

Special AAO Report: Recommendations on Screening for Hydroxychloroquine Retinopathy (2025 Revision)

Michael F. Marmor, MD,¹ Seong Joon Ahn, MD,² Justis P. Ehlers, MD,³ Ronald B. Melles, MD,⁴
William F. Mieler, MD,⁵ David Sarraf, MD,⁶ Imran H. Yusuf, MD,⁷ for the American Academy of Ophthalmology

Background: The American Academy of Ophthalmology recommendations on screening for hydroxychloroquine (HCQ) retinopathy are now a decade old. This revision provides an update based on current knowledge. Major points and changes are as follows.

Nature of Toxicity: The retina typically remains clinically normal for many years on HCQ, but there is an unpredictable point at which signs of toxicity may develop.

Pattern of Toxicity: Most eyes of patients of European heritage have a parafoveal pattern of toxicity, whereas eyes of East Asian patients tend to present with pericentral toxicity, but there are many exceptions, and screening examinations should look for both patterns.

Dosage: The recommended daily dosage remains unchanged at ≤ 5.0 mg/day/kg real weight. Keep under 400 mg/day for severely obese patients.

Risk Factors: Beyond dose and duration, concurrent renal disease and tamoxifen use increase risk, as does initiation of HCQ therapy at an older age.

Clinical Tests: The primary screening tool should be OCT, along with wide-pattern fundus autofluorescence (FAF). Visual field (VF) and multifocal electroretinography (mfERG) are secondary confirmatory tests. Newer VF algorithms such as 24-2C can screen parafoveal and pericentral regions simultaneously.

Screening: A baseline screening examination, including fundus, OCT, and FAF, is advised soon after HCQ is begun, not only to rule out preexisting conditions but also for comparison with later results. Annual screening with OCT and FAF is recommended while using HCQ, but may be deferred during the first 5 years if there are no significant risk factors.

Progression: Mild retinopathy is unlikely to progress after discontinuation of HCQ, but severe retinopathy may continue to worsen for many years.

Implications of Early Signs of Toxicity: With earlier recognition comes greater need to communicate with patients and their medical providers regarding options to stop HCQ or continue with cautious monitoring.

New Technology: There have been experimental advances in imaging and artificial intelligence analysis for HCQ screening, but none have been validated for general use or are widely available at this time.

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Retinal toxicity from hydroxychloroquine (HCQ) and its analogue chloroquine (CQ) is a well-recognized disorder. These revised recommendations apply primarily to HCQ because little additional information has been published in recent years regarding CQ. Hydroxychloroquine is currently the preferred treatment for systemic lupus erythematosus (SLE) and is also widely used for the management of rheumatoid arthritis, sarcoidosis, and related autoinflammatory and dermatologic conditions. Hydroxychloroquine also is being considered for new applications in diabetes mellitus, heart disease, and adjunct cancer therapy. Thus, it is important for ophthalmologists and other physicians to understand the prevalence and risk factors for HCQ retinopathy.

The American Academy of Ophthalmology (AAO) Recommendations on Screening published in 2016¹ are now almost a decade old, and an update and revitalization of the guideline are needed. An international group of well-known experts on HCQ retinopathy were assembled by the AAO to provide this information. Their recommendations have undergone review by the AAO Board of Trustees whose revisions were incorporated, and the new set of recommendations were approved and ratified at the October 2025 meeting of the Board of Trustees. This update takes new information into account and represents a distillation of current literature, but it is not a review article and includes only a limited bibliography. New screening tests and technology that are not validated or readily

available are noted only for information. If these recommendations are followed, the risk of visual loss from HCQ use should be low, and the historical finding of bull's-eye maculopathy (a late manifestation of toxicity) should no longer be encountered.

Key Points to Note in the New Recommendation

Nature of Toxicity

Hydroxychloroquine toxicity does not occur as a continuous evolution of damage from day 1 of therapy. Evidence suggests that the retina remains largely normal for many years on the proper dosage, but there is an unpredictable point at which early signs of toxicity (e.g., outer retinal thinning) may appear and progress within just a few years to obvious retinopathy.

Patterns of Disease

Patients of European or East Asian heritage most often have a parafoveal or pericentral pattern of disease, respectively, but not exclusively. Screening should look for both patterns.

Dosage

The recommended daily dosage of HCQ remains unchanged at ≤ 5.0 mg/kg real weight. Severely obese patients might be overdosed by weight, and they should start with a lower dosage and with a maximum of 400 mg/day that could be raised for medical need and with careful monitoring.

Risk Factors for Retinal Disease

Beyond dose and duration of use, risk factors include renal disease, concurrent tamoxifen use, as well as initiation of HCQ therapy at older ages.

Clinical Tests

The primary screening tool should be OCT, along with wide-pattern fundus autofluorescence (FAF) where available. The description of OCT signs of early toxicity is updated and expanded in these guidelines. Automated visual fields (VFs) and multifocal electroretinography (mfERG) are important adjunct tests but are not advised as primary screening tools. Newer VF algorithms such as 24-2C can screen both parafoveal and pericentral regions.

Screening

A full baseline screening examination (including OCT and FAF) is strongly advised soon after HCQ is begun to rule out preexisting disease and for comparison with later results. Annual screening is advised while using HCQ but may be deferred during the first 5 years if there are no significant risk factors.

Progression of Toxicity

If HCQ is stopped when OCT alterations are mild, significant progression of retinopathy is unlikely. However, once

outer nuclear layer (ONL) thinning and ellipsoid zone (EZ) damage are extensive, retinopathy may continue to worsen despite cessation of therapy; if the retinal pigment epithelium (RPE) is affected, progression can be relentless and eventually result in central visual loss.

Management of Toxicity

As signs of retinal toxicity are recognized earlier, it is increasingly important to communicate with both patients and their medical providers. Many patients will choose to discontinue HCQ, but some may choose continuation under close monitoring.

Technology

New imaging techniques and artificial intelligence (AI) analysis are noted briefly, and show promise for screening, but none are fully validated or widely available.

Nature of Toxicity

Mechanisms

The mechanism of CQ and HCQ toxicity is not well understood. High experimental doses disrupt the metabolism of retinal cells, but it is not clear how these short-term metabolic effects relate to the slow and chronic damage that characterizes the clinical state of toxicity. Binding to melanin in the RPE may serve to concentrate the agents and contribute to, or prolong, their toxic effects. However, melanin binding may serve as a mechanism for removing toxic agents from intracellular sites of damage. In animal studies, the inner and outer retina are damaged by CQ exposure, but human studies suggest that the inner retina is relatively spared. In clinical practice, the primary damage occurs at the level of the photoreceptors and outer retina after long exposure to HCQ. This includes the ONL, the interdigitation zone (IZ), which represents the EZ-RPE space, the EZ, and the external limiting membrane (ELM). As these regions degenerate, secondary disruption of the RPE may ensue.

Patterns of Fundus Change

Patients of European descent and those from India, Pakistan, and the Middle East most often show initial photoreceptor damage in a parafoveal distribution.² Patients of East Asian descent, including both Northeast and Southeast Asia, typically show initial damage in a more peripheral extramacular distribution (pericentral) near the arcades.³ However, a moderate percentage of patients from each group will show a contrary or mixed (combined) pattern of damage. Black patients appear to have a greater tendency toward pericentral disease than White Americans, and limited demographic data from the Indian subcontinent suggest a mix of disease patterns. No differences in the dose sensitivity or outer retinal layer predilection of HCQ retinopathy are known to correlate specifically with a parafoveal or extramacular (pericentral) pattern of damage as HCQ toxicity develops.

Overall Risk of Toxicity

Patients with rheumatoid autoimmune disease are predominantly female, and as a result, estimations of risk in this document are derived from populations who are disproportionately female. Earlier literature on the prevalence of HCQ retinopathy, including studies on large series of patients using different doses for varying long periods of time and evaluated with current OCT technology, have shown values in the general range of 7.5%.³ Any global estimation of risk applies only to the specific population being studied, taking into account the spectrum of dose and duration of use, and the degree of compliance with dosage and screening guidelines.

Onset of Damage and Visual Loss

Evidence is accumulating that HCQ is tolerated at recommended doses for many years without significant retinal abnormality. However, sequential OCT, mfERG, VF, and AI analyses all suggest that at some point in time, after years of exposure, early evidence of toxicity (e.g., retinal thinning) can rather suddenly become evident and progressive (Fig 1).⁴ This typically occurs several years before OCT signs of significant toxicity (e.g., EZ damage) become obvious in isolated B-scans and often before definitive FAF, VF, or mfERG changes are recognized. Recognition of this inflection point, when retinal decompensation and thinning begin and progress, is important for advising patients about risk and for considering the balance between medical need and stopping the drug.

Central visual acuity is usually retained in HCQ retinopathy, with either distribution pattern, until severe and late stages of damage, and most patients who develop HCQ toxicity have no visual symptoms at all. A few patients may notice paracentral scotomas, for example, while reading. However, if drug exposure continues, the area of functional disturbance can expand, the RPE can become involved, and the maculopathy can gradually encroach on the foveal center with a resulting loss of visual acuity. Cystoid macular edema may sometimes develop, and advanced cases of retinopathy can mimic dystrophies such as retinitis pigmentosa with widespread RPE and retinal atrophy, reduced full-field electroretinography (ERG), and loss of visual acuity, peripheral vision, and night vision.

Chloroquine, and less frequently HCQ, may cause whorl-like intraepithelial deposits (verticillata) in the cornea. These corneal changes are not a direct marker for retinal damage and are not associated with visual loss. In contrast to HCQ retinopathy, the verticillata are usually reversible.

Reversibility of Toxicity

A few isolated cases with mild HCQ retinopathy have shown a slight improvement of outer retinal thickness or EZ line integrity after cessation of HCQ. However, as more significant thinning and EZ loss and ELM disruption develop, the window of reversibility disappears. Advanced retinopathy can progress despite cessation of HCQ and is not reversible to any significant degree.

Proper Dosage

Dosage Recommendations

Patients using HCQ should ideally keep their daily dosage ≤ 5.0 mg/kg real weight.^{1,2} Following this recommendation should minimize the risk of retinopathy and allow long-term use of HCQ for most patients with relative safety.² Unfortunately, there is no clear consensus on the HCQ dose levels that are needed for medical control of the different diseases for which the drug is used. Many patients do well on this recommended dose (which significantly reduces ophthalmologic risk), but there may be instances where higher doses are needed to manage life-threatening disease. There are also situations where a lower dosage is advisable because of significant risk factors (see below). However, doses near 6.0 mg/kg/day markedly accelerate risk, and patients receiving twice or more than recommended levels can develop signs of toxicity rapidly, even within the first year or 2 of use. The risk of toxicity using ≤ 5.0 mg/kg/day doses has been shown to be relatively stable among patients of varying weight up to a body mass index (BMI) of 35 kg/m², although it might overdose short obese patients. No dosing formulas predict safe levels at higher BMI. Individuals with severe obesity should start with lower calculated doses and use a maximum of 400 mg/day that could be raised for medical need and with careful monitoring. Dosage always should be as low as possible for medical control and be accompanied by regular screening for signs of toxicity.

Measurement of HCQ blood levels might be considered in theory as an indicator of medical effectiveness or risk of toxicity, but several studies have shown these values to be highly variable and unreliable as predictors of HCQ retinopathy.

Duration of Use

The overall prevalence and incidence of toxicity increase with duration of use. The largest study to date has shown that for patients with dosage < 5.0 mg/kg/day of real body weight, the likelihood of toxicity within 5 years is below 1% and stays below 2% even after 10 years of use (Fig 2).² The risk is much higher, and rises faster, when the daily dose nears 6.0 mg/kg. Cumulated drug ingested or cumulated dose/kilogram levels have sometimes been suggested as risk indicators, but patients use different doses (depending on weight and other factors).

An issue of clinical concern, when patients are followed regularly, is the incremental risk of toxicity for an individual whose screening and OCT examination results are normal. Population risks do not apply once an individual's screening examination shows no evidence of toxicity. To advise patients, it is necessary to know the risk of toxicity developing in the ensuing year after normal examination results. This is shown in smooth response curves (Fig 3).² The risk increases with the duration of HCQ use but is always much lower than the population risk. Even after using HCQ for 20 years, the incremental risk in the next year is $< 5\%$ using proper dosage.

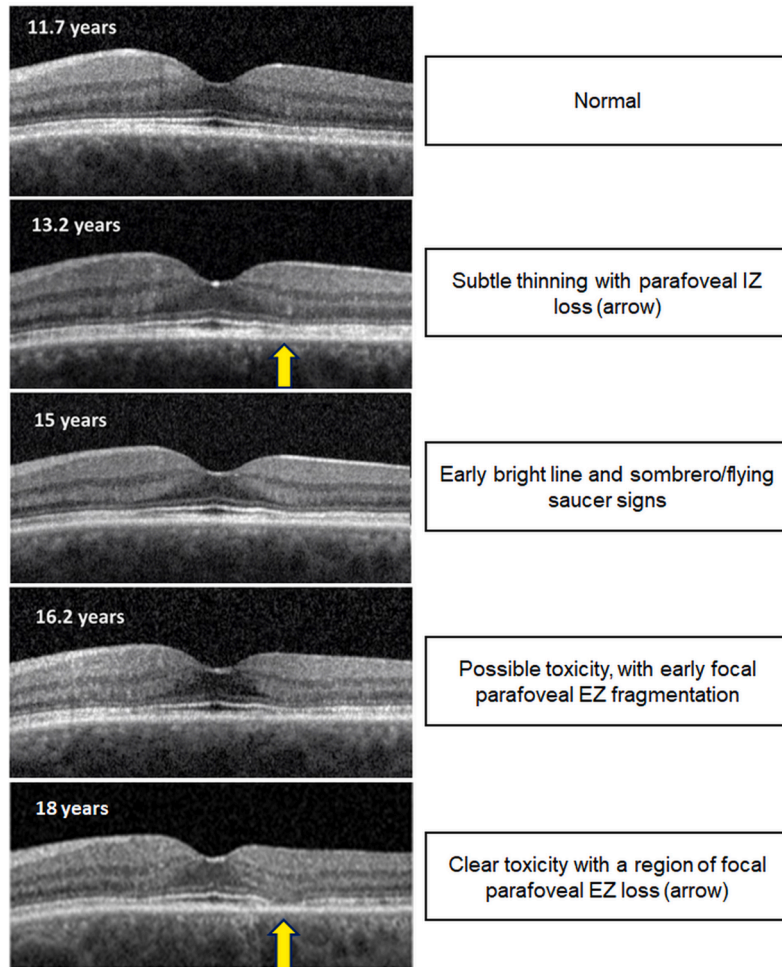
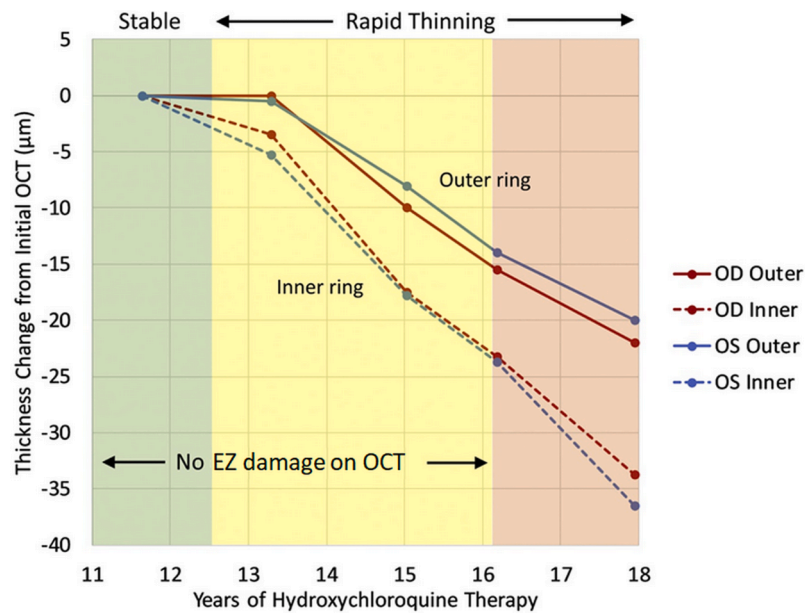


Figure 1. Retinal stability and the onset of hydroxychloroquine (HCQ) toxicity. **Top:** The commencement of retinal thinning (parafoveal more than pericentral) in a patient who had previously been stable for 12 years. Ellipsoid zone disruption (a sign of significant toxicity) did not become apparent until 4 years later. **Bottom:** The OCT scans from this patient show a sequence of relatively subtle changes until EZ damage became apparent. (From Melles et al.⁴) EZ = ellipsoid zone; IZ = interdigitation zone; OD = right eye; OS = left eye.

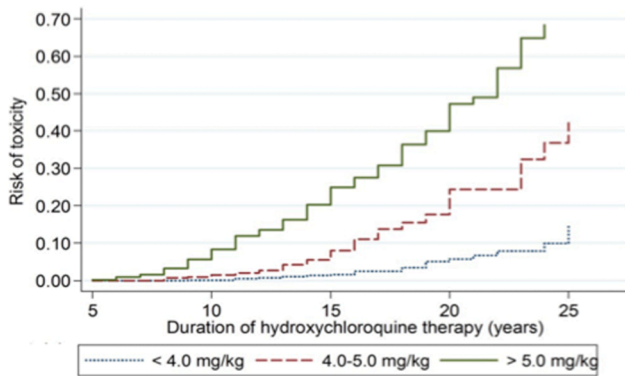


Figure 2. Plots of HCQ risk. Kaplan–Meier plots show how the risk of retinopathy increases with the duration of use for different daily doses of HCQ. At ≤ 5 mg/kg/day, the risk of toxicity is very low even up to 10 years of exposure. (From Melles et al²)

Tablet Management

Hydroxychloroquine only comes in 200 mg tablets, and thus it can be a challenge to prescribe intermediate doses. However, systemic levels of these drugs only stabilize over many weeks so that variable dosing will average out over time. Intermediate doses can be obtained by splitting tablets or simply eliminating a tablet on certain days of the week. In theory, blood levels would seem an aid to proper dosing, but as noted above these are not reliable indicators of HCQ effectiveness or retinopathy risk except when very low levels indicate noncompliance.

Chloroquine

The mechanisms of action of HCQ and CQ are presumed to be similar, and these recommendations are largely based on the HCQ literature. Chloroquine may be more toxic, but there are no recent studies to confirm that opinion, and this

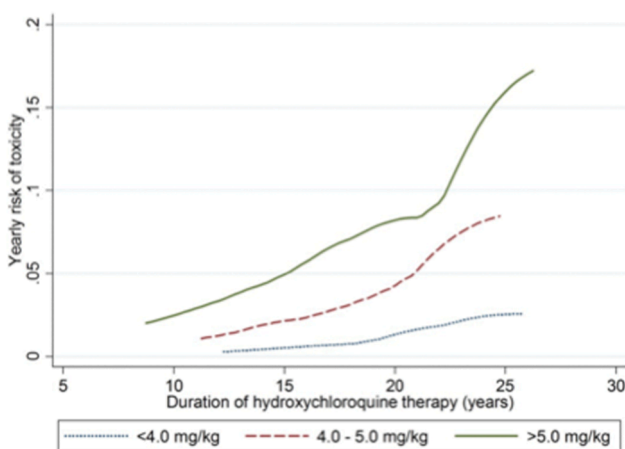


Figure 3. Plots of incremental risk of hydroxychloroquine (HCQ) toxicity. Smoothed response curves show the 1-year risk of developing HCQ toxicity in patients with no retinopathy, relative to dosage and duration of therapy. For ≤ 5 mg/kg/day, the annual risk is fairly low even after 20 years of therapy. (From Melles et al²).

may in part be an artifact of common prescription practice of 1 pill/day, because the smallest CQ tablet is 250 mg. Older clinical literature on antimalarial toxicity approximately equated 3.0 mg of CQ with 6.5 mg of HCQ with respect to dosage and toxicity, so that 2.3 mg/kg/day CQ would be equivalent to 5.0 mg/kg/day HCQ. On this basis, 1 daily tablet of CQ would be an overdose for anyone weighing less than 108 kg (238 lbs).

In the absence of more information, we suggest that CQ dosage be ≤ 2.3 mg/day/kg real weight, and CQ users can adjust the daily dose as described above for HCQ by splitting or omitting tablets on certain days.

Risk Factors for Toxicity

Several factors increase the risk of HCQ retinopathy, as noted in Table 1. Keep in mind that these are all relative, in the sense that minimal deviation from the norm (e.g., proper dosage, no other dysfunction, no exposure) may not be significant, but the further a patient is from these baselines and norms, the greater and more significant the risk becomes.

Dose and Duration

The most critical risk factors for the development of HCQ toxicity are excessive daily dose by weight (>5 mg/kg real weight) and prolonged periods of use, as described in the preceding section.

Renal Disease

Hydroxychloroquine and CQ are cleared to a large degree by the kidney, so that renal disease effectively increases the circulating level of the drug and the risk of toxicity. Renal disease is not uncommon in SLE and related diseases, so careful monitoring of kidney function is important. Patients with renal disease develop higher blood levels of HCQ, and both dosage and screening frequency may need to be adjusted accordingly. A glomerular filtration rate reduced by 50% approximately doubles a patient's risk of retinopathy.²

Tamoxifen Use

Tamoxifen (a drug used for long-term treatment of breast cancer) can increase the risk of toxicity. Tamoxifen is a retinal toxin itself, and there may be adverse metabolic

Table 1. Risk Factors for Toxic Retinopathy

Daily HCQ Dosage	>5.0 mg/kg (CQ >2.3 mg/kg) > 400 mg/day in severe obesity
Duration of use	>5 yrs
Renal disease	Subnormal glomerular filtration rate
Concomitant drugs	Tamoxifen
Macular disease	If affecting vision or ability to screen
Old age	Initiation of HCQ at older ages

CQ = chloroquine; HCQ = hydroxychloroquine.

Table 2. Clinical Examination Tests

For Annual Screening
Primary Techniques
Spectral-domain OCT
Wide-pattern FAF
Secondary or Confirmatory Techniques
VF (10-2 plus 24-2 or 30-2; or combined algorithm like 24-2C)
mfERG
Not Recommended for Annual Screening
Fundus examination
Time-domain OCT
OCT angiography
Fluorescein angiography
Full-field ERG
Amsler grid
Color testing
Electro-oculography

ERG = electroretinography; FAF = fundus autofluorescence; mfERG = multifocal electroretinography; VF = visual field.

synergy. Case reports indicate possible concern over use of other aromatase inhibitors as well.

Sex

Because women account for a large majority of patients with rheumatic diseases, the risk data in this document have been derived primarily from women. However, a recent study suggests that men are less likely than women to develop toxicity at comparable dosage and duration of HCQ.⁵

Age

The same study also showed that patients who begin HCQ treatment at older ages are more likely to develop toxicity than those beginning treatment before 45 years of age.⁵ This does not mean the drug should not be prescribed, but that the commencement of screening and adherence to guidelines are especially important for elderly patients.

Retinal and Macular Disease

Patients with underlying retinal disease may be at higher risk for toxicity, although there are no specific data to confirm this. It seems reasonable not to add a potentially toxic agent to the retina in the presence of retinal dystrophy or degeneration. Beyond this theoretical concern, however, it is important to recognize that maculopathy can interfere with the interpretation of screening procedures, including OCT, FAF, VF, and mfERG. For example, significant areas of retinal atrophy or large confluent drusen that compromise retinal architecture and have associated VF loss would be a clear contraindication to starting HCQ, because early changes from HCQ toxicity would be difficult to distinguish or detect. However, sparse macular drusen with intact overlying photoreceptor structures including the EZ should not interfere with screening or affect the VF.

Liver Disease

Although the liver participates in the metabolism of HCQ and CQ, no clear association between liver disease and toxicity has been demonstrated.

Genetic Factors

No genetic variations have been shown to be associated consistently with HCQ retinopathy. Genetic factors may underlie the difference in disease presentation between European and Asian eyes, but no specific genes have been identified.

Clinical Tests for Toxicity

Spectral-Domain OCT

OCT is recommended as the primary test for early recognition of HCQ toxicity (Table 2).⁶ As damage from HCQ progresses, consecutive OCT scans show characteristic changes in the retina.

Initial Thinning. Outer retinal thickness remains normal for many years at recommended doses, but when toxicity begins, one can recognize areas of thinning. This typically occurs in the parafovea of European patients (Fig 4) and pericentral area of East Asian patients (Fig 5), but both areas can be involved. These can be recognized using the quantitative macular thickness values in ETDRS measurement grids or comparison of sequential en face images of retinal thickness. These visualization options are currently provided by many OCT machines, and progression can be recognized by comparing one year with the next. Thinning may be evident several years before EZ alteration becomes apparent in the OCT B-scan images.

Intermediate Levels of Damage. Later OCT changes depend upon the pattern of retinopathy.

Parafoveal Pattern. Hydroxychloroquine toxicity in European patients is most often (but not always) parafoveal. An early sign after diffuse outer retinal thinning is focal thinning of the EZ-to-RPE space, which may be visualized as regional disappearance of the IZ line.⁶ Early focal degradation of the IZ or EZ may lead to the appearance of a “bright line” sign in the fovea (Figs 1 and 4, Early). This is not enhanced brightness, but preservation of central EZ and IZ signals relative to adjacent areas with signal attenuation. Continued thinning of the outer retina in the parafovea also may produce an OCT appearance resembling a sombrero or flying saucer.

Progressive EZ damage begins as focal granular fragmentation or EZ thinning, followed by focal regions of EZ loss.⁷ With continued use of HCQ, these gradually expand to involve large regions of the EZ in conjunction with outer retinal atrophy (Fig 4, Moderate). At this stage, with the ELM still intact, many of these eyes will stabilize if HCQ is discontinued, but the amount of progression becomes harder to predict the more extensive the loss of EZ. Disruption or loss of the ELM signifies a more advanced stage of retinopathy with considerable risk of progression after HCQ is discontinued.⁷ Ancillary tests such as FAF,

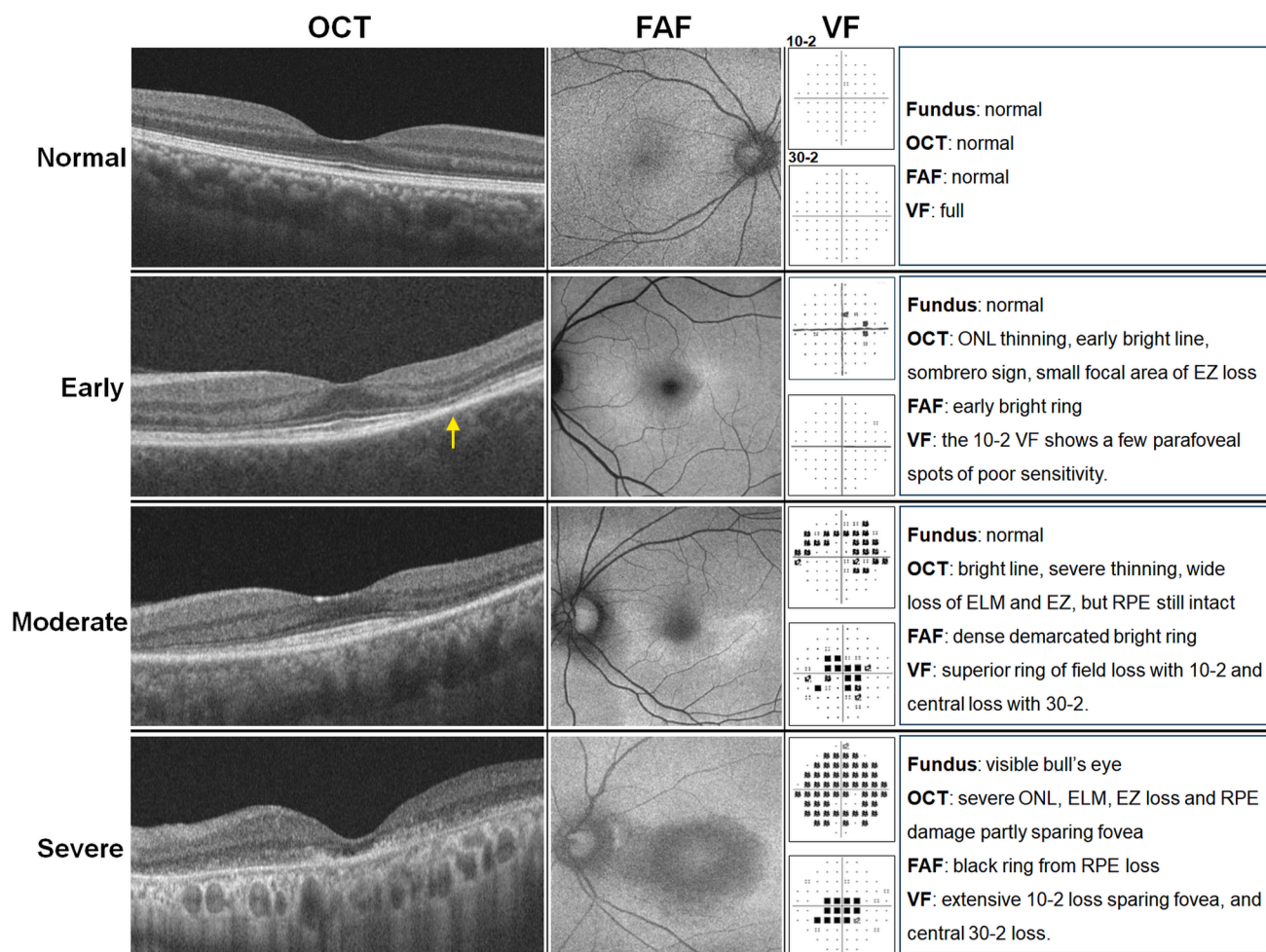


Figure 4. Progression of test results in patients with predominantly parafoveal disease. Typical OCT, FAF, and VF findings in early, moderate, and severe stages of parafoveal retinopathy. This sequence of changes is described more fully in the text. ELM = external limiting membrane; EZ = ellipsoid zone; FAF = fundus autofluorescence; ONL = outer nuclear layer; RPE = retinal pigment epithelium; VF = visual field.

VF, and mfERG may be informative in equivocal cases of toxicity that lack the classic OCT features as described previously.

Pericentral Pattern. Recognition of pericentral damage (Fig 5), as opposed to parafoveal damage, can be more challenging because OCT studies often are limited to the central macula, and normal thinning of the outer retina makes the layers and marker lines harder to identify with increasing eccentricity from the fovea. Nonetheless, pericentral HCQ retinopathy usually can be identified in wider OCT scans as marked thinning and loss of marker lines beyond the parafovea, and it can be confirmed by wide-pattern FAF.

Severe and Late Damage. Loss of the ELM can signify the beginning of severe retinopathy in either pattern of fundus disease.⁷ With further exposure to HCQ, there is RPE disruption and atrophy that destroy the outer retina and represent the latest stage of toxicity. At this point, progression of outer retinal damage is typical, and if the foveal center becomes involved there can be a loss of visual acuity. Because of RPE involvement, changes

become visible on ophthalmoscopy, with the appearance of bull's-eye maculopathy around the fovea in parafoveal disease and near or beyond the arcades in pericentral disease. Bull's-eye retinopathy no longer should be encountered if dosing recommendations are followed and regular screening is performed.

Fundus Autofluorescence

Autofluorescence imaging is now available on many fundus cameras, although it is not yet routinely used in general ophthalmology. Wide-pattern FAF that extends beyond the central macula is particularly useful for the recognition of a pericentral pattern of maculopathy (Fig 5). This can be challenging to recognize with conventional horizontal OCT scans because marker lines are difficult to discern (and some scans do not extend) much beyond the central macula. We believe that wide-pattern FAF, if available, should be used regularly, because it is an objective indicator of retinal damage and it provides a broad topographic view of potential areas of parafoveal and pericentral

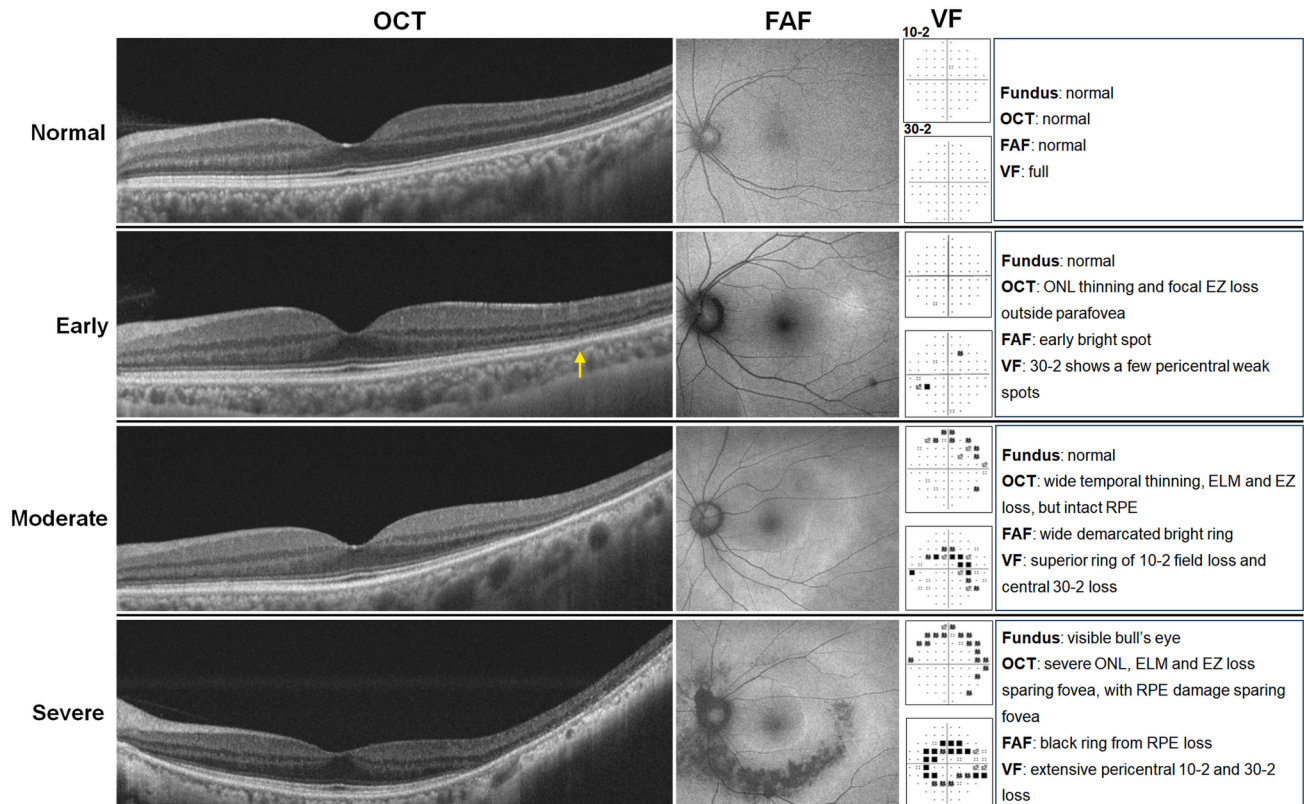


Figure 5. Progression of test results in patients with predominantly pericentral disease. Typical OCT, FAF, and VF findings in early, moderate, and severe stages of pericentral retinopathy. This sequence of changes is described more fully in the text. ELM = external limiting membrane; EZ = ellipsoid zone; FAF = fundus autofluorescence; ONL = outer nuclear layer; RPE = retinal pigment epithelium; VF = visual field.

involvement. Scans should extend beyond the arcades (~ 30 degrees), and ideally to 50 or 55 degrees.

The first signs of toxicity, in either pattern of involvement, are areas of increased autofluorescence (brightness), most often in the inferotemporal quadrant. The mechanism may involve unmasking RPE autofluorescence that is blocked by photoreceptors or represents an accumulation of retinal fluorophores in the RPE. The OCT scans from corresponding areas will show retinal thinning and EZ attenuation. Comparison with baseline and earlier FAF recordings is important because isolated images are not always easy to interpret. Dark or black areas on FAF indicate more severe levels of toxicity where photoreceptors are missing (so there is no longer any shedding) and RPE is damaged or atrophic. Ideally, FAF screening should identify patients with HCQ retinopathy before areas of autofluorescence go dark.

Automated Threshold Visual Fields

Visual field testing can be sensitive in reliable patients, but it is a subjective test with considerable variability. Thus, we consider the VF to be a confirmatory test that should not be used as a sole or primary screening procedure. If VF is used along with objective tests, we recommend using white Swedish Interactive Thresholding Algorithm (SITA) testing with pattern deviation plots, which distinguish regional loss from background sensitivity better than the standard grey scale. The 10-2

field pattern has high resolution for parafoveal toxicity (Fig 4), but wider test patterns (24-2 or 30-2) are needed to show pericentral damage (Fig 5). Because some Asian patients show parafoveal damage and some European patients show pericentral damage, effective VF screening requires both central and peripheral testing. This can be accomplished now with a single test using one of several algorithms such as the 24-2C test that add central points to a wider test pattern, which can show whether damage is parafoveal or pericentral.

Visual field findings can vary markedly between visits, and some findings are more reliable than others. Proper field interpretation requires a sensitive eye to the characteristic pattern of HCQ loss in both the parafoveal and extramacular regions, which differs from the damage patterns of macular disease, glaucoma, or cerebral disease. The most frequent early field defects are superonasal (corresponding to inferotemporal damage in the OCT and FAF). Uncertain VF changes should trigger retesting within a few months (for consistency) or comparison with changes seen in objective tests such as mfERG, OCT, and FAF.

Multifocal Electrophysiology

Multifocal electroretinography is an objective retinal test of local electrical responsiveness to light. Multifocal electroretinography generates focal ERG responses

topographically across the posterior retina that document parafoveal or extramacular regions of ERG depression in early retinopathy (Fig 6). Multifocal electroretinography is similar in sensitivity to VF, but is more objective and can be useful if properly performed. Sensitivity can be enhanced by calculating ratios between the amplitudes of response rings about the center. However, mfERG requires carefully calibrated equipment and experienced personnel, because recordings can be noisy, contaminated with artifact, and prone to false-positive abnormalities. Although mfERG is available in some large clinical centers and specialty offices, it is not widely accessible to the general ophthalmologist. Thus, it is not recommended routinely as a primary test.

Microperimetry

This procedure involves specialized instrumentation that localizes VF test flashes on the retina. In concept, it should be more reliable than automated perimetry, but in practice it is complicated by long examination times and patient fatigue, and it has not proven to be more revealing. It is only sparsely available, and different test patterns are needed for European and East Asian eyes.

Tests Not Recommended for Screening

Fundus Examination and Photography. Ophthalmoscopy is not a screening tool because photoreceptor damage is detectable with other techniques long before changes in the fundus become visible with ophthalmoscopy. Visible damage on fundus examination or in color photographs implies RPE disruption, which is already an advanced stage of toxicity.

OCT Angiography. This shows vascular changes such as capillary density in the inner retina, and it has been used increasingly for inner diseases. However, vascular changes have not been consistently correlated with HCQ toxicity until macular damage is late and severe.

Time-Domain OCT. The resolution is not sufficient to detect early toxic changes.

Fluorescein Angiography. This may reveal RPE defects, but these are late changes.

Full-Field Electrophoretinography. Full-field electroretinography is a global test of retinal function and will show only abnormalities that extend beyond the macula in very late diffuse toxicity that affects the entire retina.

Amsler Grid. Amsler grid testing is not consistent enough for reliable screening of subtle scotomas.

Color Vision Testing. Color errors may occur in late toxicity but are not sensitive or specific.

Electro-oculography. Electro-oculography has not been validated as a reliable screening test.

Screening for Toxicity

Rationale

Hydroxychloroquine retinopathy is generally not reversible except possibly at the very earliest stages of toxicity, and cellular damage can progress significantly if HCQ is not stopped before damage becomes severe. Screening is performed not only to “prevent” serious HCQ toxicity but also to recognize retinal changes while they are sufficiently early and mild so patients can consider options to extend their use of an important drug while minimizing further damage and potential visual loss.

Hydroxychloroquine is an effective therapeutic agent, especially for patients with SLE, and has fewer systemic side effects than many alternative medications for systemic immune or inflammatory diseases. With proper dosing and annual screening, most patients can take HCQ for decades with a low risk of retinal toxicity.

Recommended Screening Tests

We recommend macular OCT and wide-pattern FAF as the primary and objective screening tests. Because the VF is subjective and of variable reliability, it is no longer recommended as a primary method of screening. However, when subtle or inconclusive signs are noted with the OCT or FAF, or FAF is not available, verification of toxicity sometimes can be established with confirmatory procedures such as VF or mfERG.

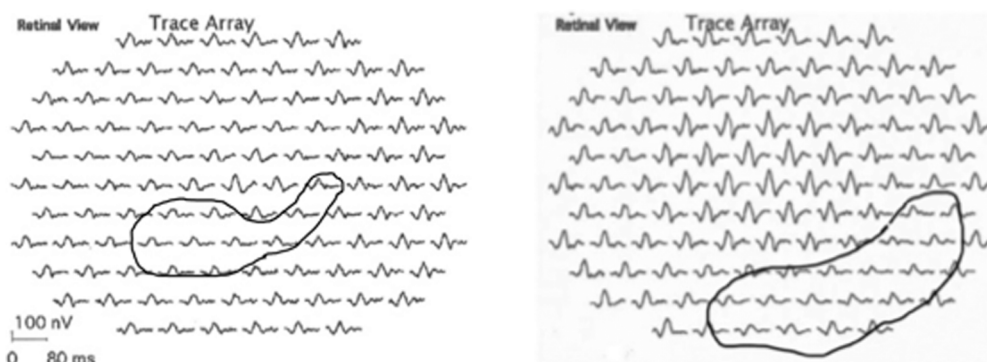


Figure 6. Multifocal electroretinography (mfERG) findings in hydroxychloroquine (HCQ) retinopathy. Trace arrays from early retinopathy. Parafoveal disease (left) shows weak signals in rings just outside the fovea. Pericentral disease (right) shows diminished signals in more peripheral rings. (Modified from Marmor et al¹).

Table 3. Screening Frequency

Baseline Screening
Obtain baseline close to the initiation of HCQ
Include fundus examination, OCT, and wide-pattern FAF
Annual Screening on HCQ
Annual screening is strongly recommended
Can defer until after 5 yrs of HCQ use if no significant risk factors
Begin at initiation of therapy if significant risk factors present
Include OCT and wide-pattern FAF

FAF = fundus autofluorescence; HCQ = hydroxychloroquine.

Baseline Examination

We strongly advise performing a baseline examination close to the initiation of HCQ therapy (Table 3). This should include fundus examination, OCT, and wide-pattern FAF. There are several reasons for this recommendation. First, other conditions such as lupus retinopathy may be present and unrecognized. Second, although the likelihood of an unrelated acquired or hereditary maculopathy is low, it could be a contraindication. Third, preexisting abnormalities in fundus appearance or test results can mimic diagnostic signs for HCQ retinopathy, thereby interfering with the ability to screen for toxicity. Fourth, baseline findings establish a reference point for comparison with later test results that might seem of uncertain relevance. Preexisting abnormalities in the OCT scan (e.g., drusen or RPE defects) or autofluorescence abnormalities on FAF need to be recognized and described at baseline.

Finally, the baseline examination provides an important opportunity for the ophthalmologist to educate patients and medical providers about HCQ dosage and risk factors, and to advise them about these guidelines and the importance of regular screening.

Annual Screening

Given the initial low risk of HCQ retinopathy on a proper dose and in the absence of significant risk factors, deferral of annual screening during the first 5 years of exposure is reasonable, as long as screening will be started reliably after 5 years. However, if significant risk factors are present (Table 1), annual screening should begin at the initiation of HCQ.

We consider screening annually to be sufficient and very important. It is sufficient because toxicity develops slowly, and this allows time to repeat tests or perform additional tests whenever results are suspicious but not definitive. It is important, because regular screening facilitates recognition of retinal thinning that signals the end of stability and the beginning of a slide into retinopathy. This becomes more likely after 5 years of HCQ, although it may not begin until 10 or more years later. More frequent screening may be considered for patients with strong risk factors that could accelerate toxicity or when ambiguous signs of toxicity are detected. It is important to check dosage relative to weight at every visit and to ask about changes in systemic status such as kidney disease, tamoxifen use, or major weight loss.

Compliance

Unfortunately, many studies have shown that compliance with HCQ screening recommendations is fair at best. In many large ophthalmology clinics and in rheumatologic (or medical) practices, a significant subset of patients take more than the recommended dose of HCQ or fail to undergo baseline and proper screening examinations. Thus, it is important for eye care providers not only to use these recommendations in their own practice but also to share the information regularly with patients and referring physicians. Hopefully, as compliance becomes more prevalent, the incidence of HCQ toxicity will decrease.

Management of Retinopathy

Progression after Stopping HCQ

If retinopathy is not recognized until RPE disruption and the appearance of bull's-eye maculopathy, the disease is likely to progress to foveal thinning and eventual loss of central visual acuity. This late progression over years may represent a gradual decompensation of cells that were injured metabolically during the period of drug exposure. However, when retinopathy is recognized earlier, before EZ loss is extensive and before loss of the ELM, there is typically only mild and limited progression for 1 year or so after discontinuing the medication.^{8,9} The OCT signs usually stabilize at that point, long before there is foveal damage, so there is minimal if any further risk of visual loss. In other words, the long-term risk to central vision is very low with HCQ use if toxicity is recognized before widespread EZ loss. We suggest that patients with extensive signs of toxicity when HCQ is discontinued be followed for several additional years to assess stability.

Some recent data suggest that lowering dosage, such as halving the daily dose, may stop the acute progression of thinning and EZ loss. However, the duration of this effect is unknown, and long-term data are not yet available.

Therapy

No diet or medical therapy has proven effective to prevent, treat, or reduce risk from HCQ or CQ retinopathy other than cessation or dose reduction of the drug. Patients with age-related maculopathy or macular dystrophies are sometimes advised to avoid excessive sun exposure and maintain intake of lutein and zeaxanthin (which are foveal protectants), and these measures might be considered for patients using HCQ or with retinopathy. However, the value of such recommendations is unknown. Discontinuing the drug and possibly lowering the dose with close observation are the only proven means of slowing or stopping the progression of damage.

Should HCQ Always Be Stopped with Signs of Retinopathy?

Once probable or definitive signs of retinopathy are recognized, the decision to stop HCQ or CQ should be

considered in collaboration with the patient and the prescribing medical physician. Many patients will choose to stop these drugs to eliminate any further risk to their vision, especially those with disorders such as rheumatoid arthritis for which other effective medications are available. However, patients with severe systemic diseases, such as active lupus erythematosus, may not have good therapeutic alternatives and may choose (in consultation with their medical caregivers) to continue HCQ as long as possible. These choices have become more difficult with our increasing ability to detect minimal or “preclinical” HCQ toxicity. Some of these patients may want to continue HCQ with cautious observation, perhaps at a lower daily dose, until signs of retinopathy are more definitive or nearer to a point that would signal visual risk. The ultimate decision should include the patient and the prescribing physician, rather than the ophthalmologist alone.

Technology on the Horizon

This section briefly highlights new diagnostic technologies that may contribute in time to HCQ screening. None are readily available at present or of proven value, but readers should be aware of active research in this area.

Adaptive optics imaging enables high-resolution visualization of retinal cells and may allow for the early detection of HCQ damage. However, adaptive optics

systems require specialized equipment and can take a long time to record.

Artificial intelligence has shown promise in automating the analysis of OCT images and mfERG records to recognize early signs of HCQ toxicity. The nature of these changes is not fully understood, but AI is likely to become a clinical tool within several years.

En face OCT imaging allows clinicians to assess specific retinal layers (e.g., EZ) at various depths, providing a fundus view that can show where early damage is occurring.^{10,11} Thinning can be observed in ETDRS plots or fundus thickness images on present machines, but more sophisticated layer analysis and tissue recognition require tools that are not yet standardized for sensitivity and accuracy.

Automated retinal layer segmentation would enable more precise tracking of thickness changes. Sequential analysis has already demonstrated retinal thinning years before other morphologic changes, and recognition of EZ-RPE thickness may have even greater specificity to HCQ toxicity. However, segmentation algorithms have not been standardized.

Advanced autofluorescence techniques are being explored.¹¹ Fluorescence lifetime imaging ophthalmoscopy is an emerging technology that may detect early HCQ toxicity by showing retinal metabolic changes. Quantitative autofluorescence and near-infrared autofluorescence can reveal paracentral rings of altered signal that correlate with retinopathy changes. These techniques hold promise but require specialized equipment.

Footnotes and Disclosures

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¹ Department of Ophthalmology, Stanford University School of Medicine, Palo Alto, California.

² Department of Ophthalmology, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Republic of Korea.

³ Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.

⁴ Department of Ophthalmology, Veterans Affairs Medical Center, San Francisco, California.

⁵ Department of Ophthalmology and Visual Sciences, Illinois Eye and Ear Infirmary, University of Illinois at Chicago, Chicago, Illinois.

⁶ Stein Eye Institute, University of California at Los Angeles, Los Angeles, California.

⁷ Oxford Eye Hospital & University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom.

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Conception and design: Marmor, Ahn, Ehlers, Melles, Mieler, Sarraf, Yusuf

Data collection: Marmor, Ahn, Ehlers, Melles, Mieler, Sarraf, Yusuf

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Abbreviations and Acronyms:

AAO = American Academy of Ophthalmology; **AI** = artificial intelligence; **CQ** = chloroquine; **ELM** = external limiting membrane; **EZ** = ellipsoid zone; **FAF** = fundus autofluorescence; **HCQ** = hydroxychloroquine; **IZ** = interdigitation zone;

mfERG = multifocal electroretinography; **RPE** = retinal pigment epithelium; **SLE** = systemic lupus erythematosus; **VF** = visual field.

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Correspondence:

Meghan Daly, American Academy of Ophthalmology 655 Beach Street, San Francisco, CA 94109. E-mail: mdaly@aao.org.

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