Information Statement

Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

A Report by the American Academy of Ophthalmology

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Introduction

Retinal toxicity from chloroquine and its analogue, hydroxychloroquine, has been recognized for many years. The first reports concerned long-term usage of chloroquine for malaria, and later reports showed retinopathy in the treatment of anti-inflammatory diseases. Chloroquine toxicity remains a problem in many parts of the world, but is seen infrequently in the United States where the drug has largely been replaced by hydroxychloroquine for the treatment of systemic lupus erythematosus, rheumatoid arthritis, and other inflammatory and dermatologic conditions. Retinal toxicity from hydroxychloroquine is quite rare relative to the many thousands of individuals who take this drug for medical indications, but it is of serious ophthalmologic concern because even after cessation of the drug there is little if any visual recovery, and sometimes a progression of visual loss. The potential permanence and severity of chloroquine and hydroxychloroquine toxicity make it imperative that ophthalmologists and other physicians be aware of this disorder and take measures to minimize its occurrence and effects.

This document has been prepared because a diversity of screening regimens have been proposed, and these vary considerably in practicality, costs and cost/benefit ratio. There is need for a consensus recommendation. The Physicians' Desk Reference, for example, recommends quarterly examinations that would potentially represent an enormous burden on health care resources. Most authors concur that some screening for early toxicity is reasonable. This statement examines the existing data on chloroquine and hydroxychloroquine toxicity, and suggests guidelines and techniques for screening that represent a balance of risks and benefits at the current state of knowledge. However, this is not intended to be a review article, and only selected references are cited.

These suggestions may be varied according to the needs of individual patients, but provide a basic framework for the management of most patients. It cannot be emphasized too strongly that whatever screening regimen is followed, the keys to early recognition of toxicity, and to the avoidance of liability, are first informing the patient (and if possible the primary care physician) of the risks and of the need for examinations, and second documenting these admonitions carefully in the record. These drugs are typically prescribed by internists, rheumatologists or dermatologists who may not be fully aware of the ophthalmic implications. Patients and primary care physicians should understand that screening helps to recognize toxicity early, before damage is too severe, but cannot prevent toxicity or guarantee that there will be no visual loss.

Hydroxychloroquine and Chloroquine Toxicity

The mechanism of chloroquine and hydroxychloroquine toxicity is not well understood. These drugs have acute effects upon the metabolism of retinal cells, including the photoreceptors, but it is not clear whether these short-term metabolic effects are the cause of the slow and chronic damage that characterizes the clinical state of toxicity. Both agents bind to melanin in the retinal pigment epithelium (RPE), and this binding may serve to concentrate the agents and contribute to, or prolong, their toxic effects. However, no anatomic features of the RPE layer predetermine the macular bull's eye pattern often seen in hydroxychloroquine toxicity. One could also argue that melanin binding serves as a mechanism for removing toxic agents from intracellular sites of damage. The macular localization of disease suggests that light absorption, or possibly cone metabolism, may play a role, but these are speculations.

The clinical picture of hydroxychloroquine and chloroquine toxicity is characterized most singularly by bilateral

bull's eye maculopathy. At this stage of the disorder, a bull's eye of RPE depigmentation is evident clinically in the central macula, often sparing a small foveal island. Observant patients will notice paracentral scotomas, but many patients have relative scotomas and are asymptomatic. On the other hand, functional loss in the paracentral retina has been found in some cases to be the first sign of toxicity, so that careful testing of the paracentral visual field often detects abnormalities before RPE changes are visible. Symptoms or fundus changes that are unilateral are generally not considered sufficient to implicate drug toxicity. If drug exposure continues, the pigment epithelial atrophy and functional disturbance may gradually spread over the entire fundus, and advanced cases show widespread pigment epithelial and retinal atrophy with loss of visual acuity, peripheral vision and night vision. Vascular narrowing may appear, so that advanced chloroquine or hydroxychloroquine toxicity affects visual function much like retinitis pigmentosa.

There may be a stage of very early functional loss where cessation of the drug will allow a reversal of the toxicity. However, clinical cases that have been studied after bilateral paracentral scotomas or visible bull's eye maculopathy are evident have not shown significant clinical recovery. In fact, some cases have been observed to show continued depigmentation and functional loss over several years after the drug has been stopped.[1] It is not clear whether this represents damage from a continued reservoir of the drug (e.g., in melanin), or a gradual decompensation of cells that had been injured during the period of drug exposure. Clearance of these drugs from the blood can take months to years after they are stopped.

Chloroquine, and to a lesser degree hydroxychloroquine, can cause whorl-like intraepithelial deposits in the cornea. Although these corneal changes are not a direct marker for retinal damage, they do suggest drug retention and reinforce the need for regular screening.

Reports in older literature on chloroquine toxicity had suggested that cumulative dose was the critical factor for toxicity. However, this probably is not the sole or even most relevant factor, judging by the many thousands of individuals who have taken hydroxychloroquine for long periods of time (and thus received a high cumulative dose) without evidence of toxicity. The great majority of reports of hydroxychloroquine toxicity have occurred in individuals taking more than 6.5 mg/kg/day, which suggests that daily dosage is of paramount importance.[2-6] Similarly, most chloroquine toxicity has occurred with doses above 3 mg/kg/day.[7-10] Almost all of the rare reports of hydroxychloroquine toxicity at lower doses have occurred in individuals who used the drug for at least 5 years. However, toxicity may appear relatively rapidly if especially high doses of hydroxychloroquine are used, as has been proposed recently for severe immunologic conditions such as graft vs. host disease.

To summarize, although chloroquine and hydroxychloroquine toxicity occurs, and can be serious, the incidence is very low. Review of the published literature on these drugs suggests that well over 1,000,000 individuals have used them, while less than 20 cases of toxicity have been reported

in individuals using the low dose levels noted above—and all of these had more than 5 years of usage.[1-10] This suggests (even accounting for unreported cases) that toxicity is exceedingly rare within the first few years of usage with a low dose. The incidence of toxicity will be higher for larger doses and longer periods of usage, although still numerically small.

Implications for Screening

Since there appears to be a rather minimal risk of toxicity for individuals using less than 6.5 mg/kg of hydroxychloroquine or 3 mg/kg of chloroquine for less than 5 years, screening practices can reasonably be modified to take these facts into account and to be maximally cost-effective. However, practitioners need remember that there are no established criteria for diagnosing hydroxychloroquine or chloroquine toxicity prior to a stage where some permanent visual loss is likely. Screening is aimed primarily at the early detection and minimization of toxicity, rather than at prevention (which can be achieved only by avoidance of the drugs). This statement recommends a screening regimen that reduces the minimum frequency of screening for relatively low-risk cases. We recognize that this might not quickly catch an exceptional case of idiosyncratic or unusually precipitous toxicity. Weighing this possibility against cost issues and legal considerations are judgments that individual physicians, health plans, and of course patients must make on their own.

If a baseline examination (as described below) is normal when chloroquine or hydroxychloroquine therapy is begun, and dosages are at the relatively safe levels (as noted above), screening during the next 5 years can be at the frequency of regular ophthalmic examinations recommended by the American Academy of Ophthalmology Preferred Practice Pattern[11] for the age of the patient. For example, the Academy recommends that individuals between 40 and 64 years of age have an ophthalmologic examination every two to four years. Annual screening during the first 5 years of usage is recommended only for individuals who are at higher or unknown risk because of their dosage (higher or unknown), duration of use (more than 5 years), or other complicating factors. We emphasize that this is a minimum recommendation that balances cost against risk, and individual users or providers of these drugs may choose to screen more often.

Several factors (other than dosage or usage more than 5 years) may enhance the risk of retinal toxicity. For example, chloroquine and hydroxychloroquine are cleared both renally and hepatically, and severe failure of these systems could in theory lead to greater drug retention and thus toxicity. There are few if any such cases in the literature, but patients with severe excretory compromise should be considered to be at higher risk. A recent article has suggested that genetic factors might affect susceptibility, but this remains to be verified.[12] Older patients (e.g., over 60 years of age), patients with macular degeneration, and patients with a retinal dystrophy would seem to be at some higher risk, although no specific data show that diseased retinas are

more susceptible. At the least, these patients have less healthy retina to lose, and their underlying disease may make it difficult to recognize early functional loss or pigmentary damage from drug toxicity. Obesity is a risk factor because the antimalarials are not retained in fatty tissues. Ingested amounts of the drug accumulate only in lean weight, and the "safe" dosage for individuals with a high percentage fat is less than 6.5 mg/kg of hydroxychloroquine or 3 mg/kg of chloroquine. Finally, previous chloroquine or hydroxychloroquine usage may be a risk factor, even though cumulative dose is not directly a determining factor in toxicity. To the extent that chronic exposure may gradually damage cells, a substrate of prior toxic exposure should be taken into account.

Hydroxychloroquine has been prescribed typically at a dosage of either 200 or 400 mg/day, because of the tablet size, rather than on a per weight basis. A 200 mg daily dose will be relatively safe for all but extremely small individuals (less than 68 pounds or 31 kg, if of average build), but a daily dosage of 400 mg puts anyone under 135 pounds (62 kg) in the higher-risk category, and the relative risk will rise as the dose increases. Similarly, chloroquine is typically prescribed at 250 mg/day, corresponding to the tablet size. Prescription of each drug by weight would be preferable, and can be accomplished if desired by varying the dose given on different days of the week (which works because of the long clearance time of these drugs).

Clinical Assessment Tools

Ophthalmologic Examination

A good ophthalmologic examination remains the basis of all screening protocols. Visual acuity should be measured with best correction in place. The cornea should be examined after pupillary dilation to best detect verticillata. The fundus examination should look carefully at the macula to assess drusen or pigmentary changes that might be confused with toxicity, and to detect the earliest signs of bull's eye maculopathy. Pigmentation or atrophy in the periphery, and the status of the retinal vasculature, should be noted.

Photographic Documentation

Fundus photography can provide a record of the fundus appearance at a particular time, against which later changes can be compared. Fluorescein angiography is not necessary to recognize bull's eye maculopathy, although it may help occasionally to enhance subtle RPE defects.

Psychophysical Tests

Examination of the central visual field is highly relevant to the recognition of early hydroxychloroquine toxicity, since paramacular functional loss may appear before changes are seen definitively on fundus examination. Threshold field testing, or subjective evaluation of the central macula (e.g., with an Amsler grid), are most likely to pick up the first signs of damage, such as paracentral suppression or scoto-

mas. There is no perfect field test for screening, and the choice depends in part on the experiences of the clinician. Amsler grid testing can be done at home as well as in the office, and perceptive patients may recognize early paracentral abnormalities before a scheduled visit. The Humphrey 10-2 program (Zeiss Humphrey Systems, Dublin, CA) is available in many offices and clinics, and results are comparable from different locations because it is standardized and automated. It will show a well-developed bull's eye, but early changes with just a few depressed paramacular spots may be hard to evaluate.

Dark-adaptometry can be affected in rather late toxicity from hydroxychloroquine, but has no role as a screening test.

Color vision testing has been reported to be abnormal in early chloroquine or hydroxychloroquine toxicity, although there is disagreement about its sensitivity and specificity. It may be a useful adjunct to central visual field testing insofar as most ophthalmologic offices have some color test materials. Red–green color deficiency screening tests, such as the Ishihara plates, are most widely available and may help to recognize early maculopathy. Male patients should have a baseline test at the onset of drug usage to recognize any underlying congenital color deficiency that might be confused later with toxicity. Acquired maculopathies are in general more likely to affect the blue–yellow tritan axis of confusion than the red–green, and tests that can test for subtle tritan errors may be useful (e.g., the desaturated Farnsworth Panel D-15 test). Color errors are not specific for antimalarial toxicity and may occur in other macular or optic nerve diseases.

Electrophysiologic Tests

Objective tests of global retinal function such as the full-field electroretinogram (ERG) or electro-oculogram (EOG) will show abnormalities in late chloroquine or hydroxychloroquine toxicity, but they are not sensitive to early functional changes that are predominant in the macula (or indeed any small region of the fundus). Thus, these "mass response" tests have little role in the screening of patients for early hydroxychloroquine toxicity. They remain useful, however, in the evaluation of any patient with manifest toxicity to judge how severe or widespread the damage may be. Some reports have suggested that the EOG is a relatively specific and early indicator of toxicity, but other reports have documented normal EOGs in patients with definite toxicity. Current evidence has not validated the EOG as a reliable screening test.

Electrophysiologic tests that specifically evaluate the macula may be useful to confirm the presence of early maculopathy. Focal ERG techniques can record an ERG response from the foveal and parafoveal regions, but it is difficult to test more than a few locations or recognize an anatomic pattern such as bull's eye maculopathy. A newer electrophysiologic technique, the multifocal ERG (mfERG), appears to be more suitable for the evaluation of hydroxychloroquine and/or chloroquine toxicity because it generates local ERG responses topographically across the posterior pole, and can document a bull's eye distribution of ERG

Table 1. Criteria of Low and Higher Risk for Developing Retinopathy

	Low Risk	Higher Risk
Dosage	<6.5 mg/kg hydroxychloroquine <3 mg/kg chloroquine	>6.5 mg/kg hydroxychloroquine >3 mg/kg chloroquine
Duration of Use	<5 years	>5 years
Habitus	Lean or average fat	High fat level (unless dosage is appropriately low)
Renal/liver disease	None	Present
Concomitant retinal disease	None	Present
Age	<60 years	>60 years

depression. Several cases of hydroxychloroquine retinopathy have already been reported that show a loss of central or paracentral mfERG responses while the full-field ERG remained normal. However, the role of the mfERG as a screening test remains to be established.

Definition of Risk

Table 1 shows criteria of "low" and "higher" risk as guidelines. Patients should understand that, even if they are in the higher risk category, the likelihood of retinopathy is actually quite low; however, screening becomes relatively more important. Conversely, patients in the low risk category should understand that while toxicity is extremely unlikely in the first 5 years, it is not impossible. Note that these criteria may need to be adjusted according to individual clinical factors.

Patients with pre-existing visual loss or scotomas may require more elaborate documentation or special examinations to establish a baseline that shows the anatomic and functional changes of the underlying ocular disease. Such patients, and the physicians caring for their systemic disease, should be aware of possible added risks when using these drugs.

Screening Recommendations

Baseline Examination for All Patients

All patients beginning hydroxychloroquine and/or chloroquine therapy should have a baseline examination within the first year to document any complicating ocular conditions, and to establish a record of the fundus appearance and visual field. This examination also allows for the risk status (low or higher) to be established, and for counseling about the risk of retinal damage. This counseling should be documented explicitly in the record.

1. Complete ophthalmologic examination including best-corrected visual acuity and dilated examination of the cornea and retina.
2. Baseline field testing with an Amsler grid, or Humphrey 10-2 fields (whichever is felt to be reliable in the testing office), to recognize any underlying or confounding abnormalities. These tests are important because they may reveal a functional deficit at a stage when pigmentary changes are still unclear.

3. Optional color testing. If color tests might be used for later screening, then it is especially important to do baseline color testing on male patients.
4. Optional fundus photography. This is desirable if the fundus shows any pigmentary changes (especially macular depigmentation) that might be confused with early toxicity.
5. Optional specialized tests such as fluorescein angiography or multifocal ERG. In general, these do not need to be performed routinely, but should be considered if there is underlying maculopathy that would need to be distinguished from antimalarial drug toxicity, or if the patient has unusual risk factors that may predispose to early or rapid toxicity.

Patients and their primary physicians need to recognize the difficulty, using present technology, of distinguishing early drug toxicity from other types of maculopathy.

Low Risk Patients

The risk of toxicity within the first 5 years of usage for these patients is so extremely low that within this initial period we suggest screening only as a component of the regular ophthalmic examinations recommended by the American Academy of Ophthalmology. However, we recognize that some patients or ophthalmologists may elect to screen more often. The current Preferred Practice Pattern advises comprehensive eye evaluations for patients with no risk factors on the schedule shown in Table 2.

At each of these examinations the cornea and retina should be examined after pupillary dilation, and Amsler grid sensitivity (or Humphrey 10-2 fields) should be tested. Other tests (as at baseline examination) are optional.

Patients should be counseled carefully that there is a very small risk of toxicity within this initial 5-year period. They should be instructed to return promptly, ahead of schedule, if they notice any change in visual acuity, Amsler grid appearance, color sensations, or adjustment to the dark. They should also return if their drug dosage is increased, if

Table 2. Comprehensive Eye Evaluation for Patients with No Risk Factors

Age	Frequency of Examination
20–29 years	at least once during period
30–39 years	at least twice during period
40–64 years	every 2–4 years
65 years or older	every 1–2 years

they have major weight loss, or if they develop hepatic or renal dysfunction.

Higher Risk Patients (including all patients with more than 5 years of usage)

Annual screening is recommended for everyone in the higher risk category, whether that status is achieved by daily dosage, length of usage, or medical status. Patients should know, however, that the absolute risk of toxicity is still very low, at least with respect to treatment for rheumatoid disorders. The risk may not be so low if very high doses (e.g. >10 mg/kg) are used (e.g., for acute immunologic reactions), and these patients may need earlier and more complete baseline studies as well as more frequent screening examinations. Patients who begin hydroxychloroquine and/or chloroquine drug therapy with possible risk factors such as age-related macular degeneration, retinal dystrophy, or renal/hepatic disease, should be counseled about these factors, and patients exceeding 5 years of usage should be told why more frequent follow-up examinations are now needed. This counseling should be noted explicitly in the record.

The annual examinations for higher risk patients should cover the same elements as for low risk patients: a complete ophthalmologic examination, Amsler grid testing (or Humphrey 10-2 field testing), with other procedures done optionally.

Depending on the risk status and the number of years of drug usage, the physician may elect to periodically add Humphrey 10-2 testing to Amsler grid results or to obtain fundus photography for comparison with an earlier baseline or to establish a new one. These tests are especially important for patients with aging changes or other eye diseases that might confound the diagnosis of drug toxicity (e.g., macular degeneration, glaucoma, cataract).

Patients should be instructed in the use of the Amsler grid, and given grids to use at home on a regular basis (e.g., monthly). Patients should be counseled to return promptly (not wait for the next scheduled examination) if there is any change in visual status.

Patients with Suggestive Visual Symptoms or Fundus Findings

If a patient returns with suggestive visual symptoms, or if any of the screening examinations raise a question of early toxicity, then more careful evaluation is needed. If Amsler grid changes or other visual symptoms are reported, the fundus should be examined and the Amsler grid test should be repeated in the office along with a Humphrey 10-2 test for confirmation. If any of the findings are suggestive of toxicity, refer to the next section for management. If the findings are doubtful or questionable, the patient should be advised to return in 3 months for re-evaluation. Consideration should be given to further evaluations that might reveal disease. For example, fundus photography and fluorescein angiography will sometimes show a bull's eye pattern of depigmentation that is hard to discern clinically. Multifocal electroretinography can provide objective data on parafoveal photoreceptor function. Full-field electroretinography can demonstrate whether there is any diffuse retinal dysfunction.

Management of Toxicity

No medical therapy has proven effective in chloroquine or hydroxychloroquine toxicity other than cessation of the drug. In practice, the management of suspected or recognized toxicity depends not only on the presence of retinal damage, but also on the medical status of the patient. Hydroxychloroquine and/or chloroquine are, for many patients, the most effective and safest way to control a serious systemic disease. Cessation can lead to worsening of the underlying disease, or to a need for other drugs such as steroids and antimetabolites that have serious systemic side effects. Thus, decisions to change medication must be made in conjunction with the internist or rheumatologist who is managing the patient, and with careful disclosure to the patient of the systemic as well as ophthalmologic implications. Another factor to consider is that hydroxychloroquine and/or chloroquine clear very slowly from the body, so that the full effects of any decision may not be manifest for 3–6 months. Visual function may well continue to deteriorate slowly even after the drug is stopped.[1]

Patients with only "possible" early toxicity may elect to be followed at 3-month intervals until there is evidence of progression. However, if the drug is not considered to be important medically, it should be stopped.

Patients with probable toxicity or definite early toxicity (e.g., bilateral bull's eye scotoma or subtle RPE bull's eye depigmentation) should have the drug stopped immediately since there may be a slight chance of improvement and, at the least, this will minimize the progression of visual loss. However, the patient and primary physician may in rare cases elect to maintain the medication if it is felt to be critical to medical management of the underlying disease, with close (i.e., every 3 months) follow-up as long as visual loss is not progressing. The patient must understand and accept a risk of more severe and permanent visual loss.

Patients with unequivocal bull's eye maculopathy, early central visual loss, or full-field ERG reduction are at serious risk for disabling loss of visual acuity and visual field. The drug should be stopped immediately unless needed so desperately for quality of life that severe loss of vision is acceptable as an outcome. As noted above, visual loss may continue to progress for many months after cessation of the drugs, so recognition of toxicity at the earliest stages is important.

If toxicity is recognized at a very early stage of functional rather than pigmentary loss, some recovery may be possible in theory. However, this occurrence has been hard to verify, in part because it is often difficult to make a firm diagnosis at an early stage. In general, patients with toxicity should be counseled that recovery is unlikely, and that there is even some risk of progressive RPE atrophy if the exposure was high. Because of the uncertainty about recovery and progression, we recommend re-evaluation three months after a diagnosis of toxicity is made, even after the drug is

stopped, and then annually until the findings are clearly stable. The choice of examinations will depend on previous results, but should ideally include procedures such as automated field testing, multifocal ERG, and full-field ERG to give accurate and objective measures of the degree of functional damage and its change over time. Fundus photography and fluorescein angiography can help to document pigmentary changes.

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