

Hydroxychloroquine Retinopathy Update

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Hydroxychloroquine (HCQ) has been used widely for the treatment of several rheumatologic and dermatologic conditions, including systemic lupus erythematosus and rheumatoid arthritis. Its toxic effects on the retina, HCQ retinopathy, is not uncommon among long-term users, and produces characteristic irreversible and progressive outer retinal damage. Recent studies of Asian populations showed different patterns of retinopathy according to ethnicity; for example, a pericentral pattern is more common in Asian populations, whereas the parafoveal type is more prevalent in Caucasian patients. The pericentral pattern, which is common in Asian patients, is likely to lead to a late diagnosis with conventional imaging modalities, thereby necessitating increased attention to the screening of Asian patients. The most recent American Academy of Ophthalmology guidelines suggest optical coherence tomography and a visual field examination as the primary screening tests, and multifocal electroretinogram and fundus autofluorescence as other recommended objective screening tests. The optimal timing and frequency of annual screening depend on the systemic and ocular risk factors. Annual screening should begin from 5 years of drug use in cases without any known risk factors, but patients with major risk factors require earlier regular screening. After a diagnosis of HCQ retinopathy, a decision regarding whether to stop the drug should be made in consultation with the prescribing physician, and the progression of retinopathy should be monitored carefully because the retinopathy can progress even after drug cessation. (*J Rheum Dis* 2018;25:153-157)

Key Words. Hydroxychloroquine, Retinal diseases, Diagnosis

INTRODUCTION

Hydroxychloroquine (HCQ), a member of the 4-aminoquinoline drug class, is an anti-malarial drug that has been widely used for the treatment of several rheumatologic and inflammatory diseases, including systemic lupus erythematosus and rheumatoid arthritis. The estimated number of patients in the United States using the drug is approximately 350,000. For this type of treatment, HCQ and chloroquine are generally safe and effective, but ocular toxicity can occur, particularly in long-term users. HCQ is known to be less toxic to the retina than chloroquine. Since the first reports of retinal toxicity, several studies have been performed on screening and management of this type of retinopathy, and expert recommendations have been developed. Recently, the American

Academy of Ophthalmology (AAO) presented revised recommendations (2016 revision) on screening for HCQ retinopathy, emphasizing early recognition of the retinopathy before it progresses to advanced stages [1].

The mechanism of HCQ retinopathy is still unclear. It has been suggested that the drug may affect the metabolism of retinal cells or the intracellular pH and function of lysosomes in the retinal pigment epithelium (RPE), resulting in cell membrane instability in the photoreceptors [2]. Binding of the drug to melanin in the RPE may serve to concentrate the drug, leading to toxic effects, but its role is controversial: it has also been suggested that melanin binding may protect against retinopathy by removing the drug from intracellular storage [1].

Interestingly, recent studies have shown racial differences in toxic effects, particularly in the pattern of retin-

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opathy [3,4]. Asian patients showed a different pattern of retinopathy from Caucasian patients, which may lead to late diagnosis when conventional screening tests are used. Taking into account recent advances in retinal imaging modalities that have been applied to retinopathy, this review aims to summarize recent advances in the screening and management of HCQ retinopathy. We also discuss special considerations that apply to Asian patients, which may be important for screening of retinopathy in this population.

MAIN SUBJECTS

Epidemiology and natural course

Only a few reports have evaluated the prevalence of retinopathy among HCQ users. The prevalence has been estimated at 1% or less among patients taking the drug for 5 years, but higher in those with longer-duration use [5,6]. However, a large study of 2,361 patients using HCQ for > 5 years reported a prevalence of retinopathy of 7.5% for users with daily consumption over 5.0 mg/kg of body weight [7]. In Korea, the prevalence was reported to be 4.1% [3] and 4.4% [8] among patients receiving HCQ who were examined for the presence of retinopathy. Thus, HCQ retinopathy is not uncommon among long-term users of HCQ, and the prevalence seems to increase markedly with the duration of HCQ use. It may also be dependent on other risk factors, among which the

AAO 2016 revision mentioned daily dosage (>5.0 mg/kg), coexistent retinal disease, concomitant drugs such as tamoxifen, and coexistent macular disease [1]. For example, in a group with daily consumption of 4.0 to 5.0 mg/kg, the prevalence of retinopathy remained less than 2% within the first 10 years of use, increasing to approximately 20% after 20 years. Patients receiving HCQ at 800 to 1,000 mg/day (up to 20 mg/kg) showed a 25% to 40% incidence of retinopathy and could present with retinopathy within 2 years of beginning use [9,10]. However, the absence of a prospective cohort study including a large number of patients using HCQ limits the accuracy of estimation. More reliable estimates of the prevalence of retinopathy would require population-based studies for various ethnicities [11].

HCQ retinopathy is irreversible and can be progressive. The retinal toxicity may not be associated with any functional defect in the early stage, while retinal damage is localized; however, it can lead to progressive visual field defects, and in advanced stages it may lead to loss of central visual acuity and permanent blindness. The retinopathy progresses in a severity-dependent manner [12], and it can continue to progress even after drug cessation [13]. Eyes with severer stages of retinopathy are more likely to show progression, with wider and more severe destruction of the retina [12,14]. Eyes in which severe retinopathy involved the RPE showed especially rapid progression of retinopathy in follow-up examinations. These

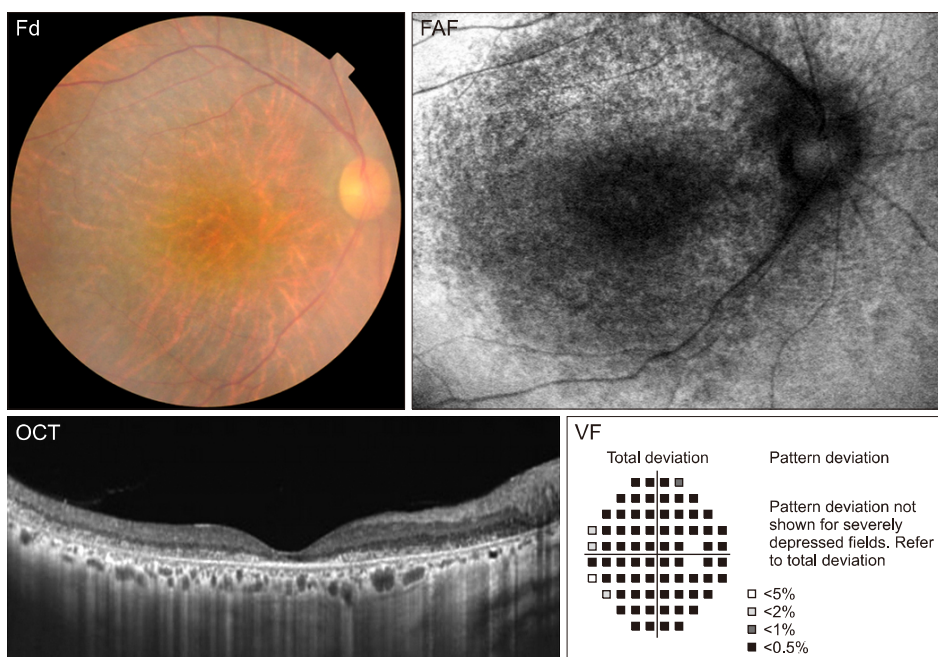


Figure 1. Fundus photograph (Fd), optical coherence tomography (OCT), fundus autofluorescence (FAF), and visual field (VF) examination of the right eye in a 54-year-old female systemic lupus erythematosus patient with hydroxychloroquine retinopathy. Retinal pigmentary changes observable in the fundus photograph correspond to outer retinal damage visible on the OCT image, hypo-autofluorescence on FAF, and complete visual field loss in visual field examination. The visual acuities in both eyes were “hand motion.”

factors demonstrate the importance of early recognition of retinal toxicity, as early intervention may minimize further progression and the corresponding risk of vision loss. In the natural course of the condition, eyes with HCQ retinopathy can also develop cystoid macular edema or epiretinal membrane, which can cause further visual loss [15]. Although the retinopathy has no definitive treatment, macular edema is treatable by oral or topical carbonic anhydrase inhibitors [15,16]. Unfortunately, the long-term progression of the retinopathy has not been described, and should be further investigated so that the natural course of the disease can be better understood.

Clinical features and toxicity screening

HCQ retinopathy is characterized by damage to the outer retina, including the photoreceptors and RPE (Figure 1). It was described classically as bull's-eye maculopathy, with a foveal island (relatively spared area) surrounded by a ring of parafoveal RPE depigmentation (damaged area); however, this is not commonly seen in newly diagnosed patients nowadays, as recommended screening tests can detect HCQ toxicity long before the advanced stage. On optical coherence tomography, macular/extramacular characteristic photoreceptor defects with or without RPE defects in the pericentral or parafoveal area are observed, and hyper- or hypo-fluorescence in the area can be observed in both eyes on fundus autofluorescence (FAF). Visual field examination reveals visual field defects that correspond to the area of photoreceptor defects. Multifocal electroretinography (mfERG) may show depression in parafoveal or extramacular electroretinogram responses. The recent AAO guidelines do not give strict diagnostic criteria; rather they state that a subjective screening test should be confirmed with an objective test prior to making a diagnosis of HCQ toxicity [1]. Therefore, according to the current guidelines, among the 4 recommended screening tests by AAO, 1 subjective finding (i.e. visual field abnormality) confirmed by abnor-

malities on any of 3 objective tests (spectral-domain optical coherence tomography [OCT], FAF, and mfERG) may lead to a diagnosis of HCQ retinopathy.

HCQ retinopathy may present as patchy photoreceptor loss and isolated visual field defects without RPE involvement (early retinopathy), photoreceptor damage and scotomas constituting a partial (>180 degrees) or full ring but without RPE involvement (moderate retinopathy), or combined RPE damage and hypo-autofluorescence on FAF (severe retinopathy). Based on the location of retinal involvement, HCQ retinopathy may be classified into a parafoveal pattern if the eyes display photoreceptor/RPE disruption in a ring 2~8 degrees from the fovea; a pericentral pattern if the damage is localized 8 degrees or more from the fovea; or a mixed pattern if they display both pericentral and parafoveal patterns of retinopathy [17]. Classification of the stage and pattern of retinopathy at baseline is important, as the progression of retinopathy is dependent on the stage, and variations in the pattern of retinopathy may lead to late recognition of the disease [4].

Asian patients with HCQ retinopathy usually show a pericentral pattern, whereas most white patients with this type of retinopathy show a parafoveal pattern. Melles and Marmor [4] showed that the pericentral type is likely to be diagnosed later, and recent studies of Asian populations showed that conventional methods for imaging structural damage may not be as effective as in White patients [3,8]; therefore, Asian populations require special measures for the detection of retinopathy. To detect problems across wider areas, wide-field OCT scans such as multiple 9 or 12-mm scans, wide FAF, and visual field examination by 30-2 perimetry have been recommended [3,8]. Thus, specific protocols for screening can be adjusted for patient demographics, particularly the ethnicity of the patient. Table 1 lists recommended protocols for screening of Asian patients taking HCQ medication [1,8].

Table 1. Screening for hydroxychloroquine retinopathy recommended for Asian patients with hydroxychloroquine use

Recommended tests	Protocols
Automated visual field examination	30-2 (for pericentral pattern) and/or 10-2 (parafoveal pattern)
Spectral-domain OCT	Wide-field (at least 9-mm [30°] scan length) OCT Macular volume scan may be useful to obtain eccentric scan images of the posterior pole
Multifocal electroretinogram	No protocols specified for Asian patients
FAF	Wide-field FAF (30° or greater)

OCT: optical coherence tomography, FAF: fundus autofluorescence.

The 2016 revision indicated that all patients beginning long-term HCQ therapy should have a baseline ophthalmologic examination within the first year of drug use [1]. The main objective of baseline screening is to rule out any underlying macular or retinal diseases, which may be added risk factors for retinal toxicity of the drug and may interfere with interpretation of screening test results. Following the baseline examination, annual screening is recommended to begin after 5 years of drug use; however, patients with major risk factors such as daily dose/body weight >5.0 mg/kg, renal diseases, and concomitant use of tamoxifen require earlier regular screening, in which case the screening frequency can be greater than once per year [1]. In real-world clinical practice, patients sometimes experience major weight loss or development of kidney diseases, which affect the risk of retinopathy and necessitate increases in screening frequency.

Standard screening examination procedures have been debated. The most recent guidelines suggest automated visual field testing and spectral-domain OCT as primary screening tests, as these can be easily performed and are widely available [1]. For subjective testing, visual field examinations are sensitive, but the reliability of the tests can vary quite widely, depending on the patient and even from test to test. In contrast, OCT is objective and highly specific for detecting structural damage caused by retinopathy [8]. Accordingly, an abnormality found by a subjective test should be confirmed by at least 1 objective test, particularly if the pattern is atypical [1]. Other objective tests recommended in the most recent guideline include mfERG and FAF, which can be useful for detecting early or pericentral retinopathic damage and RPE involvement, respectively. Table 2 summarizes the diagnostic ca-

pabilities of the recommended screening tests [18]. The AAO guidelines also mention microperimetry and adaptive optics retinal imaging as newer tests of possible value in the future [1].

It is important that patients with HCQ retinopathy should be monitored for progression. As retinopathy can continue to progress after the drug is discontinued, progression should be carefully assessed in patients diagnosed with HCQ retinopathy even after drug cessation [12,13]. There is not yet a consensus definition of HCQ retinopathy progression; however, most previous studies of progression used spectral-domain OCT, visual field examination, and FAF for evaluation [12-14]. Although no specific frequency of monitoring has been specified by the guidelines, it is usual to evaluate patients at intervals of less than a year. Associated conditions such as cystoid macular edema should also be monitored.

Management

No treatment has been developed or proven to be effective for HCQ retinopathy. Also, there is no proven method of preventing it from developing. The most important decision to be made by patients diagnosed with HCQ retinopathy is whether to cease using the drug. This decision should be made in conjunction with the patient and the prescribing physician (usually a rheumatologist) to ensure that the medical risks incurred by discontinuation of the drug can be managed [1]. There has been no specific “safe” dose recommended for HCQ use; however, a previous study showed that if the daily dose is less than 5 mg/kg real body weight, the risk is low [7]. Thus, if the medication is considered indispensable for a given patient, the dose may be reduced to this level, but in this case, retinopathy progression should be very carefully monitored.

Patients should be informed about the risk of retinopathy, together with their specific ocular and systemic risk factors, ideally by both the prescribing physicians and ophthalmologists. A proposed schedule for baseline screening may be provided by the prescribing physician, while a schedule of regular screening following the baseline examinations can be provided by the ophthalmologists. The patient should be educated about ocular and systemic risk factors by the prescribing physician or ophthalmologist in accordance with the most up-to-date evidence. A patient with HCQ retinopathy may also be advised about the risk of progression after drug cessation, depending on the severity of the retinopathy. This risk is

Table 2. Diagnostic ability, sensitivity, and specificity of the recommended screening tests for hydroxychloroquine retinopathy [18]

Examinations	Sensitivity	Specificity
10-2 VF examination	85.7	92.5
Spectral-domain OCT	78.6	98.1
Multifocal electroretinogram	92.9	86.9
Spectral-domain OCT and 10-2 VF examination	85.7	92.5

Values are presented as percentage. VF: visual field, OCT: optical coherence tomography. Data from the article of Browning DJ (Hydroxychloroquine and chloroquine retinopathy. New York, Springer, 2014, p. 219) [18].

minimal if the retinopathy is detected at an early stage, but significant at later stages, particularly those with RPE involvement. Therefore, it should be emphasized that earlier detection of retinopathy by following recommended baseline and annual screening schedules may minimize retinopathy progression and the risk of significant visual loss.

Patients with age-related maculopathies such as age-related macular degeneration are advised to avoid excessive sun exposure and to take lutein and zeaxanthin supplements. Although photoreceptor and RPE defects are commonly noted in both age-related macular degeneration and HCQ retinopathy, the role of dietary or nutritional supplementation in patients with HCQ medication and in patients with HCQ retinopathy is unclear [1].

CONCLUSION

HCQ retinopathy should be screened for carefully, particularly in patients with long-term use of HCQ, as it is not uncommon among long-term users and may lead to severe visual loss in advanced stages. The literature over the last few years revealed that there may be variable expression of this type of retinopathy according to ethnicity. Asian patients are more likely to be diagnosed at later stages, so for early detection they should be monitored by wide-field imaging and wide visual field tests. Patient education about the risk of visual loss associated with HCQ therapy is important. This, together with regular ophthalmic screening, may minimize the risk of visual loss. Future studies are required to increase understanding of the long-term progression of the disease, to develop novel screening methods for earlier detection, and to set safe dosing levels for the therapy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article is reported.

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