Optometric Management of the New Plaquenil Screening Guidelines
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Chronic use of chloroquine and/or hydroxychloroquine is associated with retinal toxicity. While this effect is rare, it could lead to irreversible vision loss. We will review new guidelines available to optometrists that incorporate advanced imaging technology such as Fundus Auto Fluorescence and OCT for the management of patients using Plaquenil.

I. Case presentation
   a. History and chief complaint
   b. Objective findings: What would you order?
      i. Image analysis
         1. Color Fundus Photo
         2. RGB Filter
      ii. Ancillary testing
         1. HVF 10-2
         2. Auto Fluorescence
         3. mf ERG

II. Plaquenil
   a. Chloroquine (Aralen)
      i. Anti-parasitic, inhibits prostaglandin
         1. Labeled use: anti-malaria, however increased drug resistance has limited its use to certain areas.
         2. Off-label: RA, SLE
   b. Hydroxychloroquine (Plaquenil)
      i. Immunosuppressant, Anti-malarial
      ii. Significantly less retinal toxicity compared to chloroquine and has largely replaced the use of chloroquine for systemic treatment of inflammatory disease.
   c. Pharmacology
      i. Cleared by the liver, kidneys
      ii. Quinolone family (Aminoquinoline)
      iii. Long half life: progressive, irreversible toxicity
         1. Toxicity with chronic use: irreversible vision & hearing loss, myopathy, neuropathy, and cardiomyopathy.
      iv. Dosing for inflammatory disease
         1. “Safe dose” < 6.5 mg/kg/day, based on ideal weight
            a. Ideal weight: women = 100 lbs. + 5 lbs. for each inch over 5 feet; men = 110 lbs. + 5 lbs. for each inch over 5 feet.
            b. Overweight, obese patients are at risk of overdosing unless the medication is based on height and what their `should be.

III. Treatment of Systemic Disease
Chloroquine and hydroxychloroquine were initially used for the treatment of malaria, but presently, off-label use of hydroxychloroquine for inflammatory disease (RA, SLE) is more common. Hydroxychloroquine is an effective treatment and significantly increases quality of life in patients suffering from chronic, debilitating pain and inflammation from RA, SLE. Consider this when making recommendations for drug cessation.
   a. Rheumatoid Arthritis
i. Overview & Symptoms
   1. Ocular Manifestations

ii. Diagnostic testing
   1. ANA, CRP, CCP, ESR, PF, Synovial fluid...

iii. Treatment

b. Systemic Lupus Erythematous
   i. Overview & Symptoms
      1. Ocular manifestations
   ii. Diagnostic testing
      1. ANA, APL, CRP, ESR, Complement...
   iii. Treatment

c. Inflammatory, dermatologic conditions: Tx and prevention of graft-versus-host disease following stem cell transplantation.

d. Plaquenil Retinal Toxicity
   i. Risk Factors
      1. Dose
         a. Cumulative dose: >1,000g Hydroxychloroquine, >460g chloroquine*
            i. *Largest risk factor
         b. Daily dose: >6.5mg/kg (of ideal body weight)
            i. Reports of toxicity even at a ‘safe dose’
      2. Time
         a. 5 or more years of the typical daily dose is enough to achieve the cumulative risk
            i. Reports of toxicity as soon as 2 mos. treatment
      3. Pre-existing retinal or macular disease
         a. Masks signs of early retinopathy
         b. Increased risk
      4. Age > 60 yrs.
      5. Renal, hepatic disease
         a. Cleared by the kidney and liver
   ii. Cumulative (see above)
   iii. Rare
      1. National Registry of Drug-Induced Ocular Side Effects
      2. 6.8/1000 (Wolfe F, 2010).

e. Plaquenil Ocular Disease
   i. Corneal verticillata
      1. Salt deposit in the corneal epithelium
      2. Asymptomatic
      3. Reversible with discontinuation of medication
      4. Non-Toxic and not correlated to retinal toxicity, therefore NOT an indication to stop medication
   ii. Retinal toxicity: bilateral pigmentary retinopathy
      1. Retinal toxicity first described in 1959 (Chloroquine), and then 1967 (hydroxychloroquine).
      2. Retinal toxicity is generally irreversible- early detection and medication cessation will limit extent of vision loss.
   iii. Symptoms
      1. c.c: difficulty reading, decreased and/ or blurred vision, central vision loss, light flashes or photopsias (whirled, flashing lights), metamorphopsia
a. Early stage: Asymptomatic
b. Late stage: Paracentral and Central Scotoma
c. End stage: loss of central vision, loss of peripheral vision, loss of night vision

iv. Signs
1. Anterior Segment
   a. Corneal verticillata
2. Posterior Segment: once visible changes occur in the retina, vision loss is irreversible and may progress even after medication cessation.
   a. Bull’s eye maculopathy indicates advanced toxicity: RPE depigmentation of the macula, foveal sparing (hence bull’s eye appearance).
      i. Largely irreversible at this stage
   b. Widespread RPE and retinal atrophy

v. Referral

a. Plaquenil Screening: early detection of retinal toxicity is key to prevent or limit vision loss. The goal of screening is to detect toxicity BEFORE visual fundus changes occur.
b. Baseline Examination once the medication is initiated, mainly to rule out macular disease that could contraindicate use or complicate screening.
   i. HVF 10-2 (subjective)
      1. Performed at each screening visit
      2. Look for subtle paracentral VF defects
         a. 10-2 white pattern deviation plots or red 10-2 fields: damage is often a loss of sensitivity 2 - 6 degrees off center.
         b. Even the most subtle change should be thoroughly evaluated with additional objective testing.
            i. Defects in the 2-6 degree zone are significant
      3. In progressive disease, look for paracentral and central/foveal defects.
      4. In late stage/advanced disease, there is paracentral scotoma.
   ii. Biomicroscopy/DFE + Color Fundus Photo (Adjunctive)
      *Color fundus photography is not part of the recommended screening but can be used for documentation.*
      1. There are NO visible changes in early disease: Document this!
      2. In advanced stage: Bull’s eye maculopathy. Look for macular pigmentation change, specifically paracentral RPE pigment loss.
         a. Image analysis of color fundus photo
         b. Software driven Red Green Blue filter
   iii. SD-OCT or mf ERG or FAF (Objective)
      At least one of these objective tests should be done in addition to above, these tests are considered more sensitive than visual fields.
      1. SD-OCT
         a. Spectral Domain (SD) versus Time Domain
         b. What are we looking at?
         c. What are we looking for?
i. Loss of IS-OS junction line in para or peri foveal region.
ii. Thinning of outer retinal layers.

2. Fundus Auto-Fluorescence (FAF)
   a. Note any change in fluorescence
   b. Late stage: Look for increased fluorescence (hyperfluorescence) in the parafoveal region (bull’s eye maculopathy)

3. mf ERG
   a. Can be used in place of HVF 10-2
   b. International Society for Clinical Electrophysiology of Vision guidelines
      i. Look for relative signal weakness in parafoveal rings.
   c. Annual screening after 5 years of Plaquenil treatment
      i. Toxicity is rare before 5 yrs., unless other risk factors are present (see above, risk factors).
      ii. Many practitioners begin annual testing during the 5 yr. hiatus to get patients accustomed to screening and prevent patient loss to follow-up.
      iii. Note what’s missing (these tests are not sensitive enough to detect retinal toxicity early enough to prevent significant vision loss).
         1. Amsler Grid
         2. Color Vision
         3. TD OCT
            a. Does not have the resolution to detect changes in the IS-OS line or outer retina.
         4. Fluorescein Angiography
         5. full field ERG
         6. EOG
   d. Annual screening after 5 years or cumulative dose> 1000 grams
   e. Sooner if additional risk factors or early toxicity suspected

V. Beyond Plaquenil
   a. Other common ocular toxic agents
      i. Bisphosphonates (osteoporosis, loss of bone mass). Assoc., w. blurred vision, anterior uveitis and episcleritis.
      ii. Cetirizine (Zyrtec, antihistamine), pupillary changes, blurred vision, keratoconjunctivitis sicca, especially in children.
      iii. Erectile dysfunction, changes in color, light perception, blurred vision, conjunctival hyperemia, ocular pain, photophobia.
      iv. Ethambutol (Myambutol, pulmonary TB), over 800 reports to Registry. Optic, retrobulbar neuritis (uni or bilateral), rare assoc. w. peripheral VF constriction
         1. Monthly ophthalmic exams are recommended for doses of ethambutol exceeding 15 mg/kg/day.
      v. Fluoroquinolones, topical: corneal precipitates, possible uveitis.
      vi. Hepatitis B vaccine, possible uveitis.
      vii. Retinoids (severe, recalcitrant acne, psoriasis, leukemia remission), intracranial hypertension, papilledema.
viii. Tamsulosin (Flomax, benign prostatic hyperplasia, hypertension), intraoperative floppy iris syndrome, caution in cataract surgery candidates.

ix. Topiramate (Topamax, epilepsy, migraines, off-label for weight loss, bipolar disorder, depression). Associated with acute angle-closure glaucoma, transient myopia.

x. Statins, diplopia, ptosis, ophthalmoplegia. May exacerbate myasthenia gravis, cataracts.

b. 2004 World Health Organization on common herbal medicine and their visual symptom reactions.


i. Note: this is not up to date with new Plaquenil screening guidelines.

VI. Suggested Reading