Chloroquine and Hydroxychloroquine Maculopathy: Case, Description, and Review of Revised AAO Recommendations

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Chloroquine/Hydroxychloroquine

Quinolone family of drugs developed in the 1940's

Chloroquine initially used as antimalarial, WWII.

Efficacy of hydroxychloroquine in treating SLE and RA first shown in 1955.

Rare Adverse Effects – tinnitis, haematologic disorders, liver disease, retinopathy

Hydroxychloroquine
- more readily excreted
- used more in USA

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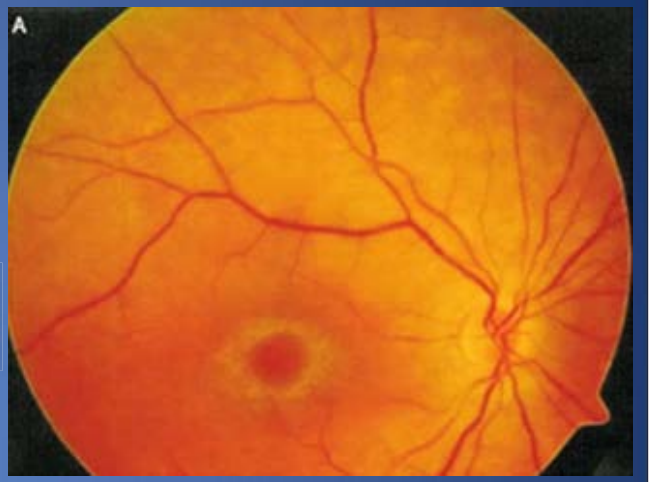
Chloroquine/Hydroxychloroquine Retinopathy

- Well described occurrence : overall rare 0.1-0.5%
- Potentially blinding
- Progressive loss of RPE and photoreceptors in a parafoveal pattern, producing a "Bull's-eye" maculopathy and paracentral scotoma
- Associated with many years of CQ/HCQ use
- High incidence of HCQ use in US makes this rare complication a serious health concern



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Retinopathy

- Mechanism of maculopathy not well understood
  - Binds to melanin in RPE, localizing to the macula
    - Parafoveal pattern
- Acute metabolic effects on photoreceptors
  - ? if this causes the slow chronic damage seen
- Histology demonstrates a loss of RPE pigmentation, along with reduction in the number of photoreceptor cells[1]

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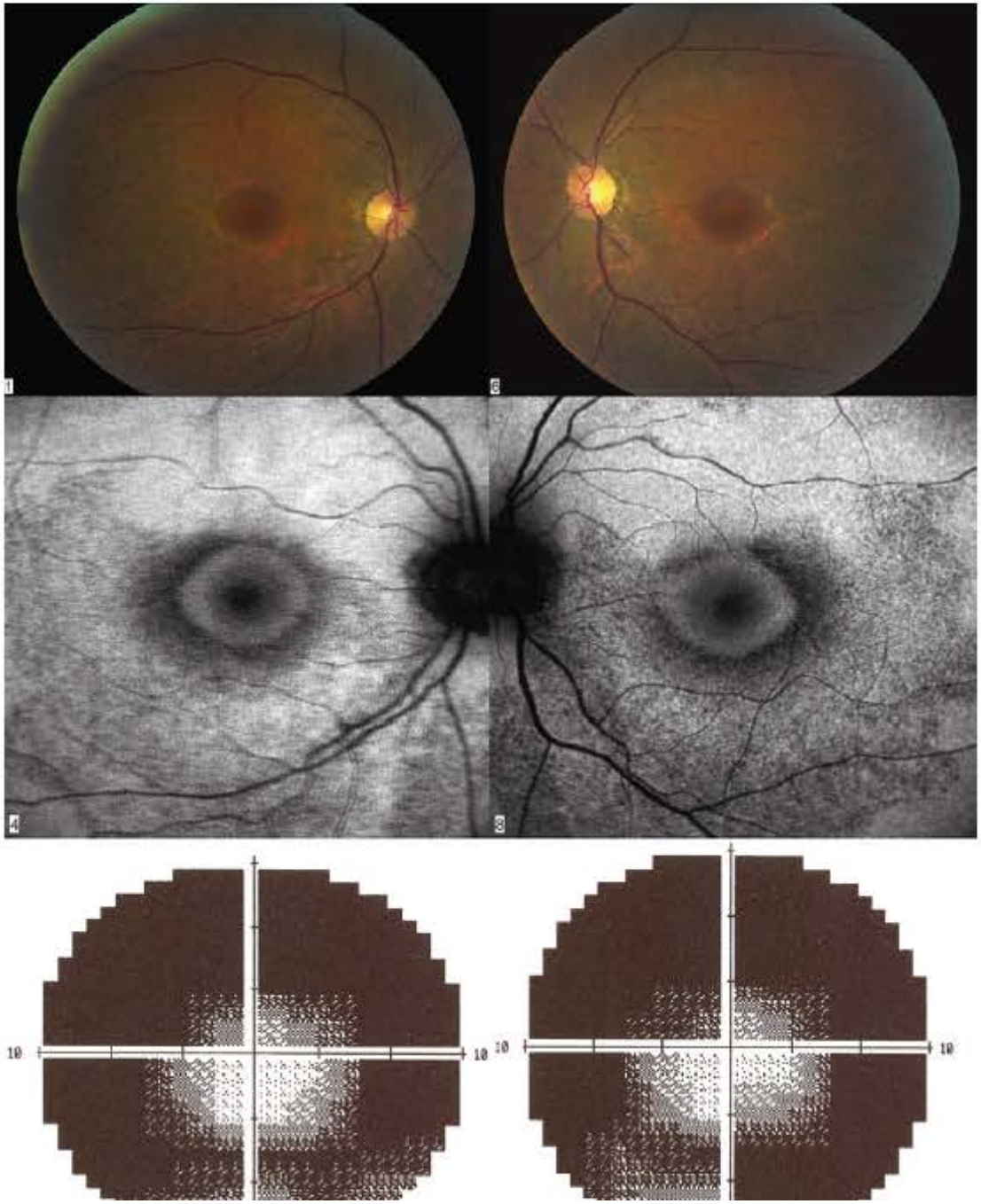
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Risk Factors for Retinal Toxicity

1. Duration of use

Wolfe 2010[4] - Retrospective analysis of 4,000 patients with RA or Lupus

- Dramatic increase in incidence (from 3/1000 to 1%) at **5 to 7 years** of use, or 1000 g cumulative dose.
- Incidence increased to 2% at **10 to 15 years** of use.

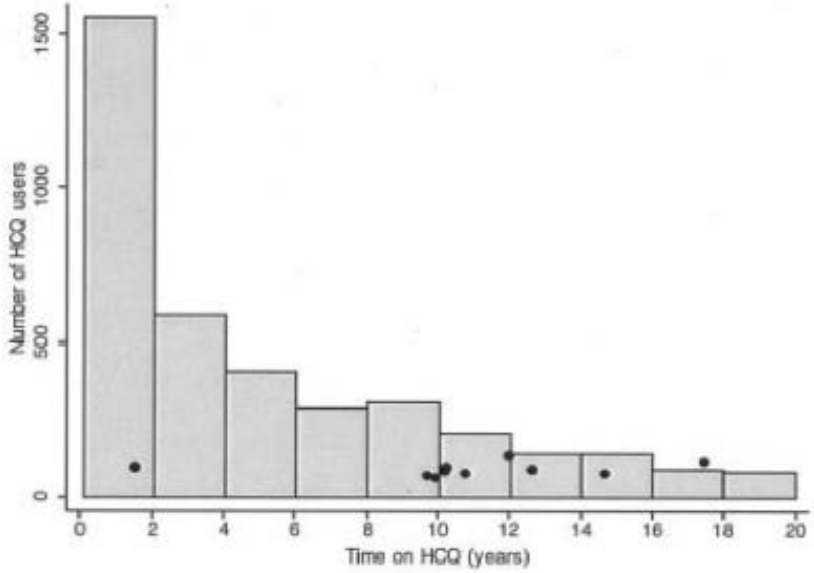
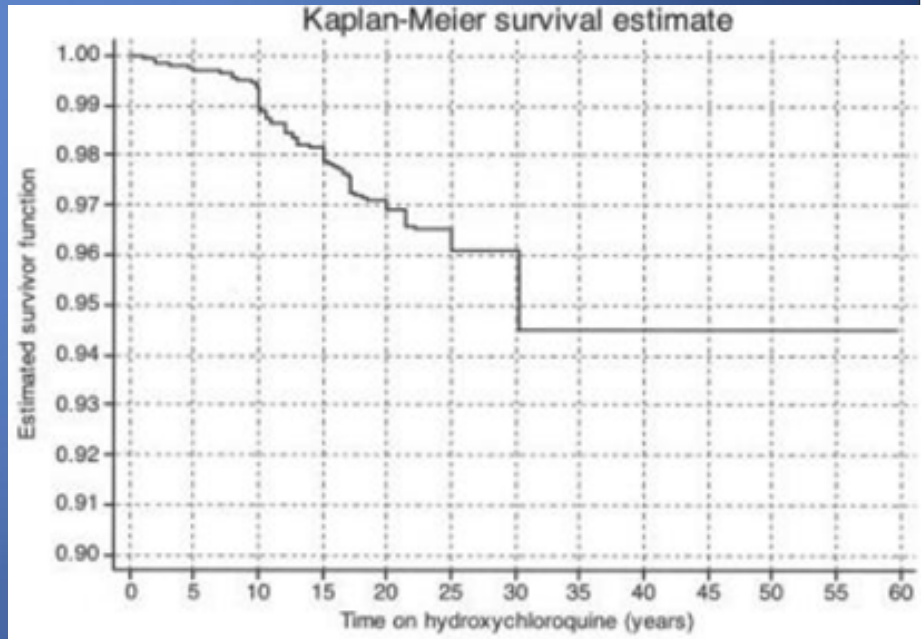


Figure 1. Distribution of duration of hydroxychloroquine (HCQ) therapy in lifetime HCQ users (histogram) and cases (n = 10) of HCQ toxicity at the time of diagnosis.



results from 200 multiply imputed data sets. Exact survivor function results are 0.997 at 5 years, 0.989 at 10 years, 0.979 at 15 years, 0.969 at 20 years, 0.961 at 25 years, 0.961 at 30 years, and 0.945 at 35 years.

Risk Factors for Retinal Toxicity

2. Cumulative dose
   - HCQ: 1000g (reached at 7 years with dose of 400mg/d)
   - CQ: 460g
3. Daily dose (more accurately, overdosage)
   - HCQ: >6.5 mg/kg/d; CQ: 3.0 mg/kg/d
   - Dosing should be based on ideal body weight, not "standard" 400 mg/day or by actual weight
     - HCQ or CQ not retained in fatty tissues
     - Overdosage can occur in shorter and/or obese patients
4. Renal or hepatic impairment
   - HCQ and CQ cleared by kidney and liver

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Risk Factors for Retinal Toxicity

5. Retinal and macular disease
   - Maculopathy is relative contraindication to HCQ or CQ
   - Decreases threshold of damage
   - Elderly more at risk for concomitant retinal or macular disease

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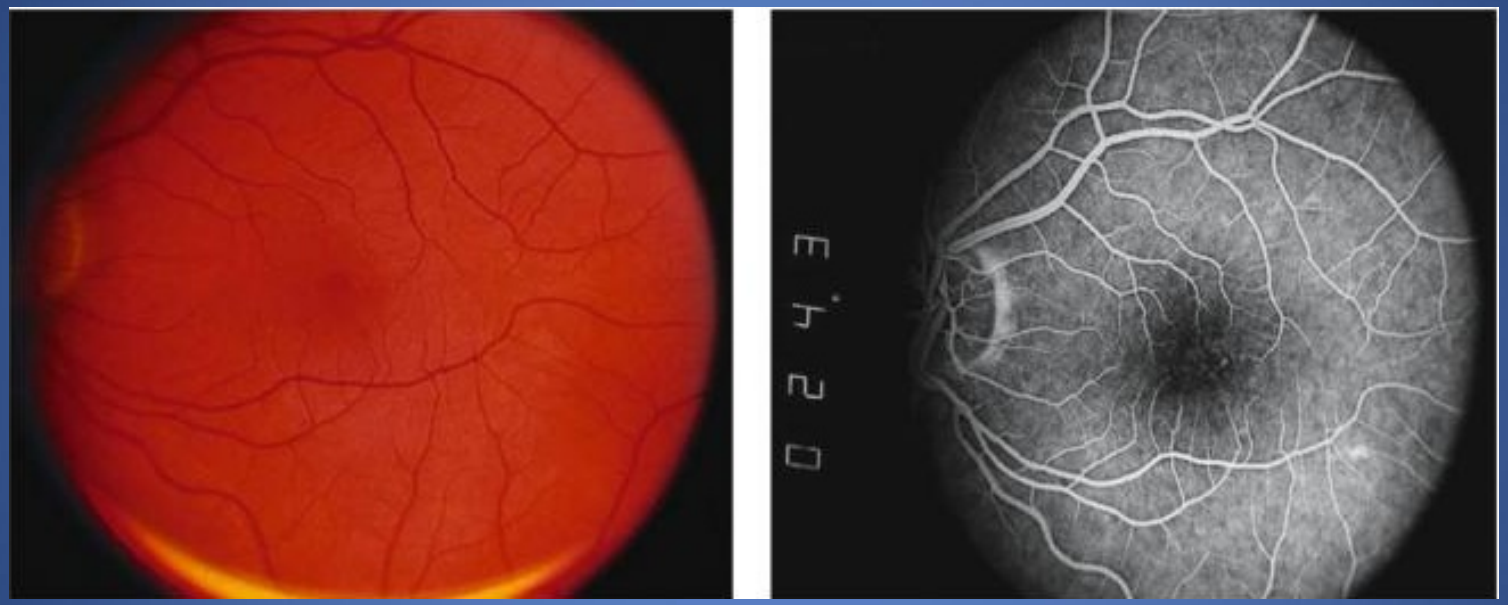
Clinical Findings

Early – subtle stippling, or granular changes, of the macular RPE and loss of foveal light reflex



Subtle pigment changes along temporal macula

Transmission defect on FA corresponds with pigment mottling

Mild paracentral scotoma is usually the earliest clinical sign of toxicity.

Presents as a subjective complaint in a perceptive patient, or on formal visual field test.

Most common early complaint is paracentral scotoma or **difficulty with reading.**[3]

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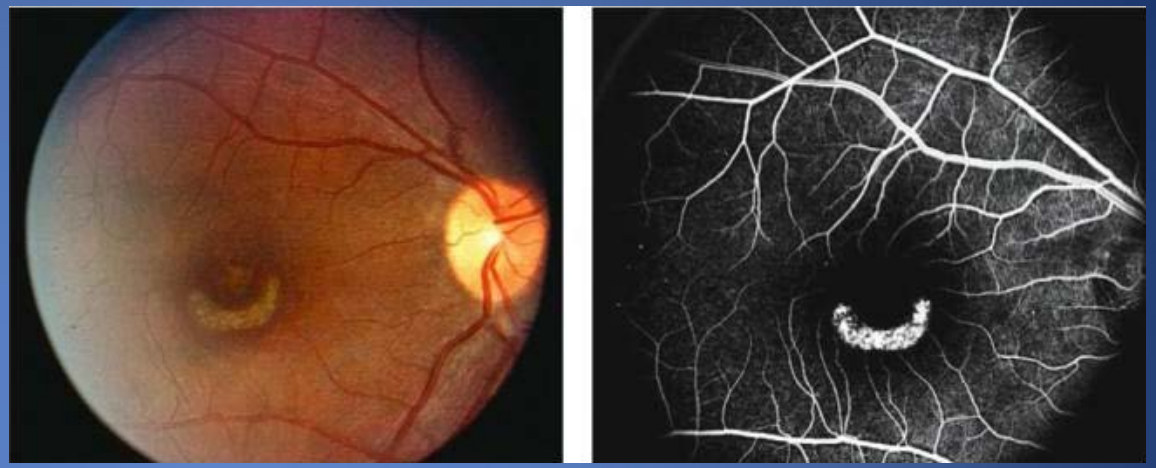
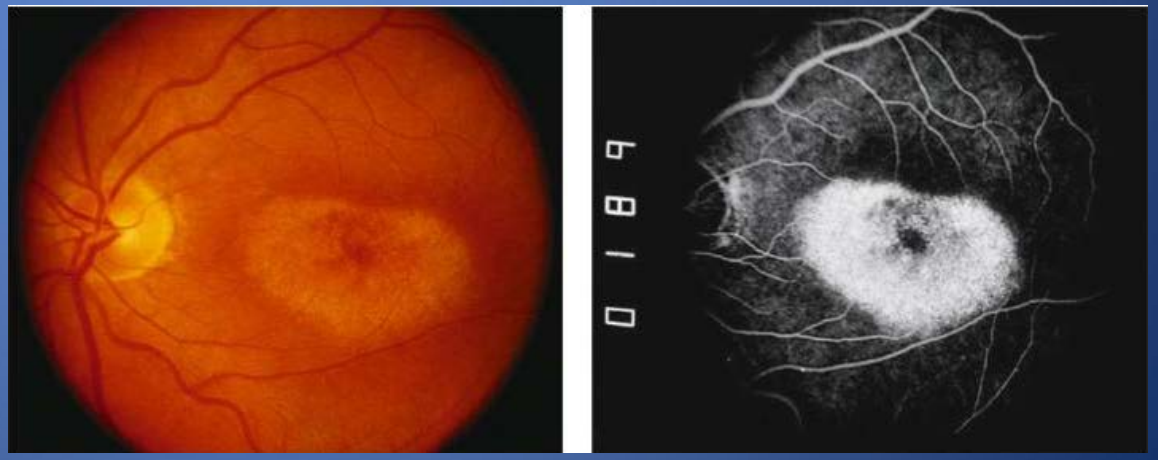
Clinical Findings

The classic picture of definite CQ/HCQ retinal toxicity is a "bull's eye" pattern of parafoveal depigmentation, surrounded by a ring of hyperpigmentation.



As maculopathy progresses, patients can complain of difficulty with night and color vision.



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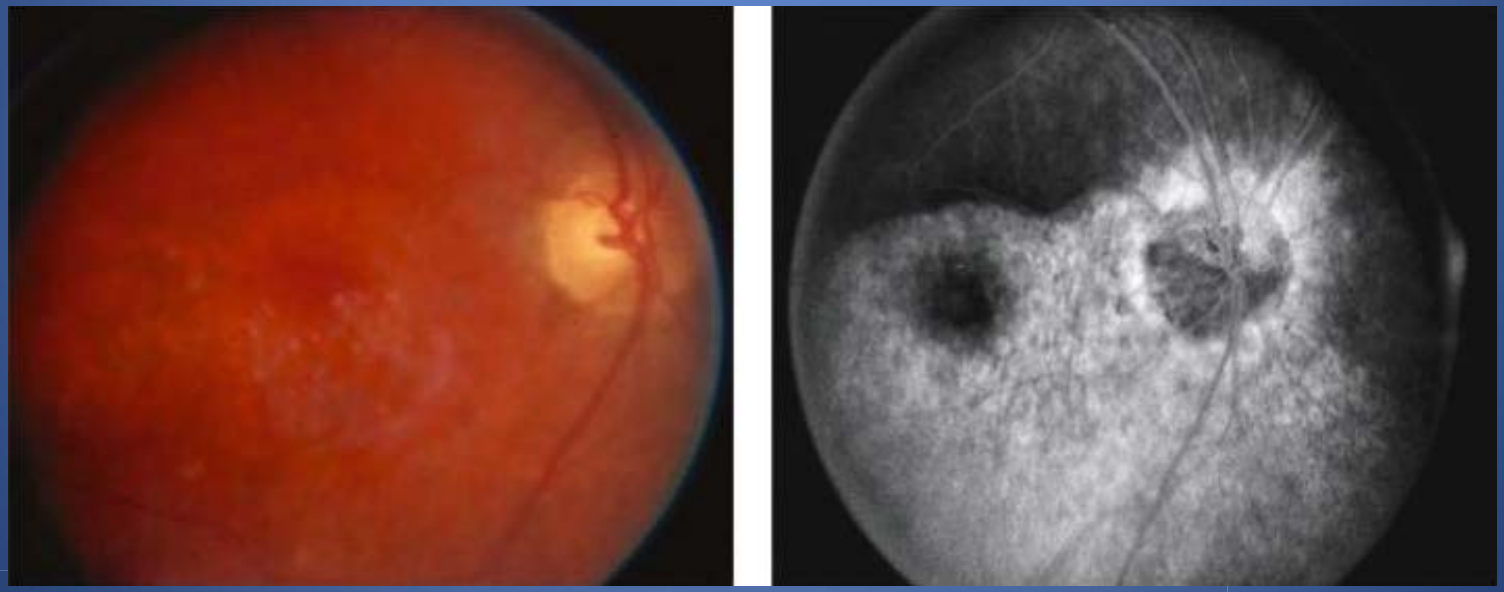
Clinical Findings

Severe retinopathy progresses to mottling of the peripheral retinal pigment.

Very severe cases result in total retinal atrophy with arteriolar narrowing, optic disc pallor, and blindness[3].



Loss of VA occurs as damage progresses into the fovea.

Field losses occur as damage extends into peripheral retina.

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Grades of Clinical Severity

Severity	BCVA	Fundus
Premaculopathy scotoma → red target	20/30 → 20/40	Faint halo of RPE pallor
Bull's-eye	20/60 → 20/80	Dark ring surrounding halo
Severe	20/120 → 20/200	Pseudohole and atrophy
End-stage	Legally blind	Large RPE atrophy, pigment clumps

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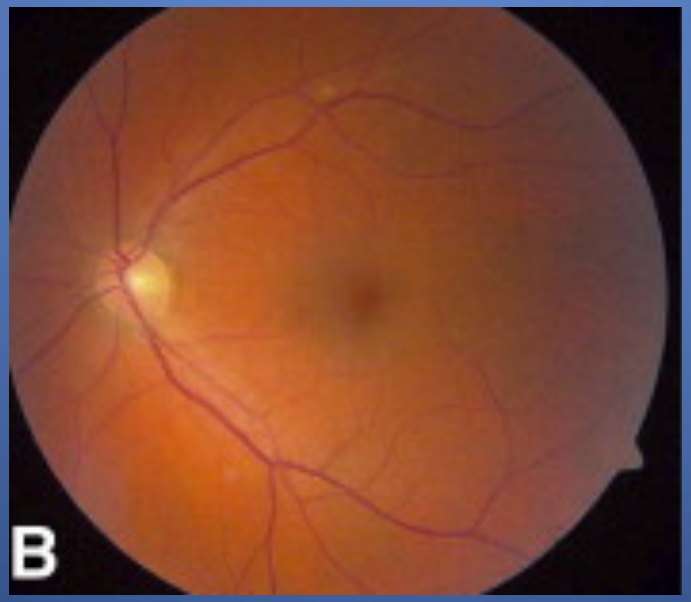
Screening Tests

Ophthalmologic Exam

- To establish baseline exam
- To detect concomitant retinal or macular disease



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Subjective Screening Tests

Color Testing

- Ishihara color plates
- Contributes in diagnosis, but not suitable for ruling out toxicity
- Lacks sensitivity and specificity

Amsler Grid

- Contributes in diagnosis, but not suitable for ruling out toxicity
- Inconsistent sensitivity for maculopathy
- Fairly nonspecific, must exclude alternate/ concomitant disease

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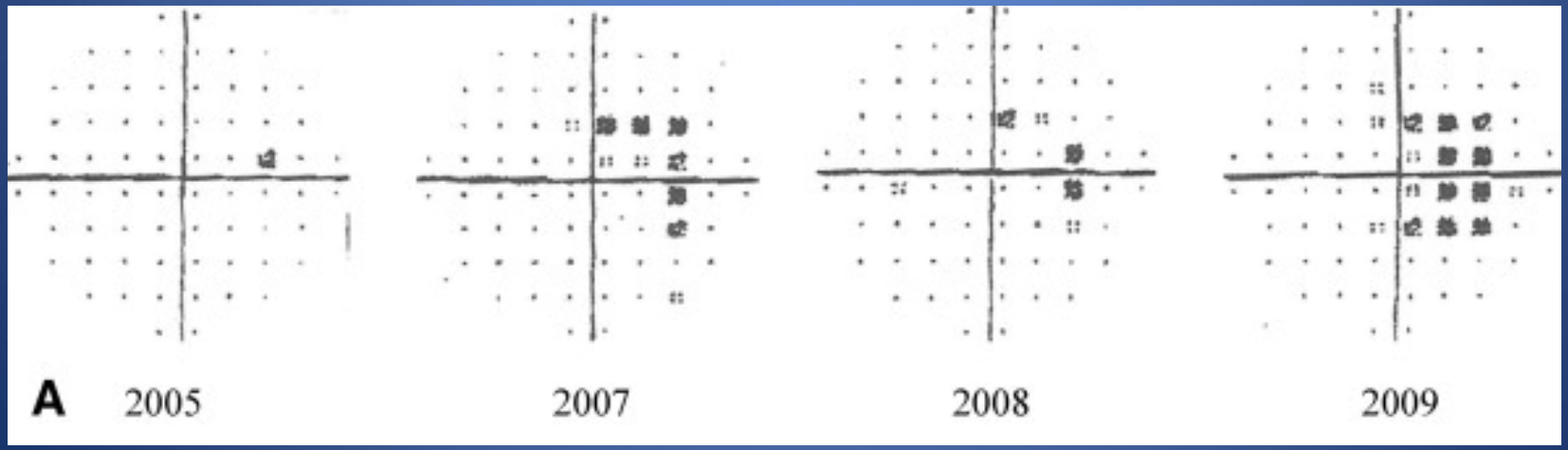
Subjective Screening Tests

Central Fields (HVF 10-2)

- Most sensitive subjective test for early toxicity
- Shows constriction of central vision
- Functional limitations
- Should be repeated and follow the trend of pattern loss, not just compare to previous



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Objective Screening Tests

Means for detecting changes of *early* changes of retinopathy are being actively explored.

A few tests have recently been found to possess superior sensitivity over HVF 10-2

Spectral Domain-OCT

Arana 2010; 48 HCQ maculopathy patients, 30 controls

- SD-OCT reveals decreased NFL thickness in HCQ patients, w/o signs/symptoms of disease
- Inverse daily dose-thickness correlation

Studies are ongoing to assess utility as a screening tool with unprecedented sensitivity

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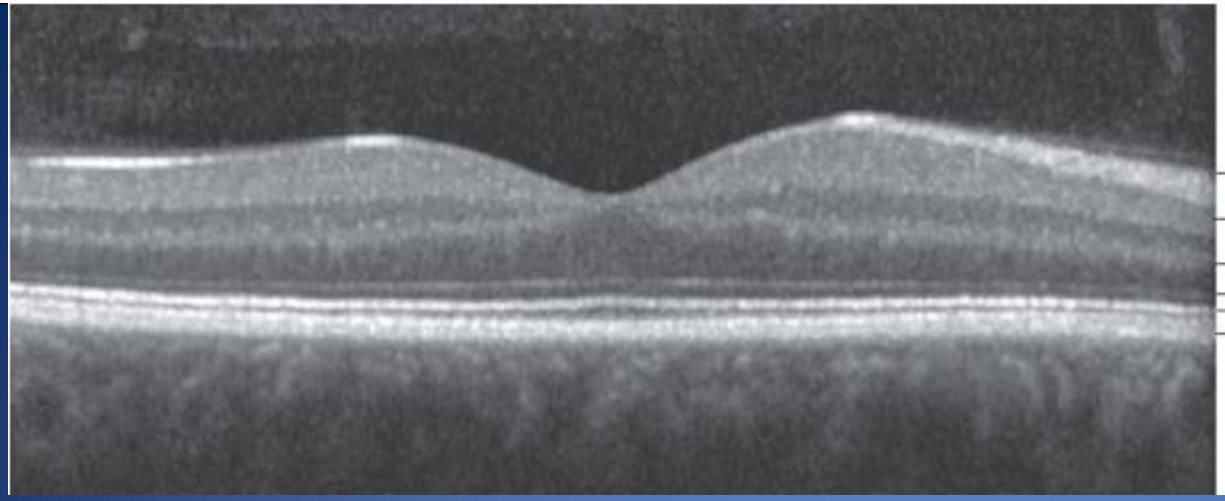
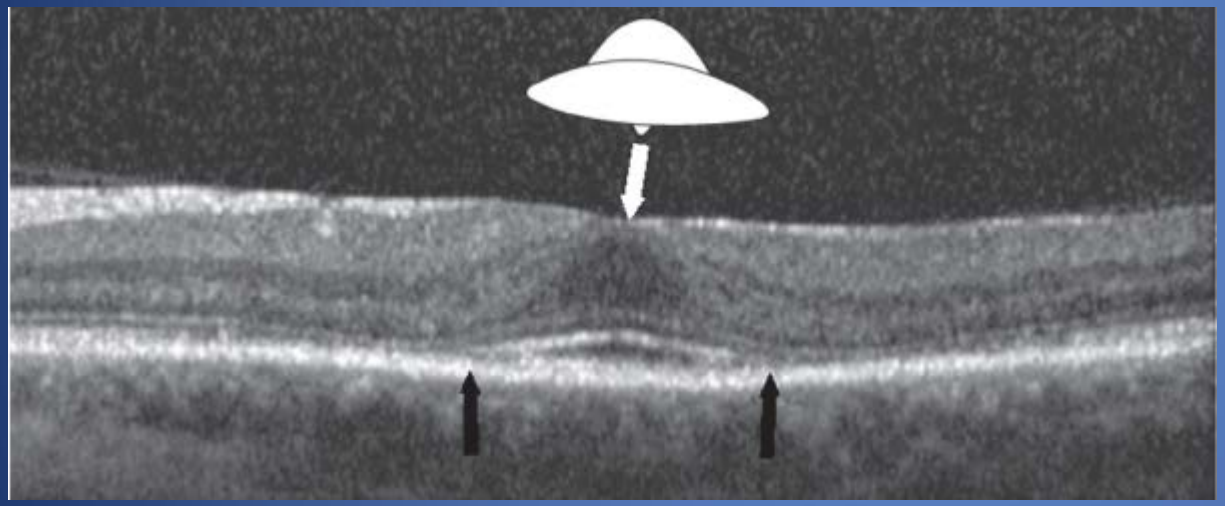


Kellner 2009; 8 patients with toxicity. Decreased ONL thickness in areas *not* identified on FA, Near-infrared autofluor, or mfERG



Chen 2010;
9 patients with early toxicity. Concludes that use of SD-OCT is effective in detecting early toxicity **before funduscopic changes.**

Early loss of the perifoveal photoreceptor IS/OS junction, perifoveal thinning of ONL, and an apparent posterior displacement of inner retinal structures toward the RPE

Loss of the normal foveal depression + preservation of foveal photoreceptor IS/OS

"flying saucer" sign.

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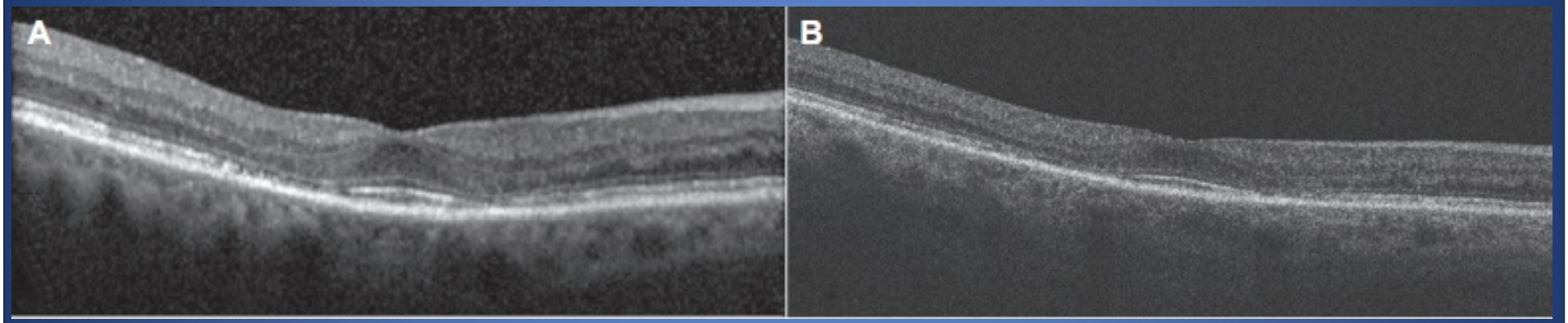

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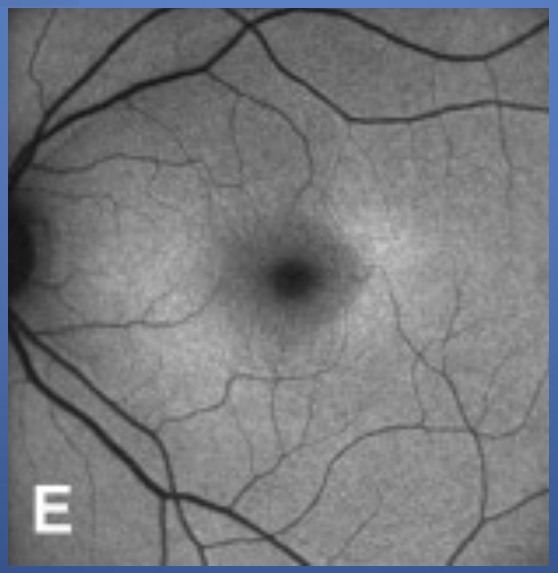
Objective Screening Tests

Fundus Autofluorescence

- May reveal subtle RPE defects
- Kellner 2009: abnormal findings on fundus autofluorescence (FAF) and Near-Infrared Autofluorescence (NIA) in all five patients with abnormal SD-OCT
- Shows abnormality in established disease, not yet shown to detect early toxicity



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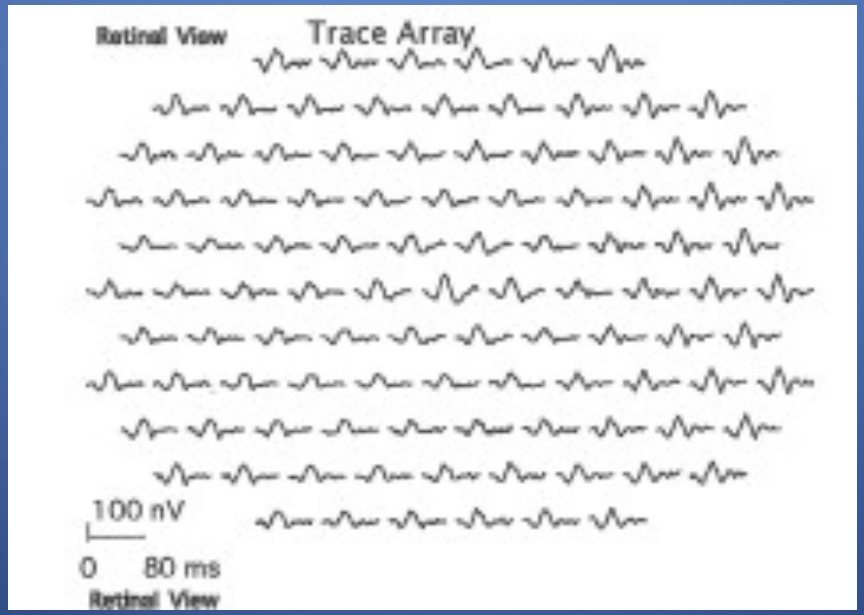
Objective Screening Tests

ERG/EOG

- Use is controversial
- Studies conflict in regard to sensitivity in early disease

mfERG

- Most sensitive of electrophysiologic tests
- Specific to focal changes (ie- pericentral)
- Recent studies show detection **earlier than VA**, Amsler, and color testing



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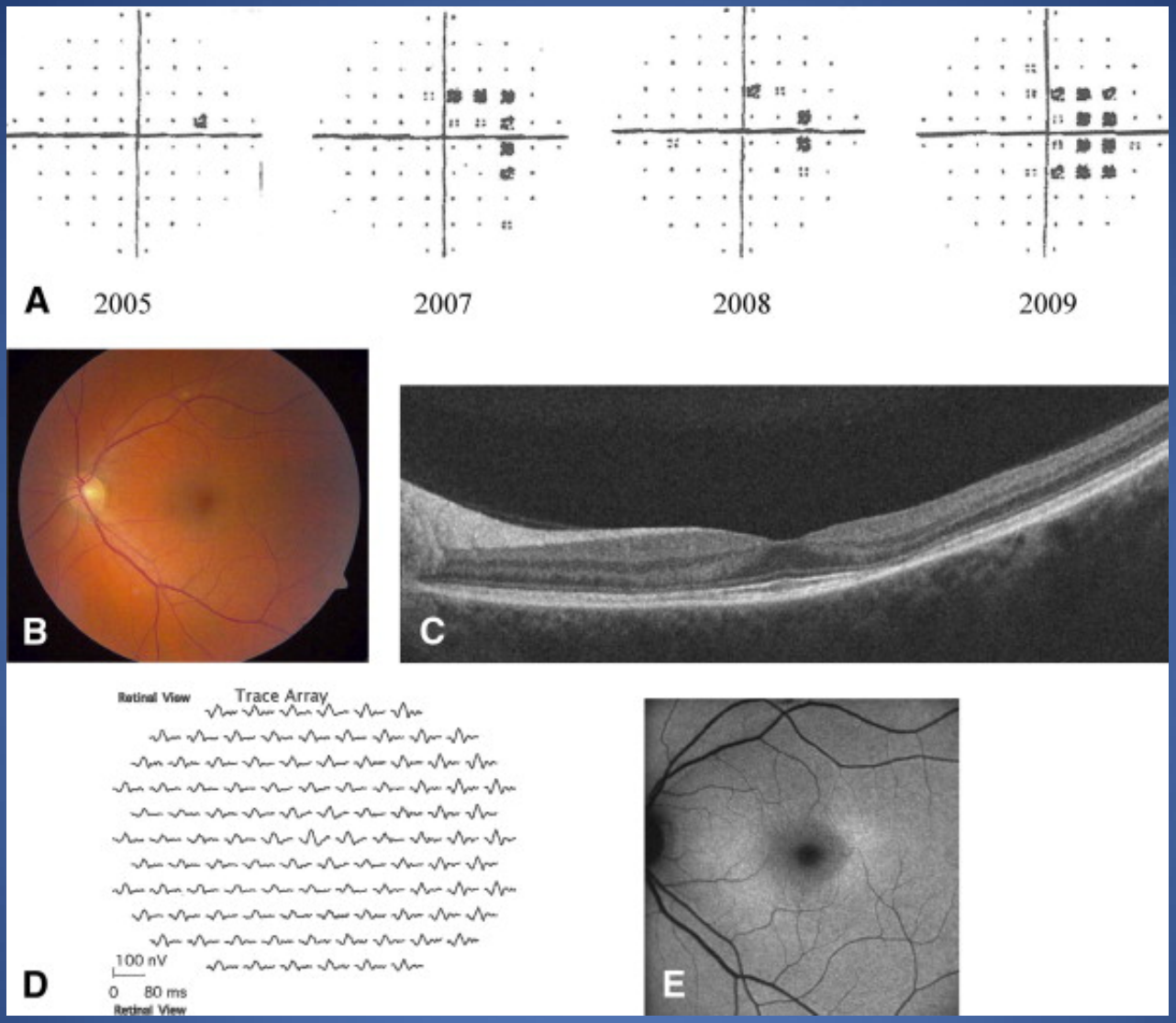

25yr use of HCQ at dose of 400mgday (8mg/kg/d)

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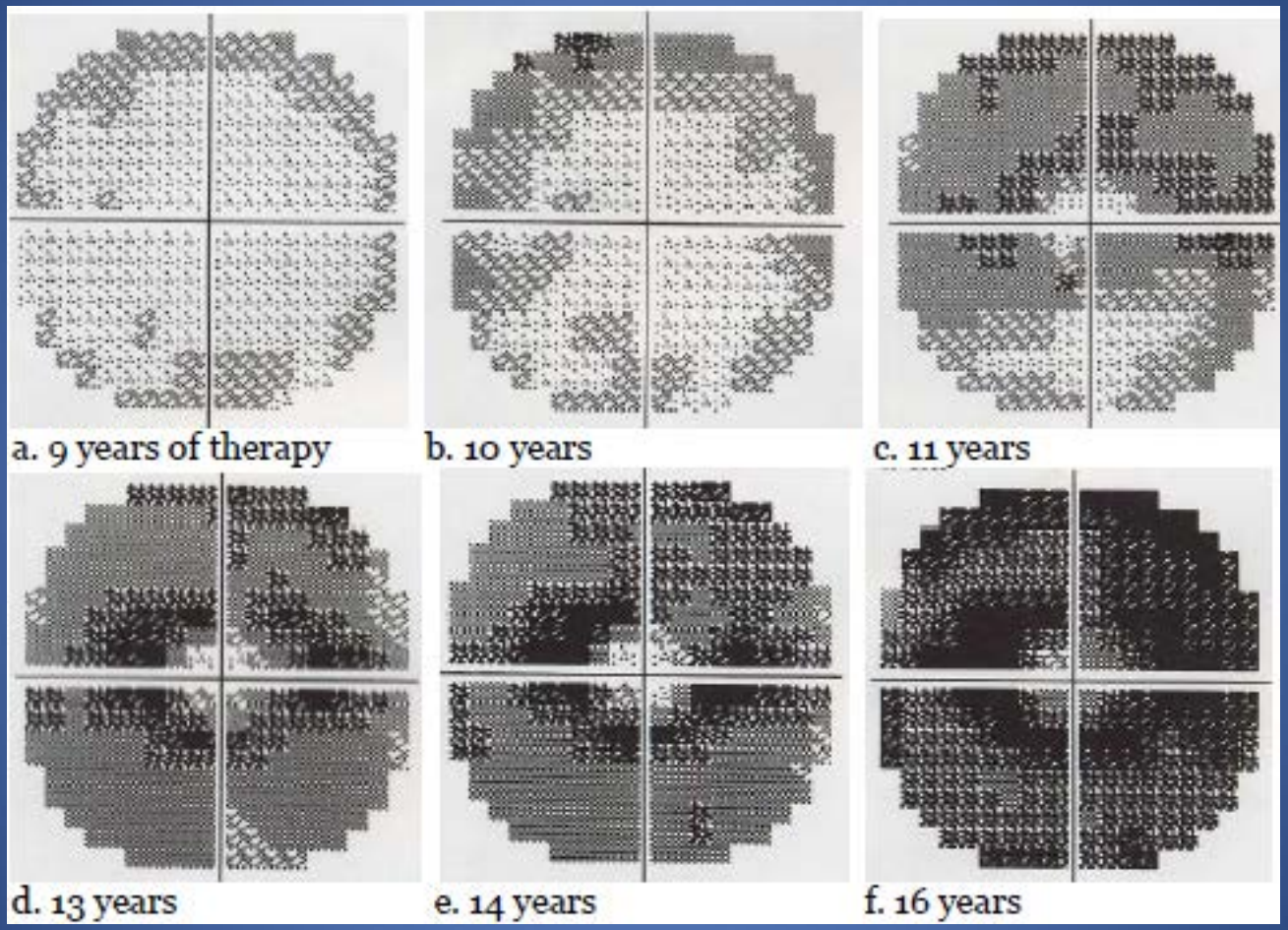
Progression of R eye Central Field Loss



HVF 10-2 Red Right eye (Right and Left eyes underwent fairly symmetric progression)

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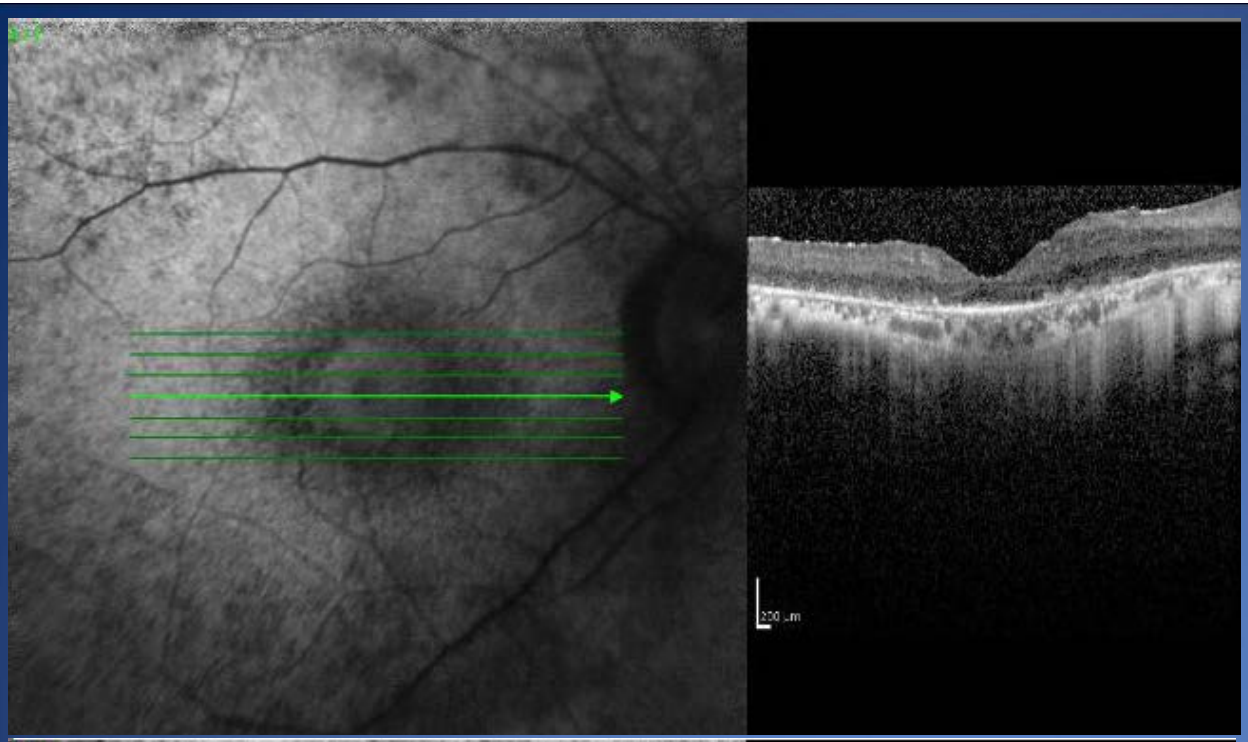

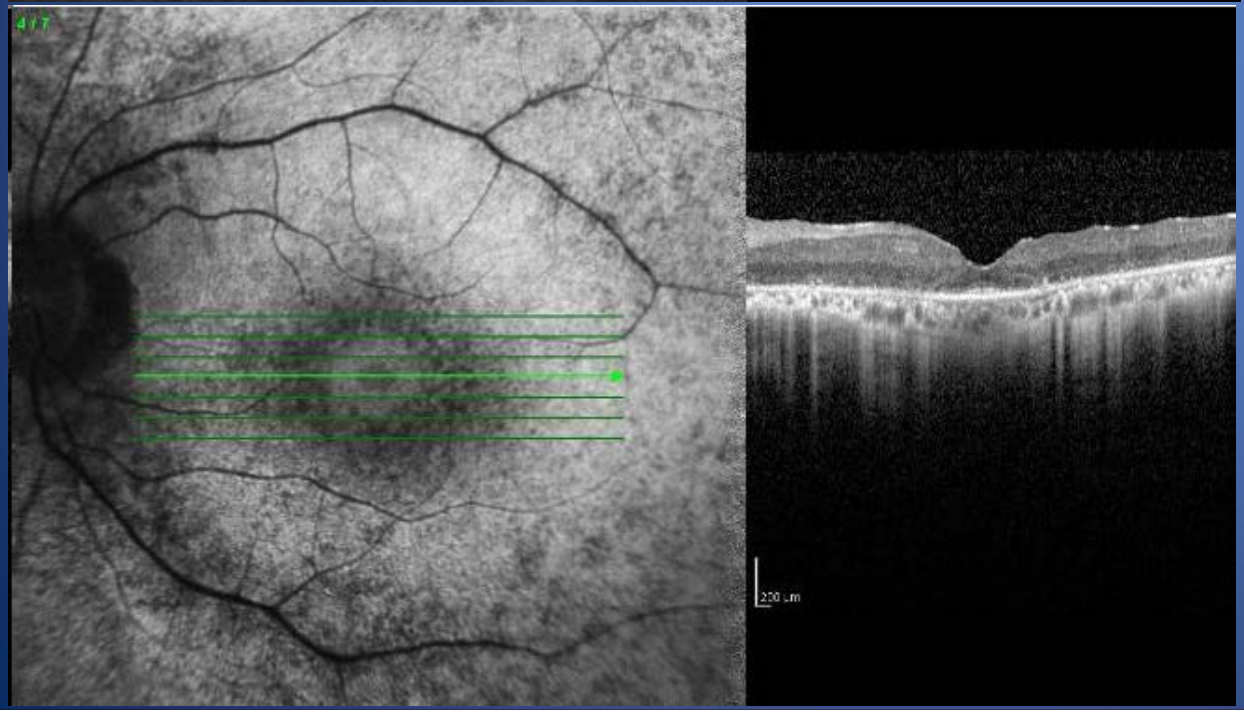

- Fundus exam and autofluorescence reveal classic bull's-eye maculopathy

- Spectral domain OCT demonstrate loss of outer retinal layers with disruption in IS/OS jxn.

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Prognosis

- Once in place, maculopathy often progresses centrally and then peripherally, and may continue despite discontinuation of drug

- No methods known to halt progression other than discontinuation of drug

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Prognosis

- Easterbrook 1992 – followed patients with visual deficits for 9 years after discontinuing CQ/HCQ therapy
  - 30 patients with absolute scotoma:
    - 19 lost ≥ 1 line VA
    - 4 became legally blind
    - Enlarging scotoma in majority (64%), new scotoma in remainder
  - 22 patients with relative scotoma:
    - all maintained central acuity
    - 16 maintained visual field
    - 2 regained some field
    - 2 lost some field
    - 1 progressed to absolute scotoma

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Prognosis

- The apparent contrast between prognosis for definite/progressed and early disease, along with a lack of treatment, is the reason for the efforts focused on prevention of early progression of disease by screening and initial detection of pathology

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Revised AAO Recommendations

ASSESSING RISK

- >5 years duration
- >1000 g cumulative dose (reached at 7 years on 400mg/day)
- > 6.5 mg/kg lean mass/day

Revised Recommended Dosing:

400 mg/day

Use BMI Charts for short/obese

- **6.5 mg/kg lean body mass/day**
- Dose alternating (ie 200 mg, 400 mg) is acceptable, with HCQ's very long half-life (30-52 days).

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Revised AAO Recommendations

ASSESSING RISK

- Renal or Liver impairment
  - Avoid anti-malarials or minimize dose
  - Insufficient data for specific guidelines
- Retinal and Macular Disease
  - Relative Contraindication to CQ/HCQ therapy
  - Potential to mask toxic changes
  - Concern for increased susceptibility to toxic insults
  - No confirming data
- Elderly
  - Age-related retinal changes
  - Difficulty in identifying depigmentation in the elderly fundus, already lacking pigmentation

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Revised AAO Recommendations

SCREENING RECOMMENDATIONS

- Baseline ocular exam when therapy initiated
  - Assess risk factors and counsel patient on importance
- Commencement of annual screening at 5 years of therapy
  - AAO takes the assumption that annual screening is justified as the risk of toxicity approaches 1%
- Screening at onset of therapy in patients with additional risk factors, pre-existing maculopathy, or providing reason for clinical suspicion

Annual screening consists of:

1. Dilated eye exam
2. BCVA
3. Automated 10-2 fields with white test object (found to be more sens than red)
4. 1 or more of the 3 specified objective tests:
   SD-OCT, fundus autofluorescence, mfERG.

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Revised AAO Recommendations

Tests no longer recommended

- FA – not more sensitive to other functional tests or non-invasive imaging
- Fundus photograph – inadequate sensitivity. Only to document, not screen
- Time-domain OCT – inferior resolution
- Full-field ERG – lacks specificity and spatial sensitivity for screening. Can be used to judge severity of toxicity
- EOG – conflicting evidence as to utility and abnormality in toxicity
- Amsler grid – too subjective for patients to notices subtle long-term changes; inadequate sensitivity/specificity. Can be used as supplemental test
- Color vision testing – inadequate sensitivity/specificity; supplemental

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Conclusions

Each patient's CQ/HCQ dosing must be considered in regard to his/her height and ideal body weight (BMI chart!), and concomitant conditions of the patient's kidneys, liver, and retina.

Screening regimens and risk assessment are becoming more standardized as recommendations become more evidence-based.

More simplified screening regimen focusing more on objective testing

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