Value of Red Targets and Pattern Deviation Plots in Visual Field Screening for Hydroxychloroquine Retinopathy

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Objective: To compare the value of red vs white 10-2 visual field testing in patients with different levels of hydroxychloroquine exposure and retinopathy in reference to recent American Academy of Ophthalmology recommendations on screening for hydroxychloroquine retinopathy that advised the use of 10-2 visual field testing with a white test object.

Methods: We studied retrospectively 13 patients using hydroxychloroquine who had undergone both red (FAST-PAC) and white (SITA) 10-2 automated visual field testing in the course of their management. On clinical grounds, they were judged to have no retinopathy, early retinopathy, or moderate or severe hydroxychloroquine retinopathy.

Results: White visual field diagrams were difficult to interpret, but pattern deviation plots consistently showed parafoveal sensitivity losses in early retinopathy. Red fields often showed more prominent scotomas in early retinopathy but sometimes showed irregular losses that were hard to evaluate. Either modality showed clear losses in moderate retinopathy. On repeated testing, the pattern deviation plots were somewhat more consistent than red fields in showing parafoveal damage.

Conclusions: With white 10-2 visual field hydroxychloroquine screening, the use of pattern deviation plots should be standard practice. Red testing appears to be more sensitive for early retinopathy but may be slightly less specific or consistent. We believe the main application for red testing is in screening for the earliest signs of retinopathy. Either red or white fields should be acceptable for hydroxychloroquine screening, as long as the clinician is sensitive to the characteristic patterns of early parafoveal damage and is prepared to retest fields and add objective tests.

METHODS

We studied a group of patients with suspected or confirmed hydroxychloroquine retinopathy who had been tested with both red and white visual fields to corroborate the presence or absence of parafoveal scotomas. The study was a retrospective medical record review from Stanford University, Southern California Permanente Medical Group, and the University of Michigan. It was approved by the institutional review board of the Stanford University School of Medicine and adhered to the principles of the Declaration of Helsinki. All patients were using hydroxychloroquine for lupus erythematosus or related diseases.

Automated 10-2 fields were obtained with Humphrey perimeters (Carl Zeiss Meditec), using the SITA protocol with white III targets or the FASTPAC protocol with red III or white I targets. All patients had SD-OCT imaging, using either the Cirrus HD (Carl Zeiss Meditec) or Spectralis (Heidelberg Engineering) systems. Some patients were tested with mfERG with a VERIS system (Electro-Diagnostic Imaging) and/or fundus autofluorescence with a Spectralis unit. Multifocal electroretinography testing followed the standards of the International Society for Clinical Electrophysiology of Vision. We present data showing the greatest disparity between red and white fields for each patient to ask whether one technique is better or worse. We also illustrate multiple paired tests from patients who had several tests at different points to judge consistency on repeated testing. Two patients were tested with white I targets as well as red.

Because the sensitivity or specificity of each technique may be influenced by the severity of retinal damage, we grouped our patients according to a rough scale of severity (used previously by Marmor) that takes a variety of clinical data into account. We define retinopathy as retinal damage primarily in the parafoveal “bull’s-eye” zone. Figure 1 shows examples of SD-OCT change that might typically be associated with early or moderate damage. Early damage was characterized by focal (partial ring) parafoveal scotomas on visual field or mfERG testing and by early (mild) parafoveal thinning on SD-OCT. Moderate damage was characterized by prominent ring scotoma in fields and

Figure 1. Spectral-domain optical coherence tomography changes in early and moderate cases of hydroxychloroquine retinopathy. Major optical coherence tomography landmarks of the outer nuclear layer (ONL), external limiting membrane (ELM), inner/outer segment junction (IS/OS line), and retinal pigment epithelium (RPE) are labeled at the right. White arrows span regions of IS/OS line loss and ONL thinning. The early case shows loss of the IS/OS line and mild thinning temporal to the fovea. The moderate case shows more severe thinning going down to almost total photoreceptor loss on both sides of the fovea. There is some pigment clumping on the damaged RPE temporally.

Figure 2. Red and white fields in cases without hydroxychloroquine retinopathy. These cases (N1, N2, and N3) had worrisome findings with one or the other modality, which led to retesting with the other color target. Spectral-domain optical coherence tomography findings were normal.

Table. Demographics and Dosage

<table>
<thead>
<tr>
<th>Retinopathy Level</th>
<th>Case No./Sex/Age, y</th>
<th>Years of Use</th>
<th>Dose/kg (mg/Ideal Weight)</th>
<th>Cumulative Dose, g</th>
<th>Eye Shown</th>
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<tbody>
<tr>
<td>None</td>
<td>N1/F/56</td>
<td>2</td>
<td>5.4</td>
<td>219</td>
<td>OD</td>
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<tr>
<td></td>
<td>N2/M/80</td>
<td>8</td>
<td>Average 4.1</td>
<td>1095</td>
<td>OD</td>
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<tr>
<td></td>
<td>N3/M/26</td>
<td>7</td>
<td>6.5</td>
<td>1022</td>
<td>OS</td>
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<tr>
<td>Early</td>
<td>E1/M/54</td>
<td>10</td>
<td>6.5</td>
<td>1460</td>
<td>OS</td>
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<tr>
<td></td>
<td>E2/F/89</td>
<td>18</td>
<td>6.5</td>
<td>2628</td>
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<tr>
<td></td>
<td>E3/F/49</td>
<td>25</td>
<td>7</td>
<td>3659</td>
<td>OD</td>
</tr>
<tr>
<td></td>
<td>E4/F/66</td>
<td>16</td>
<td>7</td>
<td>2338</td>
<td>OD</td>
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<tr>
<td></td>
<td>E5/F/62</td>
<td>3.5</td>
<td>8.7 (+ Renal disease)</td>
<td>511</td>
<td>OS</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>M1/F/62</td>
<td>14.5</td>
<td>7.6</td>
<td>2117</td>
<td>OD</td>
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<tr>
<td></td>
<td>M2/M/58</td>
<td>14</td>
<td>2.8 (Last 6 mo, 8.3)</td>
<td>1104</td>
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<tr>
<td></td>
<td>M3/F/47</td>
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<td>4.1-8.2</td>
<td>1045</td>
<td>OS</td>
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<td>7</td>
<td>1480</td>
<td>OS</td>
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<td>S5/F/77</td>
<td>7</td>
<td>11</td>
<td>1022</td>
<td>OD</td>
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mFERG and marked parafoveal photoreceptor thinning that neared the level of the retinal pigment epithelium. Severe cases also showed gross retinal pigment epithelium disruption and a degree of photoreceptor loss across the entire macula. Only severe cases had obvious bull’s-eye damage on fundus examination. The demographics of our cases are shown in the Table. All had used hydroxychloroquine more than 7 years except for case E5, who had been overdosed and had significant renal disease that presumably accelerated the retinopathy.

RESULTS

The cases with no retinopathy (Figure 2) had significant “losses” in red or white fields (which is why they had repeated testing) but showed no parafoveal damage on other tests including mFERG, SD-OCT, or autofluorescence. Most of the losses were at the periphery of the test area, which is a common site of artifactual loss. The red fields of case N2 and pattern deviation (PD) of case N3 might (erroneously) suggest parafoveal damage, but these areas were not affected using the alternative color field target nor corroborated with objective modalities.

The cases with early retinopathy (Figure 3) all had parafoveal damage documented on 1 or more of the objective tests. The white field diagrams were generally not very revealing, although they hint at parafoveal sensitivity loss in cases E3 and E4. In contrast, all of the PD plots showed at least 1 to 2 (and often more) parafoveal spots of high significance (<1% likelihood of error), and these correlated with SD-OCT and/or other test modalities. The red field diagrams showed a ring scotoma much more distinctly than the white PD plots in 2 cases (E2 and E5). In the remaining 3 cases, the red changes corroborated and amplified to varying degrees sensitivity losses that were also seen in the white PD plots.

For cases with moderate retinopathy (Figure 4), as with early cases, the white field diagrams were hard to interpret.
interpret (although there was a bull’s-eye zone of modest sensitivity loss in case M2 and a partial bull’s-eye zone in case M4). In contrast, the PD plots all showed distinct and statistically reliable losses in a rough bull’s-eye configuration. Red fields showed dense and complete ring scotomas in cases M1 and M2, although on a background of generalized sensitivity loss that almost obscured the ring. The ring scotomas to red in cases M3 and M4 were less dense and roughly comparable with the zones of loss in the white PD plots.

Case S5, with severe retinopathy (Figure 4), showed a prominent bull’s-eye scotoma in the white field diagram as well as the PD plot. Red testing showed so much diffuse sensitivity loss that a distinct bull’s-eye pattern was not discernable.

Two patients were also tested with white I targets with results essentially the same as with the red targets. Both patients said that the small white targets were much harder to see than the red targets, making the test more strenuous.

Three cases (E2, M1, and M2) had repeated testing, illustrated in Figure 5 in time sequence from top to bottom. The initial field of case E2 had only 2 distinct PD plot losses but striking red field loss. However, the final testing showed the opposite, with prominent parafoveal damage in the white PD plot and ambiguous scattered field losses using red. Thus, while red seemed more sensitive at the initial testing, it was less consistent in documenting parafoveal damage. Case M1 showed parfoveal PD losses on the first and last test, while red had only small spots of loss with PD and scattered ones with red, demonstrating the variability of field sensitivity. For case M2, both targets showed distinct parafoveal losses in all tests. The red field did not add discrimination value except perhaps in the final testing.

**COMMENT**

Easterbrook and Trope reported on 50 eyes of patients who were taking chloroquine and were felt to have retinopathy on the basis of Amsler grid testing and who were tested with both red and white III automated 10-2 fields. They illustrated a few examples, but without judgment of the severity of the retinopathy, and gave no data beyond a summary statement that red testing was 91.3% sensitive but only 57.8% specific, while white III testing was 78% sensitive and 84% specific. Pluenneke and Blomquist found red Amsler grid testing unreliable in a rheumatology clinic. Early reports advocating red tangent screen or confrontation field testing gave no data with respect to brightness. Mindel et al compared red vs white targets with a projection perimeter and found in essence that red functioned as a dim white. Consistent with this view, the 2 patients who we tested with smaller white I targets (equivalent to dimmer targets) showed results similar to red testing (although subjectively they found red easier to see).

Our data indicate that the relative value of red vs white fields depends on the stage of hydroxychloroquine retinopathy. In early cases, red can at times show a more definitive ring scotoma, but once damage is moderate or worse, either modality will document parafoveal loss. Some cases are a bit clearer with one or the other target, but the damage is evident with both (and in severe cases, red may hardly be perceived anywhere, masking the bull’s-eye pattern). Thus, the debate concerning red vs white applies primarily to hydroxychloroquine screening, where one seeks the earliest signs of retinopathy.
Our study is limited by the small number of cases (patients who had been tested with both red and white targets) and by the fact that we present clinical examples rather than a prospective series of comparisons. Nonetheless, our findings in general mirrored the conclusions of Easterbrook and Tropé.6 We had individual early cases (E2 and E5) for whom red testing demonstrated an obvious ring scotoma that was only suggested by the PD plot. However, other tests on early cases (repeated testing of cases E1 and E2) showed less distinct red patterns that could be more confusing than diagnostic, while PD plots revealed parafoveal losses. Thus, red could be more sensitive, to be expected with more points near the visible threshold, but the white PD plots seemed a bit more consistent or specific in showing parafoveal damage (as confirmed by other documentation). Both tests showed moderate retinopathy well, but with severe retinopathy, white field diagrams may be more appropriate than the overly sensitive red (a situation that may have applied to some of the Easterbrook and Tropé cases). A prospective study of red vs white would be ideal, of course, but given the variability of subjective field testing, it may not reveal much more than our most critical conclusions that either target color can be effective (with awareness of typical damage patterns and typical artifacts) and that white testing should include PD plots.

The recent American Academy of Ophthalmology recommendations for screening had stated that “attention should be drawn” to PD plots.4 Our examples add emphasis to this statement. The full white field diagrams were usually hard to interpret and did not show obvious scotomas in early and even moderate cases. However, PD plots always showed distinct parafoveal losses in retinopathy cases, the area where early change is visible in the SD-OCT.5 The PD plots show points that deviate relative to background sensitivity and normal patterns of sensitivity change across the visual field and ranks their statistical likelihood of being abnormal.10 We suggest that SITA PD plots should be the standard format for white III 10-2 field testing for hydroxychloroquine damage, with the proviso that a single parafoveal spot of sensitivity loss needs to be taken seriously.

We disagree on the best test to use for hydroxychloroquine screening. F.Y.C. and M.W.J. prefer red, whereas M.F.M. prefers white III PD plots. The choice rests partly on sensitivity vs specificity but also on physician comfort and experience with the particular patterns and artifacts of each technique with early retinopathy. It is vital that physicians be aware of the parafoveal region (2°-6° off-center) where the retinopathy first becomes manifest, just as they learn to recognize early arcuate scotomas in glaucoma. The superonasal quadrant seems most likely to be affected initially, but not necessarily.6 The finding of any points of parafoveal loss should be taken seriously; initiate retesting (or testing with the alternative color target) and, if consistent, initiate corroborative testing with objective modalities such as SD-OCT or mfERG.

The use of objective tests routinely along with field testing is recommended by the American Academy of Ophthalmology,1 and we fully agree. For one thing, patients differ as to which test shows initial damage most clearly.6 A second important reason for corroboration with objective tests (or repeated field tests, possibly with both red and white) is that hydroxychloroquine is an excellent drug for lupus and related diseases, with low systemic toxicity. Patients should not stop taking a valuable drug unnecessarily for 1 borderline or questionable field test result.

The intent of the AAO recommendation for white field targets was not to forbid the use of red; it was simply a choice of the most prevalent modality. In our opinion, either red or white field tests can be effective and acceptable screening modalities for hydroxychloroquine retinopathy, as long as physicians are sensitive to early patterns of change (parafoveal sensitivity loss 2°-6° off-center) and PD plots are used with white targets.

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Conflict of Interest Disclosures: None reported.

REFERENCES