Retinal Toxicity Associated With Hydroxychloroquine and Chloroquine

Risk Factors, Screening, and Progression Despite Cessation of Therapy

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Objective: To report the detailed clinical findings of patients with retinal toxicity that developed secondary to the use of hydroxychloroquine sulfate (n=13), chloroquine phosphate (n=2), or a combination of the agents (n=1).

Methods: Ophthalmologic examination, fundus photography, visual field testing, and detailed electrophysiologic assessment were undertaken in all 16 affected patients. Selected patients also had spectral domain optical coherence tomography (n=6) and fundus autofluorescence imaging (n=4).

Results: Sixteen women (mean age, 67 years; range, 44-85) were monitored for 7 years. The mean duration of hydroxychloroquine therapy was 13 years (range, 2-20). In patients in whom the daily dosage of hydroxychloroquine could be estimated (12 of 13), when using actual body weight, 8 were taking 6.5 mg/kg or less and 4 were taking greater than this recommended dosage. However, if lean body weight was used, 3 patients were taking 6.5 mg/kg or less and 9 were taking greater than this daily dosage. The most common (n=10) presenting symptom was difficulty with reading; 4 women were asymptomatic. Two patients had preexisting retinal disease, 2 were obese, and none had renal or liver dysfunction. Fundus findings ranged from mild retinal pigment epithelial changes to bull’s-eye maculopathy; 3 patients had a normal-appearing macula. Two patients had full-field electroretinograms that showed no abnormalities and 6 showed evidence of generalized retinal dysfunction with reduced rod and cone responses. All 15 patients who underwent multifocal electroretinography testing had evidence of bilateral macular cone dysfunction. Four patterns of visual field abnormality were observed in the 15 patients with abnormal visual fields, the most common (n=10) being isolated central loss. Repeat electrophysiologic and visual field assessment provided evidence of disease progression despite cessation of medication in 6 patients, with documented progression for 7 years in 1 woman.

Conclusions: Sustained visual improvement following cessation of drug therapy was not observed in any patient in this series, and our identification of 6 patients with objective evidence of progression serves to remind physicians of the potentially devastating visual consequences of antimalarial-related retinal toxicity. It is also of note that profound abnormalities detected with visual field and multifocal electroretinography testing can be observed in the presence of a normal macular appearance, and our findings suggest that lean body weight should be used for all patients when calculating daily dosage.


In addition to their use as antimalarial agents, chloroquine phosphate and hydroxychloroquine sulfate have a long history of use in the treatment of rheumatoid arthritis, systemic lupus erythematosus, cutaneous lupus, and other connective tissue disorders. Because of its better safety profile, hydroxychloroquine has superseded chloroquine in the majority of indications. The mechanism of action of these drugs remains uncertain but includes effects on the function of lysosomes and components of the immune system.1,2

It was hoped that the chemical modification of chloroquine to hydroxychloroquine would abrogate its retinal toxicity. However, while the toxicity is no doubt significantly reduced, the risk is still present and poses a significant clinical challenge.3,4 Several risk factors have been identified that may increase the likelihood of hydroxychloroquine-related retinal toxicity: (1) daily dosage exceeding 6.5 mg/kg, (2) obesity, (3) duration of use longer than 5 years, (4) renal or liver function impairment, (5) age greater than 60 years, and (6) preexisting retinal disease.6 Retinal toxicity is most frequently characterized by symptoms of central visual loss including reading difficulties, reduced color vision, and central scotomata. Maculopathy ranging from a subtle disturbance of the retinal pigment epithelium to bull’s-eye maculopathy has been described. Visual field (VF) testing is useful to identify areas of relative or absolute sensitivity loss.5,7 Multifocal elec-
troretinography (mfERG), fundus autofluorescence (FA) imaging, and optical coherence tomography are valuable modalities that can detect functional and structural abnormalities, potentially at an early stage, with mfERG also having an important role in monitoring progression of an abnormality.10-14 Timely detection is of critical importance to discontinue the medication and thereby stop or slow retinal damage at the earliest opportunity.

We report detailed findings on 16 patients with toxicity secondary to use of antimalarial drugs monitored for a relatively short period at a single institution. The findings suggest that, while uncommon, toxic retinopathy from quinoline use may be more prevalent than currently thought. We highlight several important considerations that are illustrated by this cohort, including our findings that toxicity might develop despite daily dosages below the recommended maximum dosage, the macula might appear normal even with profound VF and mfERG abnormalities, and that, not infrequently, patients will develop objective evidence of progression despite cessation of medication.

METHODS

Sixteen individuals with evidence of retinal toxicity secondary to hydroxychloroquine or chloroquine were evaluated at the Casey Eye Institute. The protocol of the study adhered to the provisions of the Declaration of Helsinki and was approved by the local ethics committee.

CLINICAL ASSESSMENT

A full medical history was documented and ophthalmologic examination was performed. All patients underwent color fundus photography, VF testing (static and kinetic), and electrophysiologic assessment. Selected patients also had spectral domain optical coherence tomography (SDOCT) (n=6) (Spectralis OCT Heidelberg Retina Angiograph; Heidelberg Engineering, Heidelberg, Germany) and FA imaging (n=4) (Heidelberg Retina Angiograph 2; Heidelberg Engineering) performed.

Patients’ VFs were examined with kinetic perimetry using the Octopus 101 perimeter (Haag-Streit, Inc, Koniz, Switzerland). Static perimetry was performed using the Humphrey Field Analyzer II perimeter (Carl Zeiss Meditec, Inc, Dublin, California). Goldmann stimulus size III, and the 10-2 and 30-2 grids using the Swedish Interactive Threshold Algorithm strategy. In addition, white-on-white static perimetry was performed using the German Adaptive Threshold Estimation strategy,15 the Octopus 101, Goldmann stimulus size III, and a 158-test-point full-field grid of radial-oriented and centrally condensed design.

Electrophysiologic assessment included a full-field electroretinogram in 8 patients and mfERG in 15 patients, incorporating the protocols recommended by the International Society for Clinical Electrophysiology of Vision.16-17

ESTIMATION OF HYDROXYCHLOROQUINE AND CHLOROQUINE DOSAGE

Cumulative dosage was calculated using available information as to years of therapy and total daily dosage. Inherent assumptions included 100% adherence and that the reported/documented length of use was rounded to the nearest year.

Daily hydroxychloroquine dosage (in milligrams per kilograms per day) was calculated from total daily intake (in milligrams) divided by either actual or lean body weight (in kilograms). Lean body weight for women was calculated as follows: (1.07 × weight) − 148 × (weight²/ [100 × height (in meters squared)]). Body mass index was calculated as weight in kilograms divided by height in meters squared.

RESULTS

Sixteen women (mean age, 67 years; range, 44-85) were monitored for 7 years at a single institution. The diagnosis of retinal toxicity was made on the basis of clinical history, examination, and findings from tests including VF, full-field electroretinogram, mfERG, optical coherence tomography, and FA imaging. The clinical findings are summarized in the Table and illustrated in Figures 1, 2, 3, 4, and 5.

Thirteen women had been taking hydroxychloroquine, 2 had been using chloroquine, and the remaining patient had been using a combination of the agents. Six patients were seen on a single occasion for specialist evaluation and subsequently returned to the referring ophthalmologist. In the remaining 10 patients, the mean duration of follow-up was 3 years (range, 0.5-7). Of the 2 women who had been taking chloroquine, 1 had used it for 7 years and the other for 17 years. The mean duration of hydroxychloroquine use was 13 years (range, 2-20 years) and the mean cumulative dosage was 1662 g (range, 365-2920 g). In patients in whom the daily dosage of hydroxychloroquine could be estimated (12 of 13), when using actual body weight, 8 were taking 6.5 mg/kg or less and 4 were taking more than this dosage (Table). However, if lean body weight was calculated for all patients, 3 were taking 6.5 mg/kg or less and 9 were taking more than this recommended dosage (Table). Two women were classified as obese on the basis of their body mass index and none had renal or liver dysfunction. Two patients had preexisting retinal disease: 1 had bilateral moderate nonproliferative diabetic retinopathy (no diabetic maculopathy) and quiescent neovascular age-related macular degeneration in the left eye; the other woman had bilateral mild nonproliferative diabetic retinopathy (no diabetic maculopathy) (Table).

The most common presenting symptom was difficulty with reading (n=10). Four patients were asymptomatic and were referred to us because hydroxychloroquine toxicity was suspected on the basis of clinical examination and/or central VF testing. Visual acuity ranged from 20/20 OU to hand motion. Fundus findings at the time of diagnosis ranged from mild retinal pigment epithelial changes to bull’s-eye maculopathy, were bilateral, and in most patients, reasonably symmetrical (Table). Three patients had a normal macular appearance. Mild macular changes progressed to frank bull’s-eye maculopathy during the course of follow-up in patient 7; this developed 3 years after chloroquine therapy had been discontinued. In the presence of a clinically normal macula or mild macular disturbance, marked functional abnormalities were also detected with mfERG and VF testing in these patients (Table). None of the patients in our series had documented quinoline deposition in the corneal epithelium.

Two patients had full-field electroretinograms that showed no abnormalities and 6 showed evidence of gen-
Table. Summary of Clinical Findings

<table>
<thead>
<tr>
<th>Patient No./Sex/ Presenting Age, y</th>
<th>Drug and Daily HCQ Dosage (Lean Weight)</th>
<th>Renal, Liver, or Retinal Disease; Obesity</th>
<th>Symptoms (Duration)</th>
<th>Follow-up, y</th>
<th>VA, OD/OS</th>
<th>Most Recent</th>
<th>fERG</th>
<th>mERG</th>
<th>FVs</th>
<th>Progression Following Drug Cessation</th>
</tr>
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<tbody>
<tr>
<td>1/F/44</td>
<td>CQ 7</td>
<td>1280</td>
<td>Nil</td>
<td>HM</td>
<td>HM</td>
<td>Macular RPE changes, attenuated vessels</td>
<td>Markedly ↓ rod and cone amplitudes with significant delay</td>
<td>NP</td>
<td>Central loss OU (static)</td>
<td>Yes (worsening in serial VFs following initial improvement)</td>
</tr>
<tr>
<td>2/F/61</td>
<td>HCO 20</td>
<td>1825 (2.0 mg/kg)</td>
<td>Obesity (BMI, 46.8)</td>
<td>Nil</td>
<td>20/20</td>
<td>20/20</td>
<td>Minimal macular RPE changes</td>
<td>Normal amplitudes but significantly prolonged implicit times OU (pericentral &gt; peripheral)</td>
<td>NP</td>
<td>Central loss OU (static)</td>
</tr>
<tr>
<td>3/F/54</td>
<td>HCO 15</td>
<td>2190 (6.0 mg/kg)</td>
<td>Nil</td>
<td>Reading, VF defect (1 y)</td>
<td>20/20</td>
<td>20/20</td>
<td>Mild macular RPE changes</td>
<td>↓ Amplitudes OU (pericentral)</td>
<td>Central loss OU (static)</td>
<td>No</td>
</tr>
<tr>
<td>4/F/59</td>
<td>HCO 10</td>
<td>1460 (6.2 mg/kg)</td>
<td>Nil</td>
<td>Reading, VF defect (3 y with progression)</td>
<td>20/20</td>
<td>20/20</td>
<td>Mild macular RPE changes</td>
<td>↓ Amplitudes and prolonged implicit times OU (pericentral &gt; peripheral)</td>
<td>Central loss OU (static)</td>
<td>Yes (worsening in serial VFs and mERGs)</td>
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<tr>
<td>5/F/82</td>
<td>HCO 7</td>
<td>1000 (9.5 mg/kg)</td>
<td>Nil</td>
<td>Reading (1 mo)</td>
<td>NF</td>
<td>20/30</td>
<td>NF NAD NP</td>
<td>↓ Amplitudes OU (OD central &gt; peripheral; OS central = peripheral)</td>
<td>Central loss OU (static)</td>
<td>NF</td>
</tr>
<tr>
<td>6/F/77</td>
<td>HCO 17</td>
<td>2480 NK</td>
<td>DR ARMD</td>
<td>Reading (4 mo)</td>
<td>3</td>
<td>20/30</td>
<td>20/150</td>
<td>↓ Rod and cone amplitudes with significant delay OU</td>
<td>Amplitudes and prolonged implicit times OU (central)</td>
<td>Central loss OU (static)</td>
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<tr>
<td>7/F/62</td>
<td>CQ 17</td>
<td>1940</td>
<td>Nil</td>
<td>Distance vision (2 y)</td>
<td>20/40</td>
<td>20/40</td>
<td>Mild macular RPE changes OS &gt; OD</td>
<td>↓ Amplitudes and prolonged implicit times OU (central)</td>
<td>Central loss OD &gt; OS (static)</td>
<td>Yes (worsening in serial VFs and development of BEM)</td>
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<tr>
<td>8/F/75</td>
<td>HCO 15</td>
<td>2190 (6.3 mg/kg)</td>
<td>Nil (BMI, 24.8 = normal)</td>
<td>Central and peripheral VF loss, nyctalopia (2 y with progression)</td>
<td>20/40</td>
<td>20/70</td>
<td>NF BEM OU</td>
<td>Markedly ↓ rod and cone amplitudes with significant delay OU</td>
<td>Amplitudes and prolonged implicit times OU (peripheral &gt; central)</td>
<td>Superior peripheral VF loss OU, central VF loss OU</td>
</tr>
</tbody>
</table>

(continued)

Generalized retinal dysfunction with reduced rod and cone responses. All 15 patients who underwent mERG testing had evidence of bilateral macular cone dysfunction (Table and Figure 2). Amplitude reductions without implicit time abnormalities were present in 6 patients, both amplitude and implicit time changes were observed in 8 patients, and im-

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### Table. Summary of Clinical Findings (continued)

<table>
<thead>
<tr>
<th>Patient No./Sex/ Presenting Age, y</th>
<th>Drug and Duration, y</th>
<th>Estimated Cumulative Dosage, g/ Estimated Daily HCO Dosage (Lean Weight)</th>
<th>Renal, Liver, or Retinal Disease; Obesity</th>
<th>VA, OD/OS</th>
<th>Follow-up, y</th>
<th>Most Recent Symptom</th>
<th>Symptoms (Duration)</th>
<th>Follow-up, y</th>
<th>VA, OD/OS</th>
<th>Most Recent Fundus</th>
<th>mfERG Amplitudes/Delay</th>
<th>Retinal Changes (kinetic and static)</th>
<th>Progression Following Drug Cessation</th>
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</thead>
<tbody>
<tr>
<td>9/F/85 HCO 18</td>
<td>1300</td>
<td>3.6 mg/kg (4.8 mg/kg)</td>
<td>Nil (BMI, 21.3 = normal)</td>
<td>Reading vision (8 mo)</td>
<td>0.5</td>
<td>20/40</td>
<td>20/40</td>
<td>20/40</td>
<td>NAD</td>
<td>NP</td>
<td>↓ Amplitudes OU OD &gt; OD (pericentral &gt; central)</td>
<td>Central loss OU (static)</td>
<td>No</td>
</tr>
<tr>
<td>10/F/70 CQ/HCO 20</td>
<td>1000/1200</td>
<td>4.1 mg/kg (6.3 mg/kg)</td>
<td>Nil (BMI, 26.3 = overweight)</td>
<td>Reading vision (1 y)</td>
<td>5</td>
<td>20/25</td>
<td>20/200</td>
<td>20/40</td>
<td>BEM OD</td>
<td>mfERG Amplitudes/Delay</td>
<td>↓ Rod and core amplitudes with delay OS &gt; OD</td>
<td>Central loss OU (static and kinetic)</td>
<td>Yes (worsening in serial VFs, mfERGs)</td>
</tr>
<tr>
<td>11/F/70 HCO 15</td>
<td>1640</td>
<td>4.8 mg/kg (7.5 mg/kg)</td>
<td>Nil (BMI, 29.9 = overweight)</td>
<td>Reading vision (2 y)</td>
<td>7</td>
<td>20/40</td>
<td>20/40</td>
<td>20/40</td>
<td>mfERG Amplitudes/Delay</td>
<td>↓ Rod and core amplitudes with delay OS &gt; OD</td>
<td>Central loss OD &gt; OS (pericentral &gt; central)</td>
<td>Yes (worsening in serial VFs, mfERGs)</td>
<td></td>
</tr>
<tr>
<td>12/F/59 HCO 12</td>
<td>1750</td>
<td>4.8 mg/kg (7.5 mg/kg)</td>
<td>Nil (BMI, 29.9 = overweight)</td>
<td>Reading, paracentral scotomata (3 mo)</td>
<td>Nil</td>
<td>20/30</td>
<td>20/30</td>
<td>20/40</td>
<td>mfERG Amplitudes/Delay</td>
<td>↓ Rod and core amplitudes OU</td>
<td>Peripheral and central loss OD &gt; OS (kinetic and static)</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>13/F/72 HCO 20</td>
<td>2920</td>
<td>6.9 mg/kg (9.0 mg/kg)</td>
<td>DRD, DR (BMI, 21.3 = normal)</td>
<td>Nil</td>
<td>20/20</td>
<td>20/20</td>
<td>20/20</td>
<td>20/20</td>
<td>mfERG Amplitudes/Delay</td>
<td>↓ Amplitudes OU OD &gt; OD (kinetic)</td>
<td>Peripheral and central loss OD &gt; OS (kinetic and static)</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>14/F/68 HCO 10</td>
<td>1480</td>
<td>6.8 mg/kg (9.3 mg/kg)</td>
<td>Nil (BMI, 23.0 = normal)</td>
<td>Nil</td>
<td>3</td>
<td>20/25</td>
<td>20/20</td>
<td>20/25</td>
<td>mfERG Amplitudes/Delay</td>
<td>↓ Amplitudes OD &gt; OD (central)</td>
<td>Central loss OU (static and kinetic)</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>15/F/63 HCO 7</td>
<td>1020</td>
<td>4.0 mg/kg (7.6 mg/kg)</td>
<td>Reading vision (2 y)</td>
<td>Nil</td>
<td>20/30</td>
<td>20/30</td>
<td>20/30</td>
<td>20/30</td>
<td>BEM OD</td>
<td>Normal</td>
<td>↓ Amplitudes OU OD &gt; OD</td>
<td>Central loss OU (static and kinetic)</td>
<td>Nil</td>
</tr>
<tr>
<td>16/F/64 HCO 2</td>
<td>365</td>
<td>11.7 mg/kg (14.7 mg/kg)</td>
<td>Nil (BMI, 19.0 = normal)</td>
<td>Nil</td>
<td>20/20</td>
<td>20/20</td>
<td>20/20</td>
<td>20/20</td>
<td>NAD</td>
<td>NP</td>
<td>↓ Amplitudes OD &gt; OD (pericentral &gt; central)</td>
<td>Central loss OU (static)</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Abbreviations: ARMD, age-related macular degeneration; BEM, bull’s-eye maculopathy; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CNV, choroidal neovascularization; CQ, chloroquine (given as chloroquine phosphate); DR, diabetic retinopathy; DRD, diabetic renal disease; mfERG, full-field electroretinography; HCO, hydroxychloroquine (given as hydroxychloroquine sulfate); HM, hand motion; mfERG, multifocal electroretinography; NAD, nothing abnormal detected; NF, no follow-up; NK, not known; NP, not performed; NPDR, nonproliferative DR; RPE, retinal pigment epithelium; VA, visual acuity; VF, visual field.

*Cumulative dosage was calculated using available information as to years of intake and total daily dosage. Assumptions included 100% compliance and reported/ documented length of use rounded to the nearest year. Daily HCO dose was calculated based on both actual body weight and lean body weight [lean body weight for women: (1.07 × weight) − 148 × (height/[100 × height]).

plicit time delays were the only abnormality detected in the remaining patient. The location of the greatest reduction in mfERG amplitudes observed was variable: (1) pericentral (n = 7), (2) foveal (n = 5), and (3) peripheral macula (n = 3). Ring ratios were also calculated and were in keeping with observations derived from the assessment of ring averages and trace arrays.

Four patterns of VF abnormality (Figures 1, 3, and 4) were observed in the 15 patients (15 of 16) identified with abnormal VFs: (1) isolated central loss (n = 10), (2) generalized constriction including central loss (n = 3), (3) superior peripheral VF constriction and central loss (n = 1), and (4) paracentral loss (n = 1). Static perimetry was most effective at revealing these patterns of sensitivity loss and detecting change during follow-up (Figures 3 and 4). Because follow-up data are not available for the patient with superior peripheral VF loss, it cannot be excluded that this defect is artifactual.

In 6 of! The 10 patients with follow-up data, repeat electrophysiologic (mfERG and full-field electroretinogram) and VF assessment provided evidence of disease progression despite cessation of medication (Figures 1-4). Three of these patients were using hydroxychloroquine alone, 2 were using chloroquine, and the final patient was taking both. There
was equivocal evidence of progression for a further patient who had taken hydroxychloroquine (patient 2) (Table). There was neither subjective nor objective evidence of visual improvement in the remaining 3 individuals with follow-up. In keeping with previous reports, the retinopathy associated with chloroquine in our series was more severe than that observed with hydroxychloroquine; all 3 women experienced gradual deterioration. Patient 1 had hand motion vision with no discernible field on initial testing. Three months after stopping chloroquine therapy, no recovery of central VF was present, but rims of peripheral VF were detectable on kinetic and static perimetry (Figure 1). Progressive loss of peripheral field occurred for 5 years (Figure 1).

Continued progression associated with previous hydroxychloroquine use was recorded up to 7 years after stopping the medication (Table). The age of the 3 women (patients 4, 11, and 14) with progressive retinal toxicity secondary to hydroxychloroquine ranged from 59 to 70 years, their exposure ranged from 10 to 15 years, and their cumulative dose was between 1460 and 1640 g (Table). In 1 of these 3 patients, the daily dosage based on actual exposure was 300 mg, and her dose was increased to 400 mg. A similar progression was observed in patient 14.

Figure 1. Kinetic visual field testing in patient 1 demonstrating progressive constriction of the visual fields of both eyes, from 3 months following cessation of chloroquine phosphate (A) to review 5 years later (B).
We report detailed findings of 16 patients with retinal toxicity secondary to hydroxychloroquine and chloroquine use, monitored for a relatively short period, at a single institution. Although retinal toxicity is uncommon in the large number of patients who use hydroxychloroquine worldwide and derive great benefit from the therapy, our series suggests that the prevalence of retinopathy and risk of progression despite cessation of the drug may be higher than currently thought. There are many readily apparent sources of bias that may contribute to the relative rarity of toxicity documented in the literature, including failure to report cases, inherent bias to not publish findings that are not novel, and underdetection (by either the physician or patient).

Several factors have been associated with the risk of developing hydroxychloroquine or chloroquine retinopathy. One of the most important appears to be dosage, with daily intake believed to be more significant than cumulative dosage. Indeed, the majority of cases of retinal toxicity have been associated with a daily dosage of hydroxychloroquine of 6.5 mg/kg or more (based on actual body weight). Of the 12 patients in our series who were receiving hydroxychloroquine for whom daily dosage could be calculated, we identified 8 patients who had developed retinal toxicity despite daily dosages below this recommended threshold. The guidelines produced by the American Academy of Ophthalmology and the Royal College of Ophthalmologists (written in association with the British Society for Rheumatology and the British Association of Dermatologists) have evolved throughout recent decades and currently suggest that lean body weight should be considered to determine the dosage for obese patients. Only 2 of the patients in this study were obese according to body mass index at clinical evaluation. However, if the daily dosage is estimated in all our patients on the basis of lean body weight, then 9 individuals now appear to have been taking a dosage that exceeded 6.5 mg/kg; this is in direct contrast to a calculation using actual body weight. Notwithstanding the inherent limitations of a retrospective case series, this observation suggests that it may be better to use lean body weight when calculating daily dose for all patients and that our findings may contribute to future review of hydroxychloroquine dosage recommendations.

Additional risk factors for retinal toxicity are age and length of treatment. Patients older than 60 years and with...
a duration of treatment greater than 5 years appear to be at greater risk for retinal toxicity.\textsuperscript{6,18} Four patients in our series were younger than 60 and only 1 patient had been taking medication less than 5 years (although she had been taking a very high daily dosage), suggesting that unless high-risk features are present, regular ophthalmologic assessment may not be warranted before 5 years, as per the current recommendations.\textsuperscript{5,18} These findings, when considered together, also suggest the likelihood of additional risk factors for toxicity that are as yet unknown or speculative, including ABCA4 sequence variants.\textsuperscript{20} Clearly, as with all pharmacologic agents, idiosyncratic mechanisms may play a role in the development of retinal toxicity in some individuals.

In keeping with the maxim that retinal appearance does not always correlate with function, we identified patients in our series with either a normal macular appearance or very mild retinal pigment epithelial disturbance who had profound VF and mfERG abnormalities, suggesting that significant dysfunction precedes clinically evident structural changes. The physician should remain mindful that ophthalmoscopic abnormalities are likely to represent a late stage in antimalarial drug toxicity, thereby highlighting the importance of patient education, careful assessment for visual symptoms, and detailed investigations including VF testing, mfERG, FA, and SD-OCT.

The findings from imaging studies performed in some of our patients were similar to those recently reported in cases of retinal toxicity using FA (hydroxychloroquine and chloroquine),\textsuperscript{13,14} high-speed ultra-high-resolution optical coherence tomography (hydroxychloro-

Figure 3. Static visual field testing in patient 4 demonstrating progressive central visual field loss in both eyes, from first presentation (A: 30-2 Humphrey visual field) to 3 years (B: 10-2 Humphrey visual field) after stopping hydroxychloroquine sulfate use.
roquine retinopathy), and SDOCT (chloroquine retinopathy). Using SDOCT, we also identified concentric perifoveal collapse with loss of outer retinal layers, including the junction between photoreceptor inner and outer segments and the outer nuclear layer, in both hydroxychloroquine and chloroquine toxicity. Patient 2 had significant VF changes with minimal macular disturbance on clinical examination and no discern-
reduction in the thickness of the outer nuclear layer (arrows). Interruption of the photoreceptor inner/outer segment junction and marked (hydroxychloroquine sulfate toxicity). The SDOCT shows perifoveal mfERG in all patients in whom testing was undertaken electrophysiologic testing in the assessment of potential catersing the important role of imaging, psychophysical, and appearence (1 of these patients was asymptomatic), indi-

cating the important role of imaging, psychophysical, and appearance (1 of these patients was asymptomatic), indi-

Figure 5. Fundus reflectance images and spectral domain optical coherence tomography (SDOCT) of the left (A) and right (B) eyes of patient 3 (hydroxychloroquine sulfate toxicity). The SDOCT shows perifoveal interruption of the photoreceptor inner/outer segment junction and marked reduction in the thickness of the outer nuclear layer (arrows).

Of the 10 patients with follow-up data available, repeat electrophysiologic and VF assessment provided objective evidence of disease progression despite cessation of medication in 6 of these patients. Continued progression associated with previous hydroxychloroquine use was recorded up to 7 years after stopping the drug. This serves to remind the physician that progression is not an infrequent finding, with close follow-up being required to identify the stability of retinal function and structure, and that mfERG and detailed VF testing are very helpful in monitoring change. In addition, 4 patients in our series were asymptomatic and 3 had a normal macular appearance (1 of these patients was asymptomatic), indicating the important role of imaging, psychophysical, and electrophysiologic testing in the assessment of potential toxicity.

Bilateral macular cone dysfunction was identified with mfERG in all patients in whom testing was undertaken in keeping with the increasing amount of data supporting its use in the screening and monitoring of patients using antimalarial drugs for associated retinal toxicity. \(^8\)\(^-\)\(^13\)\(^,\)\(^14\) The location of the greatest reduction in mfERG amplitudes observed was variable, although in the majority of cases it was pericentral or foveal (12 patients). In the remaining 3 patients it was peripheral, which is of interest, especially in light of the observation on SDOCT of peripheral macular abnormalities in patients with chloroquine-associated toxicity, including a reduction in the thickness of the outer nuclear layer.\(^13\) In line with the heterogeneity seen with mfERG, 4 patterns of VF abnormality were observed in our series, with isolated central loss (n = 10) being the most common. It is plausible, however, that these patterns of VF loss may be reflective of disease progression per se rather than variable characteristics of retinal toxicity. The 3 patients in our series with peripheral and central VF loss were found to have combined VF defects at presentation, making it difficult to ascertain the sequence of events. During follow-up there was progression of both central and peripheral VF defects in all 3 patients.

Patient 1 had a transient, short-term improvement in peripheral VF upon stopping chloroquine use but subsequently lost the entire recovered field within several years. We did not observe objective or subjective evidence of sustained visual improvement in any patient in this series, and our identification of 6 patients with evidence of progression, using multiple objective measures, serves to remind physicians of the potentially devastating visual consequences of antimalarial-related retinopathy.

The proposed risk factors associated with increased likelihood of hydroxychloroquine-related retinal toxicity, while highly useful, especially in determining how frequently to monitor patients and by which tests, are not absolute and cannot preclude the development of toxicity. This is illustrated by the toxicity that occurred in our patients, despite taking a lower daily dosage of hydroxychloroquine than deemed to be high risk, in 8 patients, including 4 younger than 60 years, as well as an individual with a duration of hydroxychloroquine therapy of less than 5 years. These patients were identified at a single institute during a short period, highlighting the fact that the possibility of toxicity should not be discounted due to its uncommon nature.

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