Progression of Hydroxychloroquine Toxic Effects After Drug Therapy Cessation: New Evidence From Multimodal Imaging

Mihai Mititelu, MD, MPH; Brandon J. Wong, BA; Marie Brenner, MD; Paul J. Bryar, MD; Lee M. Jampol, MD; Amani A. Fawzi, MD

IMPORTANCE Given the infrequent occurrence of hydroxychloroquine toxic effects, few data are available about the presenting features and long-term follow-up of patients with hydroxychloroquine retinopathy, making it difficult to surmise the clinical course of patients after cessation of drug treatment.

OBJECTIVE To report functional and structural findings of hydroxychloroquine retinal toxic effects after drug therapy discontinuation.

DESIGN A retrospective medical record review was performed to identify patients taking hydroxychloroquine who were screened for toxic effects from January 1, 2009, through August 31, 2012, in the eye centers of Northwestern University and the University of Southern California.

SETTING Northwestern University Sorrel Rosin Eye Center, Chicago, Illinois, and the Doheny Eye Institute at the University of Southern California, Los Angeles.

PARTICIPANTS Seven consecutive patients diagnosed as having hydroxychloroquine retinal toxic effects.

MAIN OUTCOME AND MEASURE Retinal toxic effects.

RESULTS Seven patients (1 man and 6 women) with a mean age of 55.9 years (age range, 25-74 years) developed retinal toxic effects after using hydroxychloroquine for a mean of 10.4 years (range, 3-19 years). Fundus examination revealed macular pigmentary changes in all 7 patients, corresponding to abnormal fundus autofluorescence (FAF). On spectral domain optical coherence tomography, there was outer retinal foveal resistance (preservation of the external limiting membrane and the photoreceptor layer) in 6 patients. After drug therapy discontinuation, 5 patients experienced outer retinal regeneration (3 subfoveally and 2 parafoveally), with associated functional visual improvement on static perimetry in 2 patients. Over time, FAF remained stable in 3 patients, whereas the remaining patients had a pattern of hypoautofluorescence that replaced areas of initial hyperautofluorescence (2 patients) and enlargement of the total area of abnormal FAF (2 patients).

CONCLUSIONS AND RELEVANCE Preservation of the external limiting membrane carries a positive prognostic value in hydroxychloroquine toxic effects because it may be associated with regeneration of the photoreceptor layer and with potential functional visual improvement on static perimetry. The patterns of abnormal FAF persist despite cessation of the medication, with enlargement of the total area of abnormal FAF being the hallmark of severe toxic effects. Relative foveal resistance in hydroxychloroquine toxic effects was supported by this case series. These findings emphasize the importance of early detection and the need for correlating clinical observations with multimodal imaging, particularly FAF and spectral domain optical coherence tomography.

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First described in 1963, hydroxychloroquine retinopathy has been estimated at an incidence of 0.5% to 1%. On the basis of today’s improved tools for detection, this number may be an underestimate secondary to underreporting, underdetection, or both. Although hydroxychloroquine toxic effects can be asymptomatic in early stages, patients most commonly report difficulty with night vision, glare, or a paracentral scotoma as the condition progresses.  

In animal models, hydroxychloroquine blocks the attachment of autophagosome to lysosome at the retinal pigment epithelium (RPE) level, leading to marked intracellular accumulation of indigestible material, particularly lipofuscin, and entrapment of the drug in the RPE, a process that is accelerated by the presence of light (photoactivation). Because of the slow clearance of the drug and its persistence in the RPE, hydroxychloroquine-associated toxic effects have been thought to be chronic, with little if any visual recovery and, in some cases, progression of visual loss. 

In 2011, the American Academy of Ophthalmology revised the screening recommendations for patients taking hydroxychloroquine; in addition to an ophthalmologic examination and automated threshold visual field testing with a white 10-2 pattern, an objective imaging modality is recommended, such as spectral domain optical coherence tomography (SD-OCT), multifocal electroretinography, or fundus autofluorescence (FAF), at baseline and annually at each visit after 5 years of using hydroxychloroquine. 

Given the infrequent occurrence of toxic effects, few data are available on the presenting features and long-term follow-up of patients with hydroxychloroquine retinopathy, making it difficult to surmise the clinical course of patients after cessation of drug treatment. Speculated that toxic effects could be separated into premaculopathy and true retinopathy, with the opportunity for reversibility if changes are detected in the former stage. The most characteristic imaging features of hydroxychloroquine toxic effects include disruption of normal FAF, whereas on SD-OCT there is RPE atrophy and loss of the photoreceptor layer. Other reproducible findings of progression include changes on multifocal electroretinograms (amplitude reductions with or without delay in implicit times) and visual field testing (central or paracentral scotomata), but much remains unclear about long-term evolution on SD-OCT and FAF associated with clinical progression. Similarly, controversy exists regarding whether there is stabilization, regression, or progression of toxic effects after termination of treatment, as evidenced by structural improvement on multimodal imaging and/or functional visual improvement. 

By using multimodal imaging, particularly SD-OCT and FAF, we investigated long-term outcomes in this series of 7 consecutive patients diagnosed as having hydroxychloroquine retinal toxic effects at the Northwestern University Sorrel Rosin Eye Center, Chicago, Illinois, and the Doheny Eye Institute at the University of Southern California, Los Angeles.

Methods

A retrospective medical record review was performed to identify patients taking hydroxychloroquine who were screened for toxic effects from January 1, 2009, through August 31, 2012, in the eye centers of Northwestern University and the University of Southern California. More than 2000 patients were screened, and of those, 7 were identified as having hydroxychloroquine toxic effects based on clinical, imaging, and functional studies. The institutional review board member committees at Northwestern University and the University of Southern California issued a statement of approval for this research protocol. The current study followed the tenets of the Declaration of Helsinki.

Each patient’s medical record was analyzed for basic demographic data, presenting symptoms, initial date of ophthalmic examination and diagnosis of toxic effects, follow-up interval, visual acuity at every visit, any concurrent medical or ophthalmic conditions, duration of treatment, daily dose (total in milligrams and milligrams per kilogram), cumulative dose, body weight, and ideal body weight. Our study assumed full adherence to treatment and rounded the length of use to the nearest year. Lean body weight for women was calculated using the following formula: (1.07 × weight) - 148 × (weight³/[100 × height (in meters squared)]).

Clinical diagnosis was made based on identification of macular RPE changes, typically in a concentric fashion around the fovea (bull’s eye maculopathy) in conjunction with patient symptoms of photopsias, nyctalopia, and decreased vision. 

Imaging and functional studies were used to aid in the diagnosis of hydroxychloroquine toxic effects. The following modalities were used: fundus photography, FAF (Heidelberg retina angiograph; Heidelberg Engineering), SD-OCT (Spectralis; Heidelberg Engineering), and Humphrey visual fields (Zeiss). Diagnosis of toxic effects was made based on specific findings, namely, perifoveal areas of abnormal FAF on autofluorescence testing; loss of outer retinal layers, particularly the inner segment/outer segment (IS/OS) junction and the outer nuclear layer (ONL) on SD-OCT; and central or paracentral scotoma and/or generalized constriction on static perimetry testing. 

For FAF, using the Heidelberg SD-OCT software analysis tools, 2 observers (M.M. and A.A.F.) analyzed the areas of hyperautofluorescence and hypoautofluorescence at baseline and most recent follow-up. With the use of Microsoft Office graphic tools, the total area of anomalous autofluorescence was outlined with a white line on initial FAF imaging and a red line at final follow-up. The 2 images were then superimposed for visual comparison of change in the size of the autofluorescence over time. On SD-OCT, macular volumetric thickness was measured at each study, and change in thickness was calculated if more than one study was obtained. Moreover, images were registered so that same SD-OCT raster sections were reviewed, ensuring consistent lesion and location comparison over time.
Results

Demographics
Seven patients (treated for systemic lupus erythematosus or rheumatoid disease) were identified as having hydroxychloroquine toxic effects and were included in this study. The mean age of the patients was 55.9 years (age range, 25-74 years), and the mean treatment duration was 10.4 years (range, 3-19 years). The mean cumulative dose was 1522.58 g (range, 438-2774 g). Table 1 details the main demographic data of the patients in this study.

Vision
Of these 7 patients, 5 were symptomatic with trouble with night vision, blind spots in vision, and gradual decrease in visual acuity. Two patients were asymptomatic. At diagnosis, 6 of the 7 patients had vision measuring 20/30 or better. Follow-up visual acuities improved in 4 patients (patients 2, 4, 5, and 7), remained stable in 2 patients (patients 1 and 6), and worsened in 1 patient (patient 3) (Table 2). The visual acuity status in patient 3 at the time of diagnosis was complicated by history of perioperative ischemic optic neuropathy.

Clinical Examination
Toxic effects were suspected based on findings from clinical examinations, which revealed suspicious features, including RPE mottling around the fovea to a small arc of pigmentation or a complete ring around the fovea (bull’s eye maculopathy). These clinical examination findings were confirmed with other screening modalities mentioned below.

Spectral Domain Optical Coherence Tomography
All patients underwent SD-OCT at baseline and subsequent visits. Total macular volumetric thickness decreased between baseline and most recent follow-up in 5 patients and increased in 2 patients. Total macular volumetric thickness data are listed in Table 3.

At diagnosis, all 7 patients had evidence of outer retinal disruption on SD-OCT occurring primarily in the parafovea and peripheral macula. There was evidence of foveal photoreceptor resistance to toxic effects in 6 of the 7 patients, as demonstrated by the distinct preservation of the outer retinal layers at baseline and on follow-up scans (Figure 1). Moreover, in 3 of these patients (patients 1, 2, and 4), the SD-OCT revealed a local, foveal regeneration or thickening of the IS/OS junction.
after discontinuation of the drug therapy in regions where the IS/OS junction had been previously absent or thin in the face of an intact external limiting membrane (ELM). In the remaining 3 patients with an intact ELM (patients 5, 6, and 7), the subfoveal outer retina remained preserved and stable, and 2 of the patients (patients 5 and 6) experienced regeneration parafoveally as described below.

In the area outside the foveal depression (parafovea), 4 patients (patients 1, 2, 4, and 7) had irregular RPE thickening and extension of hyporeflective material into the ONL and outer plexiform layer (OPL) with no obvious evidence of outer retinal regeneration (Figure 2). In the same area, 2 patients with intact ELM at baseline (patients 5 and 6) had regeneration of the IS/OS junction underlying an intact ELM (Figure 3).

Patient 3 had the most advanced toxic effects at the time of detection and experienced persistent, severe atrophy of the ELM, IS/OS junction, and RPE on all scans in the foveal and parafoveal areas, which progressed to exuberant RPE migration into the middle and outer retinal layers and further extension of ELM loss peripherally (Figure 4). No outer retinal regeneration was seen in this case.

The extreme periphery imaged by SD-OCT underwent the least change on follow-up. In 4 of the 7 patients (patients 1, 2, 5, and 6), this area remained stable over time. In patients 3 and 7, there was lateral expansion of outer retinal changes over time. Patient 4 had equivocal outer retinal changes in this region.

### Static Perimetry Testing

All patients underwent static perimetry testing in the form of Humphrey visual fields (Table 4). They all had perifoveal changes, ranging from scattered defects to ring scotomas, all consistent with hydroxychloroquine toxic effects. One patient had an enlarged blind spot, which we attributed to the patient's preexisting optic neuropathy.

Six of the 7 patients had follow-up visual field tests, of whom 2 patients (patients 1 and 2) experienced functional visual improvement in the reduction of depth defect or pattern standard deviation and/or reduction of the extent of scotomas on
static perimetry over time. Patient 3 had severe baseline damage, and although there was a suggestion of visual field progression on subsequent testing, this progression could not be objectively assessed because of a high amount of fixation losses. Testing in patient 4 revealed baseline functional deficits that improved significantly at follow-up; however, the follow-up testing was limited by the high number of fixation losses. Testing in patient 5 revealed mild baseline deficits; however, it had low reliability secondary to fixation losses and false-positive results; there was no follow-up visual field testing secondary to this patient being hospitalized. The field testing in patients 6 and 7 was reliable and revealed stable defects at follow-up.

Figure 2. External Limiting Membrane (ELM) Loss With Pigment Migration

Compared with the initial study (A), near-infrared reflectance on follow-up at 9 months (C) shows increased stippled hyperreflectance in a circular pattern around the fovea. Loss of ELM parafoveally is seen at the initial (B) and follow-up (D) scans, with extension of hyperreflective material into the outer nuclear layer and outer plexiform layer (arrow). There is no regeneration of the ELM or the photoreceptor layers. Same changes are identified nasally.

Figure 3. Intact External Limiting Membrane (ELM) and Photoreceptor Regeneration

Preservation of the ELM parafoveally is seen on both the initial (A and B) and follow-up (C and D) scans, associated with regeneration of the photoreceptor layer (arrow, D) at follow-up 2 months later.
All 7 patients were followed up with FAF. The prevailing pattern of FAF was that of central, ring-shaped hypoautofluorescence surrounded by hyperautofluorescence either as a sharply demarcated ring or in a diffusely circular pattern around the fovea.

The most marked change occurred in patient 1, in whom areas of hyperautofluorescence were replaced by a band of hypoautofluorescence during 9 months (Figure 5). In patient 2, regions of hyperautofluorescence at baseline were mottled with hypoautofluorescence. At follow-up at 20 months, the round areas of hypoautofluorescence expanded in size in the areas formerly hyperautofluorescent. In patient 3, the follow-up FAF (Figure 6) revealed an increase in the diameters of each of the areas of hyperautofluorescence and hypoautofluorescence, which corresponded to an increase in the total area of abnormal autofluorescence during 37 months. In patient 7, the parafoveal areas of stippled hypoautofluorescence and hyperautofluorescence noted at baseline expanded during the 6-month follow-up interval. In patients 4, 5, and 6 there were progressive changes in the diameters of each of the areas of hyperautofluorescence and hypoautofluorescence, which corresponded to an increase in the total area of abnormal autofluorescence during their respective follow-up intervals.

### Table 4. Humphrey Visual Field Findings

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Overall Pattern</th>
<th>MD at Baseline</th>
<th>PSD at Baseline</th>
<th>Follow-up Interval, mo</th>
<th>MD at Follow-up</th>
<th>PSD at Follow-up</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Ring scotoma</td>
<td>OD: 167</td>
<td>OS: 135</td>
<td>19</td>
<td>OD: 125</td>
<td>OS: 178</td>
</tr>
<tr>
<td>2</td>
<td>Ring scotoma</td>
<td>OD: −7.81</td>
<td>OS: −5.84</td>
<td>12</td>
<td>OD: −5.67</td>
<td>OS: −4.46</td>
</tr>
<tr>
<td>3</td>
<td>Central scotoma; enlarged blind spot</td>
<td>OD: −4.63</td>
<td>OS: −6.71</td>
<td>45</td>
<td>OD: −6.20</td>
<td>OS: −8.20</td>
</tr>
<tr>
<td>4</td>
<td>OD: Paracentral scotoma; OS: Ring-shaped paracentral scotomas</td>
<td>OD: −9.81</td>
<td>OS: −13.12</td>
<td>6</td>
<td>OD: −1.85</td>
<td>OS: −3.71</td>
</tr>
<tr>
<td>5</td>
<td>Central scotomas</td>
<td>OD: −7.14</td>
<td>OS: −6.22</td>
<td>2</td>
<td>OD: −2.94</td>
<td>OS: −3.38</td>
</tr>
<tr>
<td>6</td>
<td>OD: Central scotomas; OS: central scotoma; enlarged blind spot</td>
<td>OD: −1.72</td>
<td>OS: −1.70</td>
<td>2</td>
<td>OD: −1.42</td>
<td>OS: −2.64</td>
</tr>
<tr>
<td>7</td>
<td>Central scotomas</td>
<td>OD: −13.81</td>
<td>OS: −14.56</td>
<td>6</td>
<td>OD: −13.49</td>
<td>OS: −13.64</td>
</tr>
</tbody>
</table>

Abbreviations: MD, mean deviation; PSD, pattern standard deviation.

- Patient had high fixation losses for MD baseline and follow-up results.
- Patient had high fixation losses for overall pattern, MD baseline, and PSD baseline results; no follow-up because of patient hospitalization.

**Fundus Autofluorescence**

All 7 patients were followed up with FAF. The prevailing pattern of FAF was that of central, ring-shaped hypoautofluorescence surrounded by hyperautofluorescence either as a sharply demarcated ring or in a diffusely circular pattern around the fovea.

The most marked change occurred in patient 1, in whom areas of hyperautofluorescence were replaced by a band of hypoautofluorescence during 9 months (Figure 5). In patient 2, regions of hyperautofluorescence at baseline were mottled with hypoautofluorescence. At follow-up at 20 months, the round areas of hypoautofluorescence expanded in size in the areas formerly hyperautofluorescent. In patient 3, the follow-up FAF (Figure 6) revealed an increase in the diameters of each of the areas of hyperautofluorescence and hypoautofluorescence, which corresponded to an increase in the total area of abnormal autofluorescence during 37 months. In patient 7, the parafoveal areas of stippled hypoautofluorescence and hyperautofluorescence noted at baseline expanded during the 6-month follow-up interval. In patients 4, 5, and 6 there were progressive changes in the diameters of each of the areas of hyperautofluorescence and hypoautofluorescence, which corresponded to an increase in the total area of abnormal autofluorescence during their respective follow-up intervals.

**Research Original Investigation**

Hydroxychloroquine Toxic Effects

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**Figure 4. Progressive Toxic Effects Associated With Outer Retinal Atrophy and Pigment Migration Into the Retina**

[Image of fundus autofluorescence scans showing progressive changes in retinal structures]

**Figure 5. Progressive Toxic Effects Associated With Outer Retinal Atrophy and Pigment Migration Into the Retina**

[Image of fundus autofluorescence scans showing progressive changes in retinal structures]

**Figure 6. Progressive Toxic Effects Associated With Outer Retinal Atrophy and Pigment Migration Into the Retina**

[Image of fundus autofluorescence scans showing progressive changes in retinal structures]
Figure 5. Progression of Hyperautofluorescence to Hypoautofluorescence

Within the area that was originally hyperautofluorescent at baseline (A), there is an expansion of the ring of hypoautofluorescence at 9 months of follow-up (B). Overlay of the white (baseline) and red (follow-up) total abnormal autofluorescence area shows essentially stable size of this area over time (C).

Figure 6. Progression of Anomalous Autofluorescence in a Patient With Advanced Hydroxychloroquine Toxic Effects

An increase in each of the areas of hyperautofluorescence and hypoautofluorescence is seen between the initial scan (A) and the final follow-up scan at 37 months (B), with a corresponding increase in the total area of abnormal autofluorescence (C) in this patient with advanced toxic effects.
was no significant change in the area of abnormal autofluorescence between initial and follow-up scans at 6, 4, and 2 months, respectively.

Discussion

Antimalarial drugs bind to melanin in the RPE and cause cellular damage, atrophy, and ultimately photoreceptor loss.5,14 We report detailed, novel findings from multimodal imaging from 7 patients with retinal toxic effects secondary to long-term hydroxychloroquine use. In keeping with previous studies, we note that relative foveal resistance (Figure 1) is an important finding in hydroxychloroquine toxic effects. Preservation of the ELM carries a positive prognostic value because it seems to be associated with regeneration of the photoreceptor layers on cessation of the drug therapy (Figure 3) and with potential functional visual improvement on static perimetry and visual acuity testing. The patterns of abnormal FAF persist despite treatment cessation; in select cases, areas of hyperautofluorescence become hypoautofluorescent over time (Figure 5), whereas in severe toxic effects there is enlargement of the total area of abnormal FAF (Figure 4). Our study found that patients diagnosed as having toxic effects who received high total doses of hydroxychloroquine, as a result of long-term treatment, experience volumetric thinning of their macula after discontinuing the medication. These findings emphasize the importance of early detection and the need for correlating clinical observations with multimodal imaging, particularly FAF and SD-OCT.

Fundus autofluorescence provides important clues to the pathogenesis and progression of hydroxychloroquine toxic effects, particularly in advanced stages of retinopathy.15 It has been hypothesized that an increase in autofluorescence corresponds to RPE regions with anomalous metabolism and deposition of lipofuscin.16 These areas gradually experience RPE atrophy, leading to a decrease in the autofluorescence.17 In our series, areas of anomalous FAF remained stable in 3 patients (patients 4, 5, and 6), enlarged in 2 patients (patients 3 and 7), and changed from hyperautofluorescent to hypoautofluorescent in 2 patients (patients 1 and 2). These findings suggest that in the setting of hydroxychloroquine toxic effects, once alterations in FAF occur, they tend to persist over time. Future studies should focus on understanding the long-term visual and clinical implications of persistent FAF patterns. We note that severe toxic effects are associated with the expansion of the area of anomalous FAF (Figure 4). However, not all cases associated with advanced retinal atrophy on SD-OCT have a marked appearance on FAF (Figure 7). This finding suggests the importance of using more than one imaging modality when identifying hydroxychloroquine toxic effects, especially in the early stages when the FAF can appear unimpressive.

Previously described OCT signs of hydroxychloroquine toxic effects include loss of IS/OS junction line, parafoveal thinning of the ONL on SD-OCT, and damage to the RPE.15,17,18 Pasadhika et al19,20 have also noted selective thinning of the perifoveal ganglion cell and inner plexiform layers on SD-OCT in the absence of functional or structural clinical changes in the photoreceptor and RPE layers, as well as peripapillary retinal nerve fiber layer thinning in clinically evident retinopathy. In our study, hydroxychloroquine toxic effects were associated with outer retinal changes on SD-OCT, ranging from loss of the ELM to loss of the IS/OS junction and thinning of the RPE with secondary exuberant hyperplastic pigmented reaction. Our study supports the observation that relative foveal resistance is common in hydroxychloroquine toxic effects (Figure 1), as demonstrated...
by 6 patients in this study experiencing preservation of the subfoveal outer retinal layers despite damage to areas outside the fovea. Although it is difficult to pinpoint factors that promote or predict foveal resistance from this cross-sectional study, it is clear that this resistance persists despite progression of toxic effects outside the fovea, which explains preservation of central visual acuity. We note that ELM integrity in or around the fovea on SD-OCT is associated with the preservation and possibility of IS/OS junction regeneration. The ELM was long believed to have the primary role of providing structural integrity to the retina through mechanical strength. Recent evidence has additionally indicated that the ELM contains occludin, a junction protein that has a role in the outer blood retinal barrier by participating in tight junctions. In our study, patients with clinically visible disruption of the ELM at the time of initial examination had evidence of progressive outer retinal remodeling on SD-OCT after discontinuing hydroxychloroquine therapy. Specifically, the improvement in appearance of the outer retina and the partial regeneration of photoreceptors were limited to areas with ELM preservation at the time of diagnosis (Figure 3). Our study suggests that ELM preservation may carry a positive prognostic value for the restoration of the outer retinal layers in the setting of toxic effects.

Changes in the RPE are an important feature of hydroxychloroquine toxic effects because the drug binds to the melanin in this layer. There were 5 patients, 4 with changes outside the fovea (patients 1, 2, 4, and 7) and 1 with changes that involved most of the macula (patient 3), who experienced an exuberant reaction with formation of clumps of hypereflective material originating in the RPE layer, which extended both horizontally into adjacent areas of ELM loss and vertically into the inner retinal layers, including the OPL and ONL. Although the lipofuscinogenic nature of hydroxychloroquine is well documented, the histopathologic nature of the hyperreflective material invading the outer retina remains poorly understood. A histopathologic study by Wetterholm and Winter described an accumulation of pigment-laden cells in the ONL and OPL of a patient with chloroquine toxic effects, whereas Bernstein and Ginsberg found pigment migration from the RPE into the retina but not beyond the inner nuclear layer in patients treated with the same antimalarial agent. More specifically, Ramsey and Fine demonstrated the presence of curvilinear tubules (C-tubes) derived from the smooth endoplasmic reticulum, which aggregate in the RPE and inner segments of the photoreceptor cells in response to chronic insult in patients treated with chloroquine. We suspects that the dynamic nature of the retinopathy could be secondary to activated inflammatory cells (macrophages) being recruited by the damaged RPE to remove residual outer retinal debris.

Total volumetric thickness measured by SD-OCT was available for all 7 patients (Table 3). A consistent pattern of decreased macular thickness over time was noted in 5 of the 7 patients in whom the mean duration of treatment was relatively long (13.4 years). The mean cumulative dose in this group was 1956 g. Despite local RPE hypertrophy and clumping that led to an initial, transient increase in macular thickness, a long-term decrease in thickness occurred, highlighting that overall macular thinning may be a hallmark of long-term hydroxychloroquine toxic effects. We believe that this progressive thinning is largely due to remodeling that occurs at the level of the outer retina and the RPE, which become atrophic with time. By contrast, the mean duration of treatment of the 2 patients who experienced an increase in the volumetric thickness of the macula was 3.0 years, with a mean cumulative dose of 438 g. We hypothesize that this occurred as a result of shorter-term treatment with hydroxychloroquine, and we predict that the retina would continue to thin if the hydroxychloroquine treatment had been continued for additional years. We suggest that early detection and discontinuation of the drug therapy may be associated with relative sparing of the retina. Consequently, we recommend following up patients with serial examinations of retinal thickness on SD-OCT and stress the importance of clinically correlating these findings with early signs of toxic effects seen on examination (eg, pigment mottling and blunted fovea reflex). Our volumetric analysis only included total macular volume and did not include any subfield thickness analysis, which may be of future research interest.

All 7 patients had signs of visual loss on static perimetry testing at baseline, prompting discontinuation of the drug therapy. In keeping with the literature, the earliest signs consisted of isolated parafoveal changes, progressing to complete ring scotomas in cases of advanced toxic effects. Six patients underwent follow-up perimetry testing after cessation of the drug therapy, at least 2 of whom (patients 1 and 2) had functional visual improvement. On follow-up, these 2 patients not only demonstrated improvement of their visual field defects (reduction in the size of scotoma and/or improvement in the depth defect or pattern standard deviation) but also demonstrated either preserved (patient 1) or improved (patient 2) visual acuities. Although follow-up static perimetry was less reliable, patient 4 experienced significant functional improvement on perimetry, associated with improving visual acuity. In all these patients there was either foveal or parafoveal regeneration of the photoreceptor layer on SD-OCT, as mentioned previously (Figure 3). This finding highlights an important positive correlation between regeneration of the IS/OS junction and functional visual improvement on visual field testing. Given the limited follow-up in our study, we recommend that future research efforts evaluate whether any initial functional visual improvement on static perimetry is sustained long term. In contrast, progression of hydroxychloroquine toxic effects and atrophy of the ELM and IS/OS junction were associated with poor functional visual outcomes, as demonstrated by worsening of visual acuity and visual field defects in the presence of worsening test-taking parameters (fixation losses and false-positive results) in patient 3.

The association between the development of toxic effects and dosage has been under review, with the recent publication of revised screening recommendations for hydroxychloroquine toxic effects. Daily dose calculated using ideal body weight has been advocated to be a better predictor of the development of toxic effects than total dose. Only 57% of the patients in this study were overdosed when using their total
body weight, whereas 86% of the patients were taking doses that put them at risk for developing hydroxychloroquine toxic effects when calculations were made using ideal body weight calculated as lean body mass. Five patients in this study had taken doses well in excess of the 1000-g threshold dose by the time their conditions were diagnosed. The worst damage was encountered in patient 3, who had ingested the largest cumulative dose (2774 g) of all 7 patients. Only 1 patient (patient 1) developed toxic effects despite a daily dose of less than 6.5 mg/kg. We speculate that this could be due to the presence of advanced renal disease, an idiosyncratic reaction, or a potential genetic predisposition.27 Our study stresses the importance of considering lean body weight, total cumulative dose, and other risk factors, such as impaired renal function, when assessing the likelihood of developing hydroxychloroquine retinopathy. Careful thought should be given to diagnosing hydroxychloroquine retinal toxic effects because the recommendation for discontinuation of this drug poses a treatment dilemma for clinicians, who rely on hydroxychloroquine for its excellent control of rheumatologic disease.

The small number of patients enrolled in our study, despite a large screening population, limits the generalization of the findings. In addition, the measurements of areas of abnormal FAF were less quantitative than the SD-OCT findings, in part because of a lack of calibration and standardization of measuring FAF intensity. This limitation was overcome by comparing only areas with obvious intensity change on follow-up examinations, confirmed by 2 independent observers (M.M. and A.A.F.). Although not required for diagnosis, given the availability of other excellent screening modalities, the use of multifocal electroretinography in this study might have provided additional insights on correlations between structural outer retinal changes and functional outcome after cessation of treatment.

In conclusion, hydroxychloroquine toxic effects, although infrequent, may be associated with significant ocular morbidity secondary to the drug’s profound effects on outer retinal structure and visual function. Early detection of toxic effects and discontinuation of the drug before advanced toxic effects develop can be associated with potential functional visual improvement, whereas late detection may be associated with progression of structural and functional visual deterioration. Subtle findings seen on one imaging modality should lower the clinician’s threshold for suspecting toxic effects and warrant the use of additional testing, with the goal of early diagnosis before irreversible visual loss.

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Study concept and design: Mittelulu, Brenner.
Acquisition of data: Wong, Brenner, Jampol, Fawzi.
Analysis and interpretation of data: Mittelulu, Brenner, Bryar, Jampol, Fawzi.
Drafting of the manuscript: Mittelulu, Brenner, Jampol, Fawzi.
Critical revision of the manuscript for important intellectual content: Mittelulu, Brenner, Jampol, Fawzi.
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Administrative, technical, and material support: Mittelulu, Brenner, Bryar, Fawzi.
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REFERENCES

Images of a patient’s eye after accidental mitomycin C intraocular injection, with no preinjection eye pathology. Note the iris atrophy and pigmentations and temporal corneal edema (A), the prominent cystoid macular edema (B), and the low endothelial count after exposure (C). A Goldmann visual field reveals central scotoma (D), and images taken 6 months after a vitrectomy reveal that the temporal corneal edema has been reduced but that the iris atrophy and cystoid macular edema remain (E and F).