Chloroquine (CQ) & Hydroxychloroquine (HCQ) Background

Hydroxychloroquine sulfate
- Chloroquine (CQ) first synthesized in 1930s by Hans Andersag
- Alternative to quinine (found in Peruvian tree bark)
- Original use → combat malaria in WWII
- Less toxic form, hydroxychloroquine (HCQ) developed later
- Started being used in 1950's, toxicity first noted 1963
  - CQ → 1953 first use
  - HCQ → 1955 first use
- Who’s on what in today’s world?
  - 2-3% on CQ
  - 98-99% on HCQ


Chloroquine (CQ) vs. Hydroxychloroquine (HCQ)
- Similar molecular structures
- Strong absorption by melanin
  - Poor absorption in fatty tissues
- Retinal toxicity: CQ > HCQ
  - HCQ has ↓ tissue accumulation than CQ

“HCQ is a lipophilic base that passes easily across cell membranes... It has been postulated that the lower toxicity of HCQ compared with CQ may be due to the hydroxyl group limiting the ability of HCQ to cross the bloodretinal barrier.”
Many therapeutic MOA’s of CQ and HCQ...

- **MOA**: Decreased formation of peptide-MHC protein complexes required to stimulate CD4+ T cells → down-regulation of the immune response against autoantigenic peptides → immunosuppression!
  - "Disrupts T-cell receptor calcium signaling → reduces antigen processing"
  - "Increases pH that interferes with lysosome function → poor antigen presentation"
  - "Inhibits dendritic cells"
  - "Inhibits interferon-Alpha production"
  - "Counteracts neutrophil oxidant production"
  - "Inhibits prostaglandin and cytokine production"
  - "Inhibits autophagy of subset of T-cells → possible use in oncology!"


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**Bottom Line:**

- **Immunosuppression!**
  - "HCQ is used mainly in RA and SLE. Most of its benefits have been well described elsewhere, mainly in the context of lupus: reduction of flares and damage, enhancement of MMF response, improvement of survival, and reduced risk of seizures and thromboses... which translates into immunosuppressive, antiproliferative, antithrombotic and photoprotective effects."

**LUMINA Study (2007)**

- 608 patients with SLE followed over 3+ years
  - [+] Plaquenil 9/61 = 14.7% deaths
  - [-] Plaquenil 42/61 = 68.9% deaths

"It is likely that the use of HCQ in SLE will increase significantly following publication of the LUMINA study, which demonstrated a clear survival benefit of HCQ therapy in patients with SLE."


**Systemic SE’s of HCQ**

- Headache
- Anxiety/depression
- Tinnitus
- GI disturbances
- Skin rashes

**Ocular toxicities:**

- Cornea
- Retina

**Quick sidebar...**

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


**Longer survival with HCQ treatment in SLE?**

- "HCQ is used mainly in RA and SLE. Most of its benefits have been well described elsewhere, mainly in the context of lupus: reduction of flares and damage, enhancement of MMF response, improvement of survival, and reduced risk of seizures and thromboses... which translates into immunosuppressive, antiproliferative, antithrombotic and photoprotective effects."

- "It is likely that the use of HCQ in SLE will increase significantly following publication of the LUMINA study, which demonstrated a clear survival benefit of HCQ therapy in patients with SLE."

**We have to be ready for more HCQ patients walking in our doors!**
Symptoms of HCQ retinal toxicity...

- Asymptomatic!
- Decreased/blurry vision
- Central vision loss
- Scotomas
- Reading difficulty
- Glare
- Photopsia
- Metamorphopsia
- Color vision disturbances/reduction

Bull’s Eye Retinopathy

- “textbook” sign of HCQ and CQ toxicity is a ring of depigmentation near the foveal center
- Ring scotoma too

- “…the idea that these findings are “characteristic” comes from older literature and a time when retinopathy was not easily confirmed until a bull’s eye was visible. With automated fields and modern imaging technology, unmistakable signs of toxicity can be recognized years before the bull’s eye stage is apparent and before the patient has any visual symptoms. Bull’s eye retinopathy is actually a rather late and severe stage of damage that should not be seen at all with proper management.”

MOA of retinal toxicity...

- Exact pathophysiology – poorly understood & elusive

- “The actual mechanism of retinal toxicity is not well established. Primate studies suggest that the earliest detectable changes are in the neural retina (specifically ganglion cells and photoreceptors), with RPE changes occurring later. In vitro studies on cultured RPE cells suggest that HCQ alters RPE lysosome pH, resulting in higher levels of lipofuscin, a type of pigment that commonly accumulates with age and is associated with photoreceptor degeneration.”

- Can we simplify this please?!
  - RPE lysosomal disruption → accumulation of lipofuscin → photoreceptor degeneration

Why the “ring” or paracentral pattern of toxicity?

- “It is currently unclear why the photoreceptors in the parafovea/perifovea are most vulnerable to the toxic effects of HCQ seen clinically.”

What retinal layers are we actually worried about?

Which retinal layers are most affected?

• “Although the mechanism of HCQ toxicity is unclear, as animal experiments have shown the drug can affect all retinal layers, the damage observed in clinical imaging is primarily to the outer retina.”

Where does pathology/toxicity actually start in the retina?

• Based on work by Rosenthal in 1978!
  - Ganglion cell layer!

• “The exact mechanism of retinal toxicity is still under investigation. Despite the evident clinical changes in retinal pigmented epithelium (RPE) when the maculopathy is already visible, studies in animals after long exposure to chloroquine demonstrated that the first site of damage is most probably the ganglion cell layer.”

But I’m not convinced on clinical usefulness… let’s look at the numbers…

GCC in HCQ patients?

• There was significant thinning of the macular GC-IPL in the absence of clinically evident HCQ-related retinopathy and VF abnormalities. Measurements of the macular GC-IPL thickness using SD-OCT may therefore be useful in the early diagnosis and in monitoring the progression of retinal changes in patients receiving long-term HCQ therapy.

RPE vs. PIL → which is affected first?

1. RPE 1st, photoreceptors 2nd, then clinical RPE degeneration?
   • “An evaluation of ocular tissues after long term administration of chloroquine in rhesus monkeys revealed widespread binding of chloroquine in pigmented ocular tissues: the RPE, iris, choroid and ciliary body with eventual accumulation observed in the retina. Drug accumulation within the RPE may explain the progression of HCQ retinopathy after drug cessation in some patients. This may result in outer retinal and photoreceptor degeneration with later, secondary degeneration of the RPE.”

2. Photoreceptors 1st, then clinical RPE degeneration?
   • “Antimalarials bind to melanin in RPE, but clinical degeneration of RPE cells does not take place until the overlying photoreceptors are almost gone, which argues against the RPE as the primary site of pathology. The exact mechanism of HCQ toxicity remains elusive.”

Summary Pathophysiology

• “…animal models of chloroquine toxicity have demonstrated inner-retinal changes (lysosomal damage in the ganglion and bipolar cells) as the first abnormality that ultimately progresses to lysosomal disruption in the photoreceptors or RPE…”
• “…Despite this controversy, this body of research has applied novel segmentation algorithms, which consistently demonstrate paracentral outer retinal thinning in the setting of toxicity.”

Clinical Bottom Line: focus on PIL/RPE junction!
Stats for HCQ Toxicity

Old vs. New: What do we know?

<table>
<thead>
<tr>
<th></th>
<th>Old/Historical Data</th>
<th>New Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall toxicity prevalence</td>
<td>~1% patients &gt;5 yrs HCQ use</td>
<td>~7.5% patients &gt;5 yrs HCQ use</td>
</tr>
<tr>
<td>Patients that are overdosed</td>
<td>Up to 12%</td>
<td>Up to 30-56%</td>
</tr>
<tr>
<td>Ideal body weight vs. actual body weight</td>
<td>IBW</td>
<td>ABW</td>
</tr>
<tr>
<td>Daily dose considered toxic</td>
<td>&gt;6.5 mg/kg/day (IDW)</td>
<td>&gt;5.0 mg/kg/day (ADW)</td>
</tr>
<tr>
<td>Daily dose considered non-toxic</td>
<td>≤6.5 mg/kg/day (IDW)</td>
<td>≤5.0 mg/kg/day (ADW)</td>
</tr>
<tr>
<td>Cumulative dose thresholds</td>
<td>&gt;1000 g</td>
<td>&gt;1000 g</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;60 years</td>
<td>Not a risk factor</td>
</tr>
</tbody>
</table>

New Thoughts: Ideal Body Weight vs. Actual/Real Body Weight???

- ABW correlates better with retinal toxicity
- ABW is simpler to calculate
- Less risk of overdosing thinner/nobese patients with ABW

"We propose the use of real body weight for dosage calculation because it correlates better with retinal toxicity than ideal body weight... Maintaining daily use at 5.0 mg/kg or less would keep both the cumulative risk and annual risk of retinal toxicity low, especially for the first 10 years of use."


Risk Factors

- *Daily dose
- *Duration of use
- *Cumulative dose
- Renal disease
- Concurrent tamoxifen use → new!
- Lower body weight

Toxicity Risk: Daily Dose

- Based on Ideal Body Weight (IBW):
  - >6.5 mg/kg/day HCQ is typical of retinal toxicity, historically
  - ≤6.5 mg/kg/day HCQ considered safe, historically

- Based on Actual Body Weight (ABW):
  - >5.0 mg/kg/day HCQ = increased risk of toxicity
  - ≤5.0 mg/kg/day HCQ = lower risk

How many people on HCQ are overdosed?

  - n=675 patients on HCQ
  - 56% females/44% males → overdosed!

- Wolfe F, Marmor MF. Arthritis Care Res (Hoboken). 2010
  - n = 3995 patients on HCQ
  - 53.6% patients overdosed

  - 30% patients overdosed based on IDW
  - 10% patients overdosed based on ADW

Of those that develop toxicity, how many are overdosed?

  - n=121
  - 11.6% patients developed toxicity (n = 14/121)
  - 78.6% (n11/14) were overdosed

  - n=123
  - 13.8% developed toxicity (n=17/123)
  - 76% were overdosed (n=13/17)

Notable quotes on overdosing!

- "Rheumatologists should focus on the recommended dosage of HCQ≤5 mg/kg/day and start regular ophthalmologic screening according to the risk factors."

- "...we recommend that all patients using HCQ keep daily dosage <5.0 mg/kg real weight. Following this guideline will minimize the risk of retinopathy and allow long-term use of HCQ for most patients."

The Calculation: Daily Dosing

\[
\text{Body Weight(lbs)} \div 2.2 \text{ lbs} = \text{ weight in kilograms}
\]

\[
\text{Total daily dose (mg) x} \frac{1}{\text{body weight (kg)}} = \text{ dose of mg/kg/day}
\]

Example of daily dose calculation...

- 50 YO WF with history of RA
- Weighs 140 lbs (ABW)
- Takes HCQ 200 mg BID PO → 400 mg/day

\[
\frac{140 \text{ lbs}}{2.2 \text{ lbs}} = 63.63 \text{ kg}
\]

\[
400 \text{ mg/day} \times \frac{1}{63.63 \text{ kg}} = 6.29 \text{ mg/kg/day}
\]

Another example of daily dose calculation...

- Same 50 YO WF with history of RA
- Weighs 140 lbs (ABW)
- Takes HCQ 200 mg BID every other day → 300 mg/day

\[
\frac{140 \text{ lbs}}{2.2 \text{ lbs}} = 63.63 \text{ kg}
\]

\[
300 \text{ mg/day} \times \frac{1}{63.63 \text{ kg}} = 4.71 \text{ mg/kg/day}
\]
**Toxicity Risk: Duration of Use**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Duration</th>
<th>Toxicity Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5.0 mg/kg/day</td>
<td>10 yrs</td>
<td>8%</td>
</tr>
<tr>
<td>&gt;5.0 mg/kg/day</td>
<td>15 yrs</td>
<td>12%</td>
</tr>
<tr>
<td>&gt;5.0 mg/kg/day</td>
<td>20 yrs</td>
<td>16%</td>
</tr>
</tbody>
</table>

**Toxicity Risk: Cumulative Dose**

- >1000 g HCQ lifetime dose = highest risk!
- Same as it’s been forever!
- One study reported 86% of patients with HCQ toxicity had cumulative dose >1000 g

Marmor et al. Ophthalmology 2016 → Updated plaquenil guidelines

**How do you calculate cumulative dose again?**

- Same patient as before....
- 50 YO WF with RA on Plaquenil 200 mg BID x 10 years
  - 200 mg BID = 400 mg daily
  - 400 mg x 365 days = 146 g/year
  - 146 g x 12 years = 1752 grams total!

**2016 Plaquenil AAO Risk Factors**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Increased HCQ Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily dose</strong></td>
<td>&gt;5.0 mg/kg/day</td>
</tr>
<tr>
<td><em>Cumulative dose</em></td>
<td>&gt;1000 g lifetime</td>
</tr>
<tr>
<td><em>Duration of use</em></td>
<td>&gt;5-7 years (~20% risk after 20 yrs of Tx)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>(+) 2x increased risk</td>
</tr>
<tr>
<td>Tamoxifen use</td>
<td>(+) 5x increased risk</td>
</tr>
<tr>
<td>Obesity/Overweight</td>
<td>(+)</td>
</tr>
<tr>
<td>Age</td>
<td>1-risk factor per 2016 guidelines</td>
</tr>
</tbody>
</table>

**HCQ Screening**

2002 guidelines → 2011 guidelines → 2016 guidelines

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**New Screening Guidelines in 2016!**

**Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)**

Michael T. Marmor, MD; Edward Ellefson, MD; Timothy Y.V. Lee, MD; E.R. de Jager; Ronald B. Miller, MD; William F. Witter, MD, for the American Academy of Ophthalmology

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**Why the new updates to the 2016 guidelines?**

- "Despite the existence of published guidelines, screening practices often have been inconsistent or deficient...The recommendations in this revision are more concise and practical than the prior version, to encourage wider compliance."

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**Goal of screening?**

- The AAO recently proposed screening recommendations for HCQ retinopathy. These recommendations state that the goal of screening for HCQ retinopathy is not to discontinue the valuable drug when there are borderline abnormalities, but to recognize definitive signs of toxicity at an early enough stage to prevent vision loss.


- Although it is important to be sensitive to signs of damage in a typical pattern, it is also important to verify such signs with more than 1 test or by repeat testing.


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**What is purpose of screening?**

- "...screening may not “prevent” damage, but if conducted properly it enables the detection of toxicity before vision is significantly affected. It is important to emphasize that HCQ and CQ are useful drugs and that they have fewer systemic side effects than many of the alternative medications used for immune or inflammatory diseases. Thus, screening can be viewed as a means of helping patients to continue HCQ or CQ (by not stopping the drugs for uncertain findings) as much as a means of preventing serious retinal damage (by the early recognition of definitive findings)."

---

**When should annual screenings start?**

- Baseline testing recommended pre-HCQ initiation
  - Or ideally w/in 6-12 months of start date!

- When should annual screenings begin?
  - After 5 years of HCQ treatment
  - Or
  - When 1000 gram threshold is met

  “Given the initial low risk of HCQ or CQ retinopathy, with a proper dose and in the absence of major risk factors, annual screening can be deferred until there has been 5 years of exposure.”

Who is actually getting screened?

- Study location: Michigan
- Study time period: 10 year span (2001-2011)
- 6339/18,051 patients with RA/SLE treated with CQ/HCQ
- 35% taking CQ/HCQ
- 1409/6339 patients were on CQ/HCQ for ≥4 yrs
  - 8% on CQ/HCQ ≥4 yrs
- Among the highest-risk patients:
  - Only 28% had regular eye care visits
  - 6% had no eye exams
  - 35% had no diagnostic testing

**Bottom Line:** medicine needs to improve HCQ screening methods!


Recommended screening tests...

1. 10-2 VF
2. SD-OCT
3. FAF
4. mFERG

"Unless toxic changes are advanced and obvious, at least 1 objective test should confirm subjective findings before toxicity is diagnosed."


Color Photos vs. FAF

- Not used anymore for screening purposes but can be used for baseline
- 100% eyes in unaffected group labelled as normal
- ~32% of affected patients were labelled as normal (oops!)
- FAF is a good screener but not perfect
- 92% eyes in unaffected group labelled as normal
- 26% of affected patients were labelled as normal (oops!)

Don't use color photos or FAF alone for screening purposes!

Recommended screening tests...

1. 10-2 VF
2. SD-OCT
3. FAF
4. mfERG

• "Unless toxic changes are advanced and obvious, at least 1 objective test should confirm subjective findings before toxicity is diagnosed."

Visual Field Testing..

• Sita 10-2 is most common ancillary test used for HCQ since early 1990's
• White-on-white recommended
• Most at risk areas: between 2°-6° degrees from center of the field
• Toxicity → partial/full ring scotomas involving parafocal region
• New finding: 24-2/30-2 in Asian patients!
• Central visual acuity usually preserved until late stages of toxicity
• Suspicious findings with 10-2 to warrant further investigation:
  • Cluster of scotoma points in the 2°-8° degree zone
  • Scotoma that persists and grows in depth/breadth
  • Appearance of new scotomas

“…we recommend the 10-2 VF with a white target as the preferred static automated perimetric test for hydroxychloroquine retinopathy screening and staging.”

24-2 vs. 10-2....why 10-2 is needed for HCQ...

Common 10-2 VF defects from HCQ toxicity...

Characteristic Ring Scotomas
Central scotomas
Central visual field defects

VF’s

• What is most common VF encountered?
  • "The most frequent regions of the retina showing early damage are inferotemporal, with a corresponding superonasal field defect, but this is not absolute."

• Very sensitive test in reliable patients
• High variability between visits
  • Some studies show 30% of VFs are unreliable!
• Uncertain tests? → repeat!
• Uncertain tests? → correlate with objective testing!

Recommended screening tests...

1. 10-2 VF
2. SD-OCT
3. FAF
4. mfERG

• "Unless toxic changes are advanced and obvious, at least 1 objective test should confirm subjective findings before toxicity is diagnosed."
SD-OCT

- Central VF’s and SD-OCT most widely used combination of testing
- Widely available and used among practitioners
- Typical findings on OCT scans:
  - Focal disruption of outer retina, widespread thinning
- Typical findings on OCT scans:
  - Occur in paravascular locations
  - Thinning/loss of:
    - Photoreceptors
    - Ellipsoid zone (E/OS junction)
    - RPE


- In patient’s with plaquenil toxicity:
  - 84% had discontinuity/loss of ellipsoid zone
  - 3 patients did not have this
  - 0% of unaffected patients

- Interesting insight!
  - Thinning of the inner inferior subfield can serve as a useful objective screening tool for possibility of HCQ toxicity
    - <305 µm would capture ALL affected individuals, only 25% normal
    - 100% sensitivity, 25% specificity → not too bad...


Recommended screening tests...

1. 10-2 VF
2. SD-OCT
3. FAF
4. mfERG

“Unless toxic changes are advanced and obvious, at least 1 objective test should confirm subjective findings before toxicity is diagnosed.”

FAF: Hyper vs. Hypo in HCQ toxicity...

- Hyperautofluorescence
  - Photoreceptor and RPE cellular stress
  - "Sick" cells
  - Accumulation of lipofuscin

- Hypoautofluorescence
  - Photoreceptor and RPE cell loss
  - Absence of RPE

- In HCQ toxicity: hyperfluorescence before hypofluorescence


Bilateral increase in paravascular AF

Widespread increased AF signal, and patchy decreased AF signal paravascularly

Very minimal changes in AF

"...bull's eye maculopathy visible on near-infrared reflectance imaging may be an additional objective sign of early HC toxicity and, of possible importance, that this sign may disappear with late HC toxicity."

---

New Finding???

815 nm wavelength used

Recommended screening tests...

1. 10-2 VF
2. SD-OCT
3. FAF
4. mfERG

"Unless toxic changes are advanced and obvious, at least 1 objective test should confirm subjective findings before toxicity is diagnosed."


mfERG

- Objective/functional test
- Highly sensitive for macular dysfunction
- Local topographical ERG responses
  - Reflects damage at or before bipolar cells
- Paracentral ERG depression → amplitude loss!
- Not widely available
- Significant expertise needed to perform and interpret accurately
- Long testing time
- mfERG → Reflect damage at or before bipolar cells
- 61 hexagon rings are grouped into 5 concentric rings (R1-R5)
  - R1 = center ring, R5 = most peripheral ring
- Average amplitude measured as: (P1-N1)
- Definition of toxicity via mfERG alone:
  1. Increased R1 to R2 ratio (>99% confidence limits)
  2. Reduced R1 absolute amplitude (<99% confidence limits)

Best time to use mfERG???

"Multifocal ERG may provide objective, functional evidence of disease, and may be useful when the diagnosis of HCQ is uncertain: in particular when visual field analysis demonstrates scotomata in the absence of structural evidence on SD-OCT or AF."


- VF defect, but normal SD-OCT/FAF? → think mfERG!

What is the best single test?

What is the best combination of tests?

Sensitivity and specificity of the tests

- Notice → Combos are more sensitive than either test alone
Structure vs. Function: what happens first?

- Structure first, function second:

- Function first, structure second:

• Evidence for both!
• Structure before function usually!
• Rely on totality of evidence to make a decision!

Cost of screening for HCQ toxicity?

- "...revisions in the AAO hydroxychloroquine screening guidelines from the 2002 version to its current revised 2011 version resulted in a 40% increase in total associated health expenditure costs, rising from an estimated $29 million to $40.7 million."

How good are medical professionals at following AAO guidelines?

- Study location: Cole Eye Institute, Cleveland, Ohio
- n = 1294 HCQ screenings
  - Used 2011 HCQ Screening Guidelines
- Most common screening tests: OCT & HVF 10-2
  - 50% (648/1294) → appropriate screening
  - 27% (348/1294) → underscreened
  - 23% (299/1294) → inappropriately screened
  - 50% HCQ screenings were inadequately screened in this study!

Estimated HCQ Screening Adherence Patterns...
Gold standard for definition of HCQ toxicity?

- "In studies in which the sensitivity and specificity is to be determined, a gold standard against which the tests will be graded must be defined. For the purposes of this work the definition of hydroxychloroquine retinopathy (the gold standard) was that the drug was discontinued by the ophthalmologist and the prescribing physician because retinopathy was considered to be present based on the totality of the clinical evidence. This gold standard has been used before." — Browning DJ, Lee C. Clin Ophthalmol. 2014;8:1389-99.

Severity definitions of HCQ toxicity

- **Early**
  - Patchy parafoveal/pericentral photoreceptor loss on OCT
  - (R)RPE involvement on OCT
  - Isolated VF defects on 10-2 or 30-2

- **Moderate**
  - Photoreceptor damage
  - Scotomas (>180° to full 360° ring)

- **Severe**
  - RPE damage and hypo-AF on FAF

Management of retinal toxicity...

- No treatment available!
  - The use of lutein/zeaxanthin (AREDS) has been discussed by some doctors.
- Identify earliest sign of toxicity and d/c med ASAP
- Call prescribing physician to initiate process
- Do not d/c med without consulting with prescribing physician first
- My recommendation → Send a follow-up letter for a "paper trail"

- "But we must emphasize that the drugs should not be stopped for questionable or ambiguous signs of damage. Such findings should trigger retesting, or testing with additional procedures such as mfERG, or perhaps an earlier follow-up visit. One should have unequivocal abnormalities or corroborative evidence of toxicity before making a diagnosis of retinopathy and stopping a very good drug."

Let's say it again!

- "If the diagnosis of maculopathy is equivocal, screening every 3 to 6 months for the confirmation of toxicity is advised."
- "This drug should typically be discontinued once toxicity is clearly evident, but the progression of damage is slow enough to repeat borderline or questionable tests, or order additional tests for confirmation, so that a useful medication is not stopped unnecessarily."
  - Marmor MF, Melles RB. JAMA. 2015.

Progression after D/C?

Progression with discontinuation?

- Possible! Even for several years... whoa!
  - At least 3 years per some articles!
  - Can eventually involve the foveal center
- If toxicity recognized before RPE loss occurs then no progression to involve foveal center is the norm
  - Mild paracentral scotomas likely
  - PS typically not symptomatic
- MOA? Currently unknown...
  - Continued reservoir of the drug in RPE?
  - Gradual decompensation of already metabolically injured cells?

ELM: a marker for progression post-d/c???

- "Using SD-OCT, this study quantified ELM disruption and photoreceptor volume in patients diagnosed with HCQ retinal toxicity after drug discontinuation. Confirming our previous study, we found that eyes with intact ELM at diagnosis of toxicity had a good prognosis and were unlikely to progress, whereas those with different degrees of ELM disruption were more likely to show progressive changes on OCT. Importantly, the ELM did not show any signs of recovery during the follow-up."
**Miscellaneous Topics**

-- Subset of HCQ in Asian populations
-- HCQ blood draws
-- HCQ & Pregnancy
-- HCQ in cancer patients

---

**New subset of HCQ toxicity in Asian patients?**

“Much of the literature on hydroxychloroquine retinopathy has emphasized the specificity of paraviewal (bull’s eye) damage as a sign of this drug toxicity. Although this remains an excellent and relatively specific clinical finding, especially in a predominantly white population, it should no longer be considered as the unique presentation of retinal toxicity. There is also a pattern of pericentral retinal damage (typically in the region of the arcades) that affects Asian patients primarily but can be seen in all races.”

---

**Should HCQ be monitored with regular blood draws?**

- Blood concentrations of HCQ can vary more than 10-fold among compliant patients receiving similar doses...whoa!

- “...blood levels are not reliable for assessing partial levels of compliance because of the high variability among subjects.”

---

**HCQ during pregnancy?**

- HCQ can cross the placenta
- Cord blood concentrations are nearly identical to maternal blood
- But...numerous studies show safety of HCQ during pregnancy

- “…current evidence suggested no fetal ocular toxicity of antimalarial medications during pregnancy. Accordingly, experts generally recommend continuing HCQ during pregnancy when indicated.”

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**HCQ for cancer?**

- High dose HCQ in cancer patients
  - Up to 1000-1200 mg/day in some patients!
  - Accelerated retinal toxicity possible!
  - Within as little as 11 months!
- Author recommendations:
  - Examinations: q3 months
  - Minimum testing: SD-OCT and 10-2 VF

We have to be ready for more HCQ patients walking in our doors!

---

**Management after Dx**

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Management of Retinal Toxicity

- "There is no treatment for HCQ of CQ retinopathy, and despite some hints of early functional recovery in the literature, there is no clear evidence that significant recovery can occur."

Patient has stopped HCQ...now what?

- "There are no established guidelines for following patients with toxicity."

- Don't forget about Low Vision referrals!

Conclusion

My humble approach!

- Baseline exam within 6-12 months of starting HCQ
- Baseline testing includes:
  - 10-2 VF (white-on-white): 24-2/30-2 for Asian populations
  - SD-OCT (mac cube, 21-line raster and/or radial scans, GCC?)
  - FAF
- Yearly exams with DFE
  - Review history & medications (has dose, weight, etc. changed?)
  - Calculate daily dose & total dose
  - No screening tests unless Sv/Sx suggest toxicity or overdose
- Year 5 → start annual screenings with testing
  - 10-2 VF (24-2/30-2 for Asian populations)
  - SD-OCT (mac cube, 21-line raster and/or radial scans, consider GCC?)
  - At SCO, Spectralis allows raster & FAF in same scan!
- Suspicious/equivocal case?? → mfERG
- Communicate with PCP/Rheumatologist in timely fashion!

Billing & Coding

- "The optimal algorithm for hydroxychloroquine toxicity screening using different methods is still being debated."

- "There remains no established criterion for diagnosing HCQ toxicity and, as such, the physician must rely on a combination of characteristic functional and anatomic abnormalities to diagnose a patient with HCQ toxicity. An understanding of each screening modality and a keen eye to detect subtle abnormalities is critical to diagnosing early disease."
How do I code exam to rule out toxicity?

- Appropriate 99xxx or 92xxx exam code
  - HVF 10-2 (92083)
  - Macula SD-OCT (92134)
  - FF/FAF (92250)
  - Multifocal ERG (92275)

- 1) Rheumatoid Arthritis (M06.9)
  - SLE (M32.9)

- 2) High-Risk Med (Z79.899)

What if patient develops HCQ maculopathy?

- Appropriate 99xxx or 92xxx exam code
  - HVF 10-2 (92083)
  - Macula SD-OCT (92134)
  - FF/FAF (92250)
  - Multifocal ERG (92275)

- 1) Rheumatoid Arthritis (M06.9)
  - SLE (M32.9)

- 2) Toxic maculopathy (H35.38x)

Thank you!!!

Questions??

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