Effect of Disease Stage on Progression of Hydroxychloroquine Retinopathy

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IMPORTANCE Hydroxychloroquine sulfate retinopathy can progress after the drug is stopped. It is not clear how this relates to the stage of retinopathy or whether early screening with modern imaging technology can prevent progression and visual loss.

OBJECTIVE To determine the relationship between progression of retinopathy and the severity of disease using objective data from optical coherence tomography and assess the value of early screening for the toxic effects of hydroxychloroquine.

DESIGN, SETTING, AND PARTICIPANTS Clinical findings in patients with hydroxychloroquine retinopathy were monitored with repeated anatomical and functional examinations for 13 to 40 months after the drug was stopped in a referral practice in a university medical center. Eleven patients participated, with the severity of toxic effects categorized as early (patchy parafoveal damage shown on field or objective testing), moderate (a 50%-100% parafoveal ring of optical coherence tomography thinning but intact retinal pigment epithelium), and severe (visible bull’s-eye damage).

MAIN OUTCOMES AND MEASURES Visual acuity, white 10-2 visual field pattern density plots, fundus autofluorescence, spectral-density optical coherence tomography cross sections, thickness (from cube diagrams), and ellipsoid zone length.

RESULTS Visual acuity and visual fields showed no consistent change. Fundus autofluorescence showed little or no change except in severe cases in which the bull’s-eye damage expanded progressively. Optical coherence tomography cross sections showed little visible change in early and moderate cases but progressive foveal thinning (approximately 7 μm/y) and loss of ellipsoid zone (in the range of 100 μm/y) in severe cases, which was confirmed by quantitative measurements. The measurements also showed some foveal thinning (approximately 4 μm/y) and deepening of parafoveal loss in moderate cases, but the breadth of the ellipsoid zone remained constant in both early and moderate cases. A few cases showed a suggestion of ellipsoid zone improvement.

CONCLUSIONS AND RELEVANCE Patients with hydroxychloroquine retinopathy involving the retinal pigment epithelium demonstrated progressive damage on optical coherence tomography for at least 3 years after the drug was discontinued, including loss of foveal thickness and cone structure. Cases recognized before retinal pigment epithelium damage retained foveal architecture with little retinal thinning. Early recognition of hydroxychloroquine toxic effects before any fundus changes are visible, using visual fields and optical coherence tomography (along with fundus autofluorescence and multifocal electroretinography as indicated), will greatly minimize late progression and the risk of visual loss.
he potential for chloroquine phosphate and hydroxychloroquine sulfate retinopathy to progress after cessation of the drug has long been recognized, primarily in patients with severe ring scotoma or a visible bull’s-eye lesion in the fundus. Such progression could continue for many years after the drug was stopped. Some of the early studies also suggested that early or mild disease does not advance after years after the drug was stopped. Kellner et al reported a small series of retinopathy cases in which all those with severe damage progressed over a period of years in contrast to one with minimal fundus autofluorescence (FAF) changes. The progression of retinopathy had been measured traditionally by subjective field testing and relatively insensitive fundus examination. The development of multifocal electroretinography more than 15 years ago introduced an objective test for field measurement. However, multifocal electroretinography has considerable variability and technical challenges that have limited its use and made it poorly suited for monitoring subtle changes over time. Modern spectral density–optical coherence tomography (SD-OCT) provides a critical objective tool for grading severity and judging progression in early cases of retinopathy.

The relevance of understanding late progression is that modern guidelines for screening, which include technology such as SD-OCT, FAF, and multifocal electroretinography, allow recognition of toxic effects well before the development of visible bull’s-eye retinopathy. Bull’s-eye retinopathy is now considered to represent late and severe damage that may be preventable with proper screening. Thus, important clinical issues are whether early screening limits progressive loss and whether it reduces or eliminates the risk of losing visual acuity.

We monitored 11 patients receiving hydroxychloroquine categorized as having early, moderate, or severe toxic effects for 13 to 40 months after cessation of the drug. These examinations, using quantitative SD-OCT measurements as well as functional tests, allow accurate and sequential evaluation of progression relative to the initial degree of damage.

Methods

The present study, approved with waiver of informed consent by the institutional review board of the Stanford University School of Medicine, derived information from a review of clinical records. We report data on 11 cases of hydroxychloroquine toxic effects that were monitored for 13 to 40 months after the drug was stopped. Some of these cases have been described in an earlier review that compared diagnostic techniques in screening for hydroxychloroquine toxic effects, and these are labeled the same way in the present study to assist readers who may wish to correlate information. Cases are designated as early (E), moderate (M), or severe (S) according to the prior criteria, which in brief define early as patchy damage within the parafoveal zone shown by field or objective testing; moderate as a 50% to 100% parafoveal ring of damage and marked thinning of the parafoveal retina on SD-OCT without retinal pigment epithelium (RPE) damage; and severe as bull’s-eye damage with RPE involvement on SD-OCT (visible retinopathy).

Diagnostic techniques used were automated Swedish Interactive Threshold Algorithms (SITA) 10/2 white visual fields (Humphrey Field Analyzer; Carl Zeiss Meditec); SD-OCT, including Early Treatment Diabetic Retinopathy Study cube thickness diagrams (Zeiss Cirrus 4000 model; Zeiss Meditec); and FAF (Heidelberg Engineering).

For all quantitative studies, we determined mean values by combining data from both eyes. Visual acuities were the best Snellen-refracted notations near each visit and were converted to logMAR values for graphing. Fields were evaluated primarily as pattern deviation plots and pattern SD values.

The SD-OCT measurements were made in 2 ways. The Cirrus cube diagram provided thickness values for 9 Early Treatment Diabetic Retinopathy Study zones in the fovea, parafovea, and peripheral macula. Using cursors, we also measured the length of the ellipsoid zone (EZ, sometimes called inner/outer segment line) up to regions of parafoveal damage (Supplement [eFigure 1]). For early and moderate cases, we measured the EZ between the foveal center and the point of EZ disappearance (on whichever side showed EZ loss most distinctly; some cases were affected on only 1 side). The EZ line was not measured in cases E1 and E4 because it was not clearly disrupted. For severe cases, the EZ was always interrupted on both sides of the fovea, and we measured the full width of the EZ (on both sides of center). Because our primary interest involved the degree of progression, the data were graphed as change relative to the initial recording after toxic effects were diagnosed and hydroxychloroquine was stopped.

Results

The demographics of our patients, history of drug exposure, and follow-up period are reported in the Supplement (eTable). All patients had significant hydroxychloroquine exposure in dose and time, and there was clear evidence from functional tests and/or objective tests to diagnose toxic effects. Most patients were monitored for more than 2 years and some for more than 3 years.

Visual acuity, as shown in the Supplement (eFigure 2), was initially better than 20/40 (logMAR 0.3) in all patients except S2. Cases S1, S2, and S7 had very poor foveal structure (minimal EZ line, as described below). Cases S2 and S4 showed a suggestion of mild visual loss toward the end of the follow-up period.

Visual field pattern deviation plots demonstrated moderate variability on repeat testing, but no consistent change (given test variation) for any of the patients or patient groups (Figure 1). The pattern SD values (shown for each plot) were also relatively constant. The 5 cases had at best a small foveal island of sensitivity that became threatened as foveal cone structures were compromised.

The progression of damage in autofluorescence (FAF) images depended on the severity of retinopathy (Figure 2). None of the early cases showed any change in autofluorescence during the period of observation. Cases E1 and E4 did not show FAF abnormality, and cases E2 and E3 showed parafoveal hyperfluorescence that was constant. The moderate cases were...
at the cusp between minimal and severe damage and showed variable degrees of progression. The M2 case showed a trace of parafoveal hyperfluorescence at diagnosis that expanded to a distinct hyperfluorescent ring (although without visible RPE loss). The M3 case showed some subtle and stable RPE abnormalities in the left eye, but the right eye began with a small region of RPE loss that expanded over time. The M6 case did not show FAF abnormality or change. All severe cases experienced RPE damage that expanded progressively and sometimes involved the arcades. The pattern of RPE damage varied from diffuse central loss (S1 and S7) to a bull’s-eye pattern in S2 and a demarcated arcuate zone of RPE loss in S4.

Progression of abnormality in SD-OCT cross sections also depended on the severity of initial damage (Figure 3). Early cases showed little or no change over time. Cases E1 and E4 initially had an unremarkable OCT appearance (hydroxychloroquine toxic effects were diagnosed on the basis of ring scotomas and multifocal electoretinogram abnormalities); cases E2 and E3 showed mild parafoveal thinning and EZ disruption. Case E2 had developed some possible darkening and lengthening of the EZ line at the end of follow-up. All moderate cases demonstrated prominent parafoveal thinning on either side of the fovea (“sombrero” sign), which deepened somewhat over the observation period. However, the central fovea did not obviously lose thickness, and the RPE remained uninvolved (except for preexisting damage in the right eye of case M3). There is a suggestion of some EZ line improvement in the final records from M2 and M3. However, the interdigitation zone line is seen variably in different views from the same patient (eg, in M2 it seems to become thicker foveally but thinner beyond the parafovea) so that imaging variability needs to be considered in diagnosis. The severe cases all showed a great deal of RPE damage at the time of diagnosis and increasing disruption and hyperplasia over time. There were varying degrees of foveal cone damage, but in all severe cases the central thickness diminished clearly over time. Case S4 had good EZ preservation in the fovea initially, but the EZ shrank during observation. The EZ was hard to visualize initially in S1, S2, and S7, and by the last examination it had all but disappeared.

Changes in foveal and parafoveal retinal thickness over time are shown in Figure 4. These values are from the Cirrus Early Treatment Diabetic Retinopathy Study cube, and the parafoveal numbers represent the mean of the 4 zones (temporal, superior, nasal, and inferior) to encompass eyes with different regional patterns of damage. Foveal thickness was stable
for some early cases and decreased slightly in others. There was definite foveal thinning in moderate cases (approximately 4 μm/y) that continued for 3 years. Severe cases showed the most prominent foveal thinning (approximately 7 μm/y). Parafoveal thickness similarly demonstrated minimal change in early cases but definite (although somewhat variable) loss in moderate cases. The parafovea in severe cases showed either no change or thickening over time, but in these cases the parafovea was already largely devoid of photoreceptors by the time of diagnosis. Thus, the late changes no longer represent the toxic effects on photoreceptors and more likely relate to progressive RPE remodeling.

The stability or loss of the EZ line after hydroxychloroquine was discontinued is presented in Figure 5. The data are from measurement of OCT cross sections (Supplement eFigure 1); data from both vertical and horizontal cross sections are included because vertical scans were not performed at all visits, and 2 measurements help to validate trends of change. The EZ length stayed essentially constant over time for both early and moderate cases, indicating that outer segment architecture was not being disrupted (even though some foveal and parafoveal thinning was evident in Figure 4). There is even a suggestion of slight lengthening of the EZ in cases E2 and M3, as noted in the SD-OCT cross sections. In contrast, the severe cases demonstrated a dramatic and progressive loss of EZ length in the range of 100 μm/y.

Discussion

Our data from SD-OCT measurements indicate that, in severe cases of hydroxychloroquine retinopathy (ie, cases with RPE damage and visible bull’s-eye), there is a steady progression of retinopathy for at least 3 years after the drug is stopped. This is manifest most critically as continued thinning of the fovea and loss of EZ length and architecture. This is not reflected in visual acuity, however, until late in the disease when the EZ is disappearing from the central fovea, similar to other disorders, such as retinitis pigmentosa, in which acuity may remain good until late in the disease process.

The FAF images show a progressive loss of RPE even after the drug is stopped, and this loss can spread toward the outer reaches of the macula. These findings are consistent with much of the literature on late progression of retinopathy. Longer studies will be needed to assess whether and when this process reverts, but it is clear that delaying the discovery of hydroxychloroquine’s toxic effects to a stage of visible RPE damage risks an eventual loss of foveal structure and visual acuity.

In contrast, when hydroxychloroquine retinopathy is detected before RPE damage, the progression of retinopathy, both on examination of SD-OCT cross sections and on quantitative analysis, is much less severe and has a good likelihood of stabilizing without a loss of visual acuity.
Detection at our defined early stage is almost certain to prevent serious progression or visual loss (beyond the existing field damage) because the EZ zone did not change and progression of foveal or parafoveal thinning was minimal. Even in moderate cases, which demonstrated progressive parafoveal thinning, there was no encroachment within 3 years on the foveal EZ line (which is critical for visual acuity). Thus, the region of parafoveal damage may deepen as injured cells die without necessarily widening the zone of damage. There was also some progressive foveal thinning in the moderate cases, but these measurements were obtained from a central region that likely includes some of the bordering parafoveal tissue; the foveolar center did not obviously become thinner in the OCT cross sections.

The major limitation of this study is the length of follow-up. Monitoring for more than 3 years with more cases will be needed to fully confirm stabilization, in particular of early and moderate cases, and to gain confidence in the prediction that central vision will be maintained. Furthermore, we do not know which SD-OCT measure is most critical for evaluating early toxic effects. A recent study by Kellner et al10 reported similar preservation of function in patients with hydroxychloroquine retinopathy without RPE changes and progression in those with RPE damage. However, mild cases in that study were also monitored for only up to 3 years and without quantitative measures during that time. In addition, the severe cases with longer follow-up did not have sequential measurements to judge whether or when progression ceased. Our patients (who were largely derived from an earlier report7) showed a clear difference in daily dose levels: patients with mild and moderate retinopathy received near-recommended levels, and all those with severe cases received higher doses (Supplement [eTable]). However, the relative influence of daily and cumulative dose on hydroxychloroquine retinopathy remains an issue to be resolved through demographic studies. Excessive dosage is likely to be a significant factor in accelerating retinopathy, but the present series is too small to judge whether dosage has any effect on progression independent of the severity of retinopathy.

Visual fields showed no clear progression in our patients, which may seem surprising, especially in the early and moderate cases (severe cases have too little field remaining to measure accurately). However, visual fields can demarcate zones of photoreceptor injury before anatomical loss is prominent,11 and later anatomical loss in such regions may deepen scotomas more than expand them. The subjective variability in repeated fields suggests a...
need for caution in judging either progression or recovery from only 1 or 2 field measurements.

The literature\textsuperscript{1,2,4,12} includes several suggestions that retinopathy may improve if the drug is stopped, although most of these cases were based on evaluation of only 1 or 2 fields or vaguely described granularity. A recent report\textsuperscript{13} showed high-resolution OCT traces suggesting EZ improvement as early as 2 months after cessation of the drug. We did not make similar observations, although we hope that finding can be verified. Our data indicated progressive loss of thickness in the early and moderate cases and a suggestion of improvement in the EZ only after approximately 2 years. However, there was fluctuation in interdigitation zone visibility, and we are wary of drawing conclusions from subtle SD-OCT changes because of variations in foveal localization and image brightness. Some restoration of the EZ line can occur in other retinal disorders\textsuperscript{14,15} but more hydroxychloroquine cases need to be monitored with repetitive studies to verify the potential for recovery.

The graphs show change from baseline near the time hydroxychloroquine was discontinued. Mean values were determined using data from the 2 eyes; parafoveal values are the mean of the temporal, superior, nasal, and inferior regions. OCT indicates optical coherence tomography.
The mechanism of progressive hydroxychloroquine retinopathy after the drug is discontinued is unclear given the complex pharmacodynamics of the drug. Hydroxychloroquine binds strongly to melanin, which could be either a reservoir for damage or a protective mechanism.16 Clearance of hydroxychloroquine from the body takes many months after it is discontinued,17,18 and a very low concentration may be detectable in blood a year later. But it is unclear whether the small amount bound to RPE melanin is high enough to maintain a local retinal concentration that would cause continued neural damage for many years. It seems more likely that photoreceptor cells become metabolically compromised after long exposure, and the greater the insult, the greater the likelihood that these cells will eventually decompensate and die. In early and moderate cases, there is some continued cell loss in parafoveal regions where the metabolic damage is greatest, but elsewhere cells survive. In severe cases, the toxic effects have already compromised the foveal cones (even when vision remains 20/20), and the RPE is compromised as well. Thus, contin-

The graphs show change from baseline near the time hydroxychloroquine was discontinued. Mean values were determined using data from the 2 eyes; results are shown for vertical and horizontal slices (cross sections).
ued photoreceptor death occurs as both these injured cones and RPE decompensate.

Conclusions

Our data from objective SD-OCT measurements indicate that effective screening to detect early retinopathy associated with hydroxychloroquine can greatly minimize the extent of late progression and the risk of central visual loss. We cannot confirm functional stability beyond approxi- mately 3 years, but the data are encouraging and should help in managing the care of and advising patients receiving this drug. The critical predictor for severe progression appears to be the presence of RPE damage, and the critical predictor for retaining visual acuity appears to be integrity of foveal outer segment structures (including the EZ). As recommended by the American Academy of Ophthalmology, annual screening should use both 10-2 fields and SD-OCT (along with FAF and multifocal electroretinography as indicated) and look for early changes before there is any visible bull’s-eye.

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REFERENCES