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Plaquenil Toxicity

What is plaquenil?

Hydroxychloroquine, also known as plaquenil, is a medication that has been in use for several decades. It is effective as a prophylaxis for malaria, but in practice we are more accustomed to seeing it as a treatment for certain autoimmune conditions such as rheumatoid arthritis or systemic lupus erythematosus. These conditions are chronic diseases that require long-term immunosuppression. As such, patients are typically on plaquenil for several years.

Although plaquenil is typically well-tolerated, as with any immunosuppressant it does have side effects. Of particular interest to our specialty are the ocular side effects. Plaquenil is known to affect the cornea, ciliary body, and retina. In the cornea it can produce whorl-like intraepithelial deposits that are usually not visually significant and are reversible upon discontinuation of the medication. In the retina, however, plaquenil can lead to permanent damage to the macular photoreceptors, and—if not addressed in a timely manner—significant and permanent loss of central vision.[1]

Eye doctors are often tasked with screening for and detecting early signs of plaquenil toxicity. The mechanism of toxicity is not completely clear, but it is known that plaquenil tends to deposit in tissues with high melanin content such as the retinal pigment epithelium (RPE). By slowly accumulating within the RPE over years of repeated dosing, it is believed that plaquenil adversely impacts retinal metabolism, which can lead to slow and chronic toxic effects that ultimately damage photoreceptors.[2]

Findings in plaquenil toxicity

The classic exam finding in plaquenil toxicity is a b ull's eye maculopathy, in which there is bilateral and symmetric granular depigmentation of the RPE in the macula (Fig. 1). This ultimately progresses to concentric rings of hyper- and hypopigmentation surrounding the fovea. Along with these findings, patients may experience changes in color perception and dark adaptation, as well as central or paracentral scotomas. If plaquenil use continues, they will ultimately experience frank vision loss. However, bull's eye maculopathy and such symptoms occur in the late stages of toxicity, and our role is to ideally detect toxicity long before these changes develop.

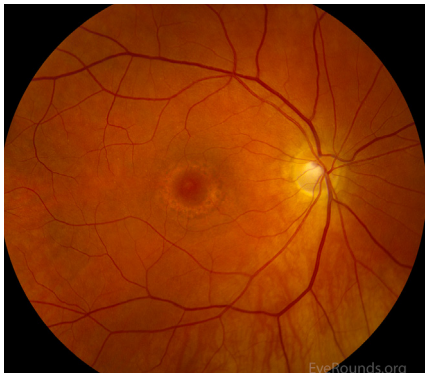

Figure 2: Bull's eye maculopathy on fundus photography.[6]

Some of the earliest signs of plaquenil toxicity are detectable on ancillary testing, even before fundus findings develop. Optical coherence tomography (OCT) shows disruption in the parafoveal ellipsoid zone, which is the junction between the inner and outer photoreceptor segments (Fig. 2). Ultimately this can progress to parafoveal outer retinal atrophy with an island of foveal sparing. In similar fashion, fundus autofluorescence (FAF) can show hyperautofluorescence in a concentric ring aroundthe fovea (Fig. 3a). This is an early sign of parafoveal photoreceptor damage and can even precede OCT findings. Eventually this can evolve into a hypoautofluorescent ring as the RPE atrophies from ongoing damage (Fig 3b).[3] Interestingly, recent evidence has shown that patients of

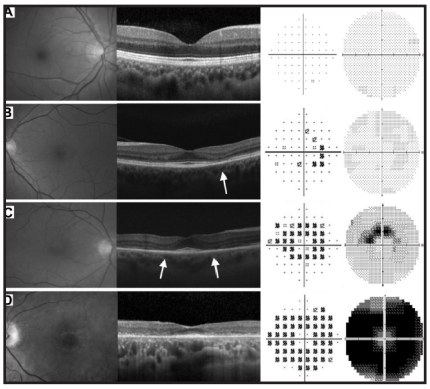

Figure 2: Evolution of plaquenil toxicity on infrared reflectance imaging (left), spectral domain OCT (middle), and HVF 10-2 (right).5 In 2a there is a healthy-appearing OCT with intact ellipsoid zone (EZ) and full HVF; in 2b there is some thinning of the EZ temporally (arrow) and some corresponding paracentral VF defects; in 2c there is now a symmetric thinning of the EZ in the paracentral area (arrows), which spares the fovea, and a ring-like defect developing on the VF; in 2d there is nearly complete atrophy of the parafoveal outer retina (again sparing the fovea) and much more significant paracentral scotoma on VF. In 2d a bull's eye maculopathy is now visible on the infrared relfectance imaging.

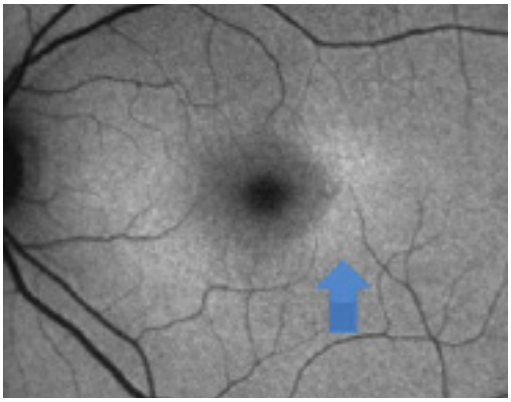

Figure 3a: Fundus autofluorescence showing hyperautofluorescence (arrow) in early plaquenil toxicity.[5]

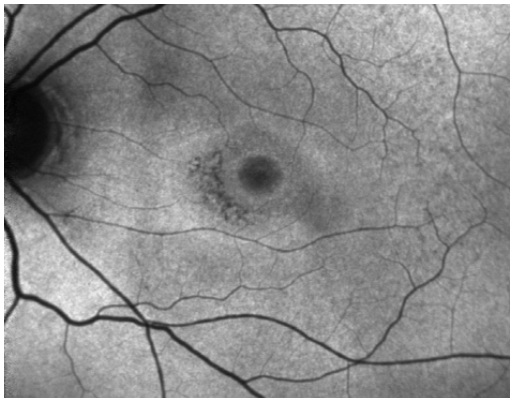

Figure 3b: Fundus autofluorescence showing mottled hypoautofluorescent changes in later stages of plaquenil toxicity.

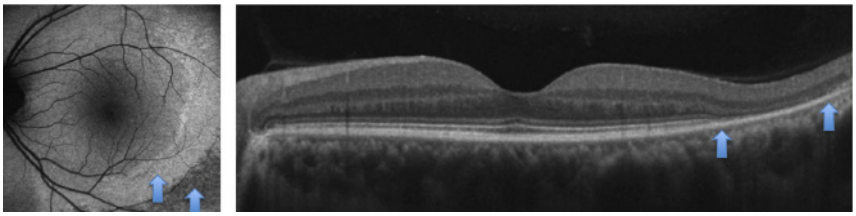

Figure 4: Fundus autofluorescence (left) and SD-OCT (right) in an Asian patient showing hyperautofluorescence and outer retinal thinning due to plaquenil toxicity in a more peripheral distribution.[5]

Asian descent develop toxicity in a more peripheral distribution, oftentimes near the arcades (Fig. 4).[4] It is important to keep this in mind when examining patients with this background, as testing that is focused only on the parafoveal area may easily miss early signs of toxicity.

Functional studies such as Humphrey Visual Fields (HVF) and multifocal electroretinogram (mfERG) are also useful in detecting plaquenil toxicity. As expected, patients with toxicity will demonstrate a paracentral scotoma on HVF. Since findings are typically central, an HVF 10-2 will effectively pick up any abnormalities (Fig. 2). However, as mentioned previously, Asian patients may have more peripheral findings, so a 24-2 or 30-2 is more appropriate in these scenarios. Evaluation with mfERG requires specialized equipment. This is typically only available at large academic centers and therefore not used widely in general clinical practice. It is quite effective at detecting toxicity, however, and shows depression in the parafoveal or extramacular area even in the earliest stages.[5]

Risk factors

Plaquenil toxicity does not affect everyone on the medication, and so knowing the risk factors for toxicity is useful in evaluating and counseling patients:[5]

Daily dose

The most critical risk factor is daily dosage of plaquenil. The recommended daily dose has changed a few times since the first recommendations on plaquenil screening were published by the American Academy of Ophthalmology (AAO) in 2002. In 2016, the AAO published revised recommendations,[5] which established the recommended daily dose as <5.0 mg/kg/day of REAL body weight. Note that this is different than the 2011 guidelines which recommended a maximum dose of 6.5 mg/kg/day of IDEAL body weight. The rationale behind using ideal body weight was that short, overweight patients were at risk of being overdosed if their actual (real) body weight was used to calculate plaquenil dose. Further research, however, has indicated that real body weight is a better predictor of toxicity, and so the 2016 guidelines were amended to recommend a dose of <5.0 mg/kg/day of REAL body weight.

Cumulative amount of medication

A cumulative amount of plaquenil above and beyond 1000 grams significantly increases risk. Keep in mind that at a dose of 400 mg/day (a typical dosing regimen), this equates to approximately 6.8 years of use.

Duration of use

The risk of toxicity increases in an exponential manner in relation to duration of use. Up to five years of use, the risk is very low—less than 1%. Up to ten years, the risk increases a bit, but stays below 2%. The risk rises dramatically to 20% after 20 years of use.

Prior macular disease

Any prior macular disease can theoretically predispose patients to further toxicity as the macular health is already compromised. Additionally, macular disease can interfere with testing and potentially obscure early signs of toxicity. Concurrent use of other medications that can cause macular toxicity, such as tamoxifen, can also increase risk.

Renal disease

Plaquenil is cleared from the body through the kidneys, so kidney disease can prolong the time that plaquenil is in the body and in contact with the RPE.

Screening Recommendations

Since the goal of managing patients on plaquenil is to detect toxicity at an early stage (ideally before the patient is symptomatic), proper screening is of utmost importance. Screening recommendations have evolved over time, but as of the revised guidelines from the AAO in 2016,[5] it is recommended to get a baseline exam and imaging when the patient is started on plaquenil. After five years of use, examinations and imaging should be performed on at least an annual basis. Earlier and more frequent screening may be more prudent in patients with baseline macular changes or any of the above risk factors.

As far as imaging modalities are concerned, screening should be performed with an HVF and one of the following: FAF, spectral domain OCT, or mfERG.[5] Although patients will usually get a fundus exam at each visit, fundus exam/photography is not considered an effective screening tool as any detectable fundus changes are usually late findings of toxicity.

For visual field testing, an HVF 10-2 white-on-white pattern is usually sufficient, but as previously mentioned, a 24-2 or 30-2 is recommended in Asian patients in order to pick up more peripheral abnormalities. The central points in an HVF are very sensitive, and so any abnormality should be taken seriously and the test should be repeated to determine reproducibility.

Management

If plaquenil toxicity is detected, it is crucial to promptly notify the prescribing physician (usually a rheumatologist). Most of the time this will result in discontinuation of the plaquenil and transitioning to another medication. However, in some situations the patient may elect to stay on the plaquenil given the underlying systemic disease and potential side effects of alternative medications. In these situations it is important to have a discussion with the patient and prescribing physician and ensure all parties are aware of the risks of continuation. Fortunately, plaquenil toxicity is usually asymptomatic in its earliest stages, but its effects are permanent and can continue to progress even after discontinuation. However, the amount of progression largely depends on the severity of the toxicity when discontinued; if detected early, progression is fairly minimal, but if detected late, progression can continue for years.[5] This further highlights the importance of screening and early detection.

References:

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NJRetina continuously conducts clinical trials at key locations. Our clinical research coordinators will be happy to discuss the inclusion/exclusion criteria or any other aspect of these studies with you or your patients. If you have any questions, please feel free to contact:

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Enrolling Studies:

Wet AMD

Edison

Opthea Coast: A Phase 3, Multicenter, Double-masked, Randomized Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Aflibercept, Compared with Aflibercept Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

Toms River

Opthea Shore: A Phase 3, Multicenter, Double-masked, Randomized Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Ranibizumab, Compared with Ranibizumab Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

Teaneck

Elevatum: A Phase IIIB/IV, Multicenter, Open-Label, Single-Arm Study to investigate Faricimab treatment in response to treatment-naïve, underrepresented patients with Diabetic Macular Edema

Teaneck

Luna: A Multi-Center, Randomized, Double-Masked Phase 2 Study to Assess Safety and Efficacy of ADVM-022 (AAV.7m8-aflibercept) in Anti-VEGF Treatment Experienced Patients with Neovascular (Wet) Age[1]related Macular Degeneration

Teaneck

Eye Point: A Phase 2, Multicenter, Prospective, Randomized, Double-Masked, Parallel Study of EYP-1901, a Tyrosine Kinase Inhibitor (TKI), Compared to Aflibercept in Subjects with Wet AMD

Diabetic Retinopathy

Teaneck

Ocuterra: A Phase 2 Randomized, Double-Masked, Vehicle[1] Controlled, Multicenter Study to Evaluate the Safety and Efficacy of OTT166 Ophthalmic Solution in the Treatment of Diabetic Retinopathy (DR)

Upcoming Studies:

GA / Dry AMD

Teaneck

Alexion: A Phase 2, Double-Masked, Placebo-Controlled, Dose Range Finding Study of Danicopan (ALXN2040) in Patients with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

Janssen: Phase 2/3, Randomized, Double-masked, Multicenter, Dose-ranging, Sham[1]Controlled Clinical Trial to Evaluate Intravitreal JNJ-81201887 (AAVCAGsCD59) Compared to Sham Procedure for the Treatment of Geographic Atrophy (GA) Secondary to Age-related Macular Degeneration

RVO

Teaneck, Toms River, Edison

Bayer Study: A Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of Aflibercept 8 mg With Macula Edema due to Retinal Vein Occlusion

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