ACR, AAD, RDS, and AAO 2020 Joint Statement on Hydroxychloroquine Use with Respect to Retinal Toxicity

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Conflicts of Interest

Costenbader: Stock ownership: Alkermes, Generex; Consults: Neutrolis, Merck; Research support: Merck, Janssen, Astra Zeneca, GSK, Royalties: UpToDate

Fett: Research support: Lilly and Pfizer; Royalties: UpToDate

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KEY POINTS

1) Four major medical societies involved with hydroxychloroquine therapy concur on the need for common principles and cooperation to minimize the risk of ocular toxicity. Effective communication among prescribing physicians, patients, and eye care providers will optimize the utility and safety of hydroxychloroquine.

2) At a daily dosage of ≤ 5 mg/kg/day actual body weight, the risk of retinal toxicity is less than 2% for use up to 10 years.

3) Widespread adoption of more sensitive testing modalities such as optical coherence tomography (OCT) and automated visual fields by eye care providers can now detect early toxicity and thus preserve visual function. Baseline testing is advised when starting hydroxychloroquine to rule out confounding disease. Annual screening with sensitive modalities should begin no more than 5 years later. Providers should be sensitive to the medical value of hydroxychloroquine, and not stop the drug for uncertain indications.

INTRODUCTION

Prescribing clinicians and eye care specialists share responsibility for safely prescribing hydroxychloroquine (HCQ) and screening for the potential risk of retinopathy. Two relevant national societies, the American College of Rheumatology (ACR) and the American Academy of Ophthalmology (AAO), have independently offered management guidelines (1, 2), but this is the first joint statement to emphasize points of agreement that should be recognized by practitioners in all specialties. The ACR and AAO are joined in this statement with the American Academy of Dermatology (AAD) and Rheumatologic Dermatology Society (RDS)

METHODS

A working group consisting of 7 rheumatologists, 2 ophthalmologists, and 2 dermatologists was recruited based on their clinical experience and publication record regarding the use of hydroxychloroquine and its toxicity from the perspective of the rheumatology, dermatology, or ophthalmology community. The selection process considered gender, age, and US geographic diversity. In 2016, the AAO issued guidelines for monitoring for HCQ retinal toxicity (2). Committee members consulted the literature carefully to take into account whether new developments in their fields might alter these basic principles of management. The committee viewed its major task as determining what components of those 2016 recommendations were jointly acceptable to the physicians most likely to prescribe HCQ.

OBJECTIVES

The need for collaborative management has triggered this joint statement, which applies only to managing the risk of HCQ retinopathy and does not include consideration of cardiac, muscle, dermatologic or other toxicities. All treatment involves a risk-benefit assessment, but unfortunately there is a dearth of information on dosage of HCQ in relation to the efficacy of treatment. We recognize that this is a critical unmet need if HCQ risks and benefits are to be balanced effectively. There have been concerns about greater potential toxicity from chloroquine (3), but as data are sparse, this document focuses on the use of hydroxychloroquine. Basic recommendations for chloroquine are currently the same except for an adjustment of dose to $\leq$2.3 mg/kg/day (2).

The ACR, AAD, RDS and AAO stress the importance of effective communication between healthcare providers in the management of HCQ. It is the responsibility of the rheumatologist, dermatologist, or other non-ophthalmic clinician to prescribe HCQ properly, but the responsibility of the ophthalmologist or other eye-care professional to screen correctly for toxicity, and the responsibility of both to advise patients about the risk of retinopathy and to work together to ensure optimal care.

The ACR, AAD, RDS, and AAO emphasize that HCQ is a valuable drug and quite safe at proper rheumatic disease doses and with appropriate eye screening. It should not be avoided for fear of retinopathy (although additional risk factors to consider are discussed below) and should not be stopped casually for borderline findings. The goal of retinal screening is to safely maintain the use of this valuable medication for as long as possible for patients with rheumatic diseases, including cutaneous manifestations of rheumatic diseases.

DOSING

Recent representative studies have a reported a range in the prevalence of HCQ retinopathy from 4.3% to 13.8% (4-8). These studies cannot be directly compared because they vary in many important aspects including the number of participants who have taken HCQ for ten years or more.

The most extensive data to date on HCQ dosage relative to retinopathy come from a large Northern California population of 2361 patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) or related disorders. These data showed that an average usage prescription of ≤ 5.0 mg/kg (actual weight) of HCQ provided a low risk of toxicity (less than 2% for use up to 10 years) (8). Similar results were reported in a more recent study from Korea (7). Higher average daily usage increases the risk of retinopathy to approximately 10% after 10 years, and the risk continues to rise with longer duration of use (8). Nonetheless, many patients can safely use HCQ for decades without retinopathy (8). For a patient with a normal screening exam in a given year, the risk of developing retinopathy in the ensuing year is low (e.g. less than 5%), even after 20 years of use (8). When using dosing by actual weight, these risks were statistically similar for body mass indices (BMI) from 15 to 35 kg/m^2.(8) Blood levels of HCQ

might help in the future to monitor both clinical effect and risk of toxicity (6, 9), but they are not yet widely available, and as presently performed, they show great variability relative to drug intake among individuals. Ultimately, better data on the efficacy of different treatment regimens will allow better judgments on how much HCQ is needed for disease control.

RISK FACTORS

High daily dosage relative to body weight and cumulative dose are the primary risk factors for retinopathy (8). Because the drug is excreted in urine, reduced renal function is the greatest additional risk factor, as it increases systemic levels of HCQ (10) and the risk of toxicity (8). Patients with renal insufficiency may need lower doses and closer monitoring. The balance of risks should be discussed between physicians and patients. Current data are not adequate to advise a precise dosage reduction. These same principles apply to concomitant use of tamoxifen, which can itself be retinotoxic, , and which also increases the risk of retinopathy (8).

CLINICAL APPEARANCE OF RETINOPATHY AND RACIAL FACTORS

HCQ retinopathy has been classically described as appearing to be a “bull’s-eye” lesion in the macula, sparing the foveal center. However, visible damage (with an ophthalmoscope) represents an advanced stage of disease that should no longer occur, since damage can be detected much earlier with modern retinal scanning techniques. Examples of early changes are thinning of retinal layers or mild disruption of critical areas of the retina such as the ellipsoid zone. Both of these are detectable with optical coherence tomography as discussed below. In addition, the phenotype of initial parafoveal toxicity is not universal, and in many patients (East Asians particularly) the retinal changes may appear initially along the pericentral vascular arcades (11). The importance of this finding is that East Asian patients should be screened by tests that reach beyond the central macula.

SCREENING

Screening is vital to detect early retinopathy before a bull's-eye becomes visible on ophthalmoscopy, since at that severe stage the damage tends to progress even after discontinuing the medication and may eventually threaten central vision (12). A baseline retinal exam should be performed within the first few months of hydroxychloroquine usage to rule out underlying retinal disease that might already compromise retinal function or complicate the recognition of retinopathy. Examples include significant macular degeneration, severe diabetic retinopathy, or hereditary disorders of retinal function, but these are judgments best made by the ophthalmologist since mild and stable abnormalities that do not interfere with interpretation of critical diagnostic tests may not be a contraindication (2). If there are no special risk factors (such as a high daily dose, kidney disease, or concurrent tamoxifen usage), screening for the development of retinopathy after baseline exam may be deferred for 5 years, but thereafter should be performed annually.

The mainstays of early detection, if available, are optical coherence tomography (OCT) (an objective test that generates high-resolution “cross-sections” of the retina to show individual cell layers and potential regions of thinning) and automated visual fields (which are subjective tests of visual function). Damage detected at an early stage can stabilize without serious visual loss if HCQ is discontinued (12). It is critical that screening be performed by practitioners experienced with the interpretation of these techniques.

Visual fields should typically focus on the central 10 degrees of the retina (e.g. 10-2 protocols), looking for areas of low visual sensitivity in central vision. For East Asian patients, screening should preferably include a broader OCT (e.g. 30° line scans) and/or wider field test (e.g. 24-2 or 30-2). As a subjective test, fields can vary considerably from test to test and are difficult for many patients; thus, they should not be considered definitive evidence for retinopathy until repeat testing shows a consistent partial or full ring scotoma. Whenever possible, screening should start with an OCT retinal scan, since anatomic changes are more specific for detecting toxicity.

QUESTIONABLE OR BORDERLINE FINDINGS

HCQ is an important drug for the control of many rheumatic diseases and should not be discontinued without adequate cause. The earliest changes on OCT and especially visual fields can be subtle and hard to distinguish from normal variation. Retinopathy generally develops slowly (over several years), and so there is time for suspicious findings to be rechecked after a few months or for the patient to be sent for retina consultation (with further tests such as multifocal electroretinography or fundus autofluorescence imaging). Suggestive or uncertain findings should be discussed with the patient and prescribing physician to justify further examinations, but the drug need not be stopped until evidence for retinopathy is definitive, in particular for patients with active rheumatic or cutaneous disease. The decision to discontinue HCQ should be reached through shared decision-making involving the patient, prescribing physician, and eye care provider, considering the severity of the rheumatic disease and estimated risk of visual loss if the drug is continued.

LIMITATIONS

This consensus opinion is limited by the relative dearth of data on dosage of hydroxychloroquine required to achieve clinical benefit, the lack of prospective data on toxicity, the need for additional studies on the value of blood levels in achieving efficacy or avoiding toxicity, and the need for pharmacogenomic studies that might identify those at greater (or lesser) risk.

SUMMARY

The key to effective management of HCQ to avoid retinopathy is proper dosing, awareness of additional risk factors, and effective screening with modern techniques, in particular OCT. For this to succeed, eye care providers need to communicate with patients and with clinicians who prescribe HCQ. It is important that the drug is not stopped prematurely, but also that it is not continued in the face of definitive evidence of retinal toxicity except in some situations with unusual medical need. It is essential that patients are aware of the risks, dosage, the importance of screening,

and how HCQ contributes to control of their disease. Overall the risk of retinopathy is very low if these principles are followed.

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