/kg/day using absolute body weight	• Baseline ophthalmology exam • Annual screening from initiation of CQ or if on HCQ with risk factors • Annual exam after 5 years of HCQ	• 10-2 Humphrey VF testing using white stimulus • Pupillary dilation exam • Both SD-OCT and FAF if available • If abnormalities on FAF with normal 10-2 VF test results, 30-2 visual field testing is warranted • mfERG if VF deficits and no other imaging abnormality	• If warranted, cessation after discussion between prescriber and patient, not ophthalmologist • Cessation if definite toxicity (2 tests – 1 subjective and 1 objective) • Patients with possible retinopathy (1 abnormal test) should continue treatment with annual review	Scope: 100% SI: 100% Rigor: 98% Clarity 100% Applicability: 98% EI: 92% Overall: 7/7

HCQ: hydroxychloroquine; CQ: chloroquine; VF: visual fields; mfERG: multifocal electroretinography; IBW: ideal body weight; SD-OCT: spectral domain optical coherence tomography; FAF: fundus autofluorescence; SI: stakeholder involvement; EI: editorial independence.

mendations from the American and British sources agree on a HCQ dose of ≤5 mg/kg/day using real body weight. Ideal body weight was initially recommended in guidelines as hydroxychloroquine distributes mainly in lean tissues and thus there was a theoretical risk of overdosing obese patients (6). However, the most recent guidelines advocate for the use of real weight as it better predicts retinal toxicity in one study, where very thin patients had been at increased risk with doses using ideal body weight (6). Their analysis also showed that 6.5 mg/kg/day of ideal body weight corresponds to approximately 5 mg/kg/day of real weight (6). Despite these recommendations, many patients are prescribed higher doses, with a recent UK study reporting that 38% of women were excess-dosed us-

Table II. Recommendations from Rheumatology Associations.

Recommendations	Maximum HCQ dose	Frequency of Screening	Method of Screening	Management of Toxicity	Quality of Guideline (Agree II Instrument)
American College of Rheumatology (2016)	≤5 mg/kg/day using real body weight	• Baseline ophthalmology exam • Annual screening in patients with risk factors • Annual screening after 5 years if no risk factors	• Dilated retina exam • Humphrey 10-2 automated VF test • If available, mfERG, SD-OCT, or FAF also recommended	• Cessation if toxicity suspected or demonstrated • If early toxicity and/or the diagnosis of maculopathy is uncertain, collective decision between ophthalmologist, rheumatologist and patient to stop or cautiously continue treatment with close monitoring	Scope: 33% SI: 36% Rigor: 26% Clarity 67% Applicability: 0% EI: 0% Overall: 2/7
CRA Consensus Conference (1998)	≤6.5 mg/kg/day IBW or real body weight, whichever is less	• Baseline ophthalmology exam • Follow-up every 12-18 months, more frequently if risk factors	• Fundoscopic examination of macula • Central 10-degree VF testing using manual or automated methods • Visual acuity • Colour vision • Slit lamp dilated pupil examination	N/A	Scope: 83% SI: 89% Rigor: 42% Clarity 72% Applicability: 6% EI: 0% Overall: 4/7

HCQ: hydroxychloroquine; VF: visual fields; mfERG: multifocal electroretinography; SD-OCT: spectral domain optical coherence tomography; FAF: fundus autofluorescence; IBW: ideal body weight; SI: stakeholder involvement; EI: editorial independence.

ing actual body weight (26). Prescribers would benefit from further research to confirm whether the drug is as efficacious when patients' doses are reduced to reflect the recommendation of 5 mg/kg/day of real body weight.

Baseline ocular assessment and annual screening after five years of treatment is recommended for patients at average risk of toxicity. Although no clear universal consensus exists on screening methods, automated visual fields and SD-OCT are warranted to detect early changes, with additional imaging as necessary and if available. A recent study by Garrity *et al*. found that patients with normal visual field testing may first develop abnormalities on OCT, suggesting that structural alterations precede functional impairment and emphasising the importance of multiple screening modalities (27). Further research into the optimal tests to detect early hydroxychloroquine toxicity is warranted.

Patients with renal impairment, tamoxifen use, high antimalarial dose, or underlying macular disease may be at higher risk of developing antimalarial induced retinal toxicity (4, 6, 14). Current guidelines suggest annual screening from the initiation of treatment in these patients, using the same screening modalities as those at average risk. Preexisting significant central photoreceptor loss is mentioned as a contraindication to antimalarials in the American guidelines since these findings may interfere with the interpretation of screening tests, however these guidelines also state that there is no specific data to confirm whether patients with underlying retinal disease are at higher risk of toxicity (14).

The available guidelines evolve similarly over time, with the exception of the Canadian sources which have not published recommendations since 2012. The British guidelines were developed jointly by ophthalmology, rheumatology and dermatology associations, while the Canadian and American ophthalmology and rheumatology associations have published separately. A study assessing implementation of the American guidelines by both rheumatologists and ophthalmologists concluded that the majority are not aware of specific details in the recommendations, nor are they adherent to the guidelines (28). Future collaborative efforts between specialties is recommended to develop recommendations supported by all specialists prescribing and monitoring use of antimalarials.

This review was intended to systematically analyse guidelines and recommendations for common themes including antimalarial dosing, frequency and method of ocular screening and management of antimalarial-induced retinal toxicity. The search results obtained were from Canada, the United States and the United Kingdom. It is limited to English, journal-published guidelines and therefore other guidelines from other areas of the world may have been missed if not formally published. The quality of the guidelines were evaluated and earlier guidelines were generally of lower quality. The AGREE II instrument used to assess methodology and quality was developed in 2009, after some of these recommendations had been published, which may partially account for this (23). Although several of the guidelines were updated from older ones, the ADAPTE process was not implemented. It would be wise for future recommendations to be developed using this systematic process of adapting guidelines, as it would enhance quality and validity (29).

Retinal toxicity from HCQ/CQ is irreversible and the risk increases over time. More recent studies suggest higher prevalence rates than previously reported, with a rate of almost 20% after 20 years of HCQ/CQ therapy (6). Recommendations do not specify if an ophthalmologist or optometrist should perform the screening. It is uncertain whether the magnitude of retinal toxicity is increasing due to early detection

with more sensitive tests or if newer recommendations are based on best evidence. In patients with definite toxicity, antimalarial therapy should be stopped. However, in cases of possible toxicity, decisions about cessation of treatment *versus* close monitoring should be made on an individual basis with open discussion between the patient, rheumatologist and eye specialist.

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