

Complications of Pharmaceuticals Every Optometrist Should Know!

Greg A. Caldwell, OD, FAAO
Optometric Education Consultants
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Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

- Lectured for: Alcon, Allergan, Aerie, B&L, BioTissue, Kala, Maculogix, Optovue, RVL, Heru, Santen
 - Disclosure: Receive speaker honorariums
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- Envolve: PA Medical Director, Credential Committee
- Healthcare Registries – Chairman of Advisory Council for Diabetes and AMD
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Which of these ocular complications have you seen?

1. Hydroxychloroquine / chloroquine retinopathy
2. Amiodarone – corneal whorls or optic neuropathy
3. Tetracycline: pseudotumor cerebri or other complications
4. Ethambutol optic neuropathy



Thoughts

- Always check the medication list
 - ★ Review it with the patient (techs don't always update)
- Medications to H.A.T.E in neuro-op (Andy Lee, MD)
 - ★ Hydroxychloroquine / chloroquine retinopathy
 - ★ Amiodarone optic neuropathy - Anterior ischemic optic neuropathy
 - ★ Tetracycline: pseudotumor cerebri
 - ★ Ethambutol optic neuropathy
- ★ The Erectile dysfunction agents (Viagra) -Anterior ischemic optic neuropathy

Andy Lee, MD

Antibiotics (anti-inflammatory)

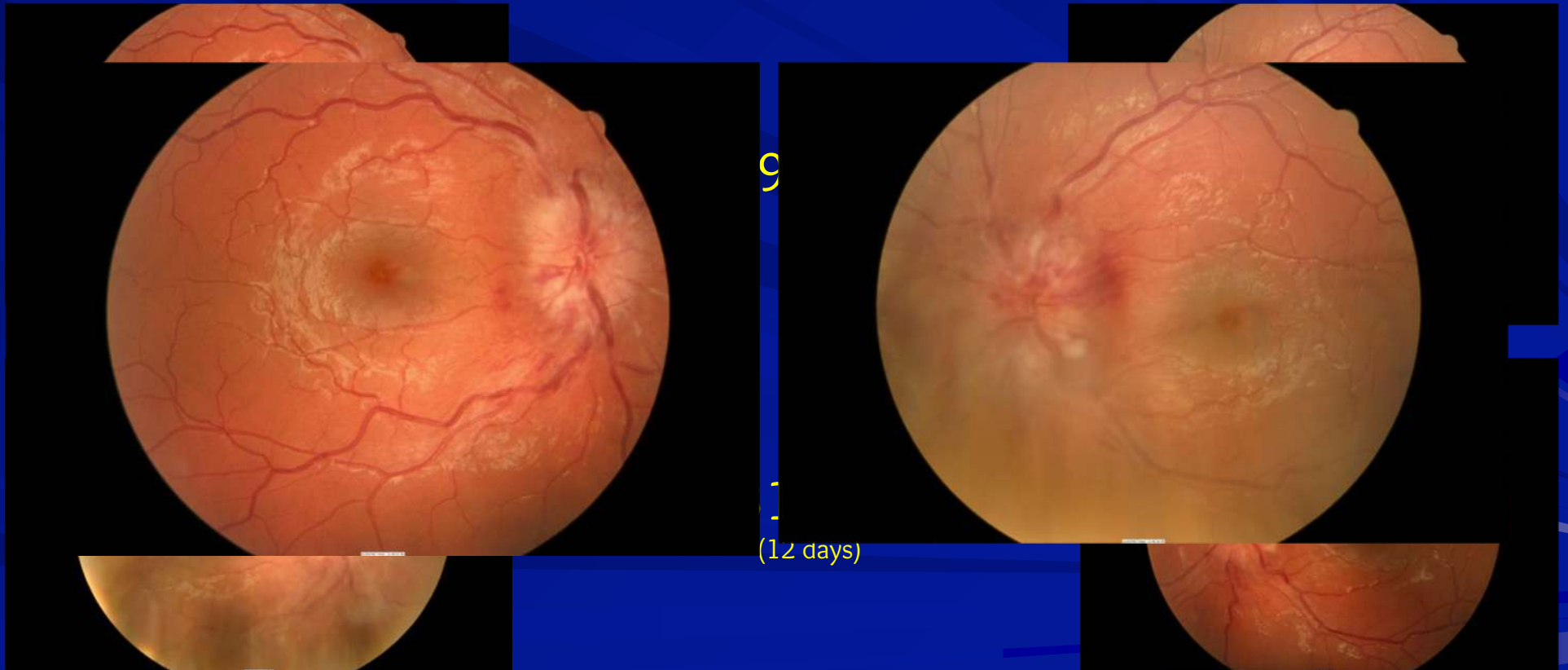
Adverse Drug Reactions

- Tetracycline analogs
 - ★ Doxycycline
 - ★ Minocycline
- Enhanced photosensitivity
- Avoid in children and pregnancy (Category D), and in breastfeeding women
 - Stained teeth
 - Small incisors
- Enhances the effects of
 - ★ Coumadin
 - Comment on antibiotic drug interactions...
 - ★ Digoxin
- Idiopathic intracranial hypertension
 - ★ Pseudotumor cerebri
- Hyperpigmentation



Benign intracranial hypertension

“It’s not rare if it’s in your chair”





9-13-2010
(25 days)



10-6-2010
(48 days)



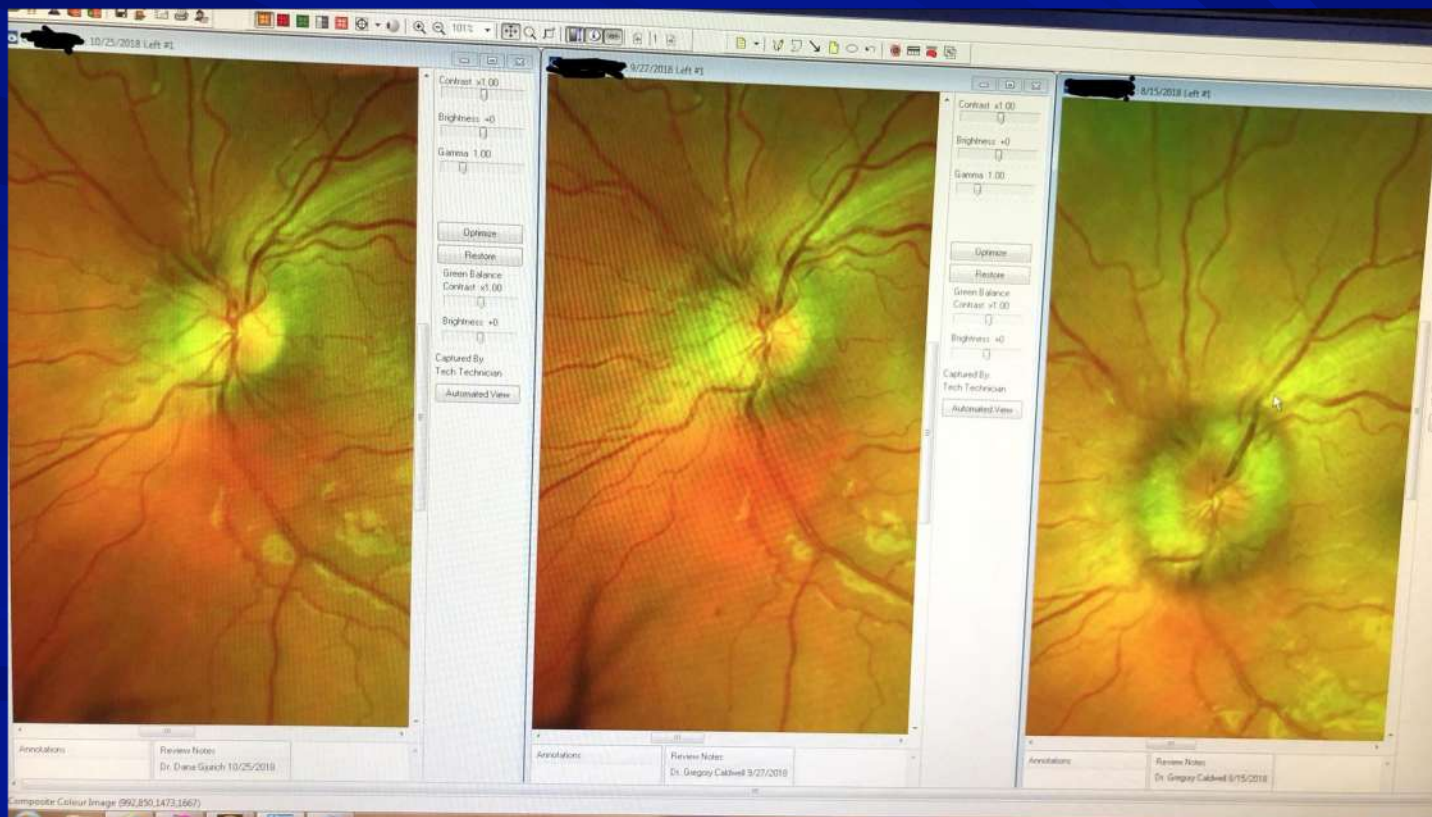
8-19-2010



PTC VS. IIH (THANKS DR. JOE SOWKA)

- **Pseudotumor Cerebri (PTC)**
 - Increased intracranial pressure in the absence of an intracranial mass lesion
 - Many causative agents have been identified
 - IIH, venous sinus thrombosis, drugs
- **Primary PTC - IIH**
- **Secondary PTC - venous sinus thrombosis, drugs**
- **Idiopathic Intracranial Hypertension (IIH)**
 - Increased intracranial pressure without an identifiable cause
 - Young, obese females are at risk
 - Poor CFS drainage
- **Secondary Intracranial Hypertension (IIH)**
 - venous sinus thrombosis, drugs
 - ex. doxycycline

Minocycline Optic Nerve Edema



Minocycline Optic Nerve Edema



OMG



6 Months Later



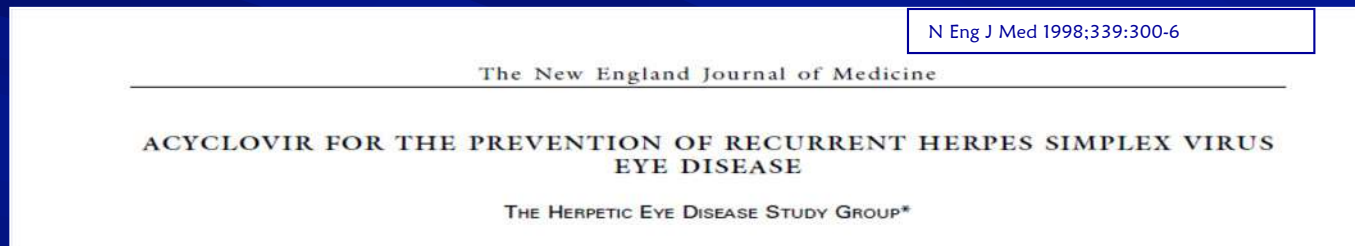
1 Year Later



Antivirals

Beside the dosing frequencies...

🕒 What is different about the oral antivirals?



- 🕒 Main reason for early discontinuation of oral acyclovir in HEDS

- 🕒 Gastrointestinal side effects

- 🕒 Rash

Many patients on oral acyclovir have GI symptoms

Acyclovir vs. Valacyclovir vs. Famciclovir

What is the difference?

ZOVIRAX is the brand name for acyclovir, a synthetic nucleoside analogue active against herpesviruses. ZOVIRAX Capsules, Tablets, and Suspension are formulations for oral administration. Each capsule of ZOVIRAX contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C Blue No. 2, and titanium dioxide. May contain one or more parabens. Printed with edible black ink.

Acyclovir

Zovirax® contains lactose
Presence or absence of lactose in
generic acyclovir varies

VALTREX (valacyclovir hydrochloride) is the hydrochloride salt of the *L*-valyl ester of the antiviral drug acyclovir.

VALTREX Caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 gram valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated caplets are printed with edible white ink.

Valacyclovir

Valtrex® and all generics are free of
lactose

FAMVIR tablets contain 125 mg, 250 mg, or 500 mg of famciclovir, together with the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycols, sodium starch glycolate and titanium dioxide.

Generics available in the US contain lactose

* In Europe you can get generic famciclovir without lactose (Teva Pharmaceuticals, Israel)

Acyclovir vs. Valacyclovir vs. Famciclovir

What is the difference?

CNS Effects in Elderly Patients

- Acyclovir and valacyclovir carry a higher risk of CNS adverse effects in the elderly:
 - ★ Agitation
 - ★ Hallucinations
 - ★ Confusion
- Clinical Take Home Point:
- Consider famciclovir in older patients who CNS side effects with acyclovir or valacyclovir
- Other major concern with elderly patients is age-related reduced kidney function

Alpha 1 Blockers

- Floppy iris syndrome!
- Treatment of enlarged prostate:
 - ★ Uroxatrol™ (Alfuzosin)
 - ★ Flomax™ (Tamsulosin)
 - 📋 These two agents **LIKELY** have the highest incidence of causing floppy iris syndrome, as they are selective for alpha 1a receptors, which also predominate in the eye
 - 📋 Complications can be intraoperative (eg. iris trauma) or postoperative (eg. intraocular pressure increases)
 - 57-100% incidence with tamsulosin
 - there may also be a correlation with higher doses?
- Treatment of CHF and/or hypertension
 - ★ Coreg™ (Carvedilol)
 - 📋 Alpha1/beta 2 blocker
 - ★ Hytrin™ (Terazosin)
 - 📋 Alpha 1 blocker

Alpha 1 Blockers

- Floppy iris syndrome and miosis!
- After 4 rounds of phenylephrine, tropicamide, and cyclopentolate, if poor dilation
 - ★ Iris hooks
- What happens at the time of making the incision?
 - ★ Tricks with different viscoelastic agents
- Post op day 1, IOP 43
 - ★ What's the caution?

I have seen cornea verticillata cause vision loss?

1. Yes
2. No
3. It doesn't cause vision loss



Anti-arrhythmics

👓 Treatment of cardiac arrhythmia

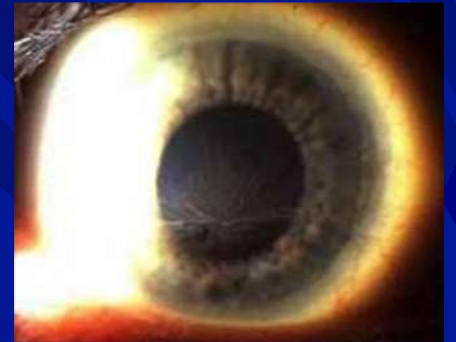
★ Cordarone™ (amiodarone)

📋 Corneal deposits - nearly universal in patients on amiodarone

- usually bilateral with 10% complaining of blurred vision and halos around lights

📋 Optic neuritis - 2% incidence

- can occur anytime after starting amiodarone



Stages

Grade I	Punctate opacities in a horizontal linear pattern in the inferior cornea
Grade II	More aligned deposits in a linear pattern that extend into the inferior pupillary margin toward the limbus
Grade III	Increased numbers of branching patterns in the inferior pupillary area into the visual axis
Grade IV	Deposits form additional clumps compared with grade III

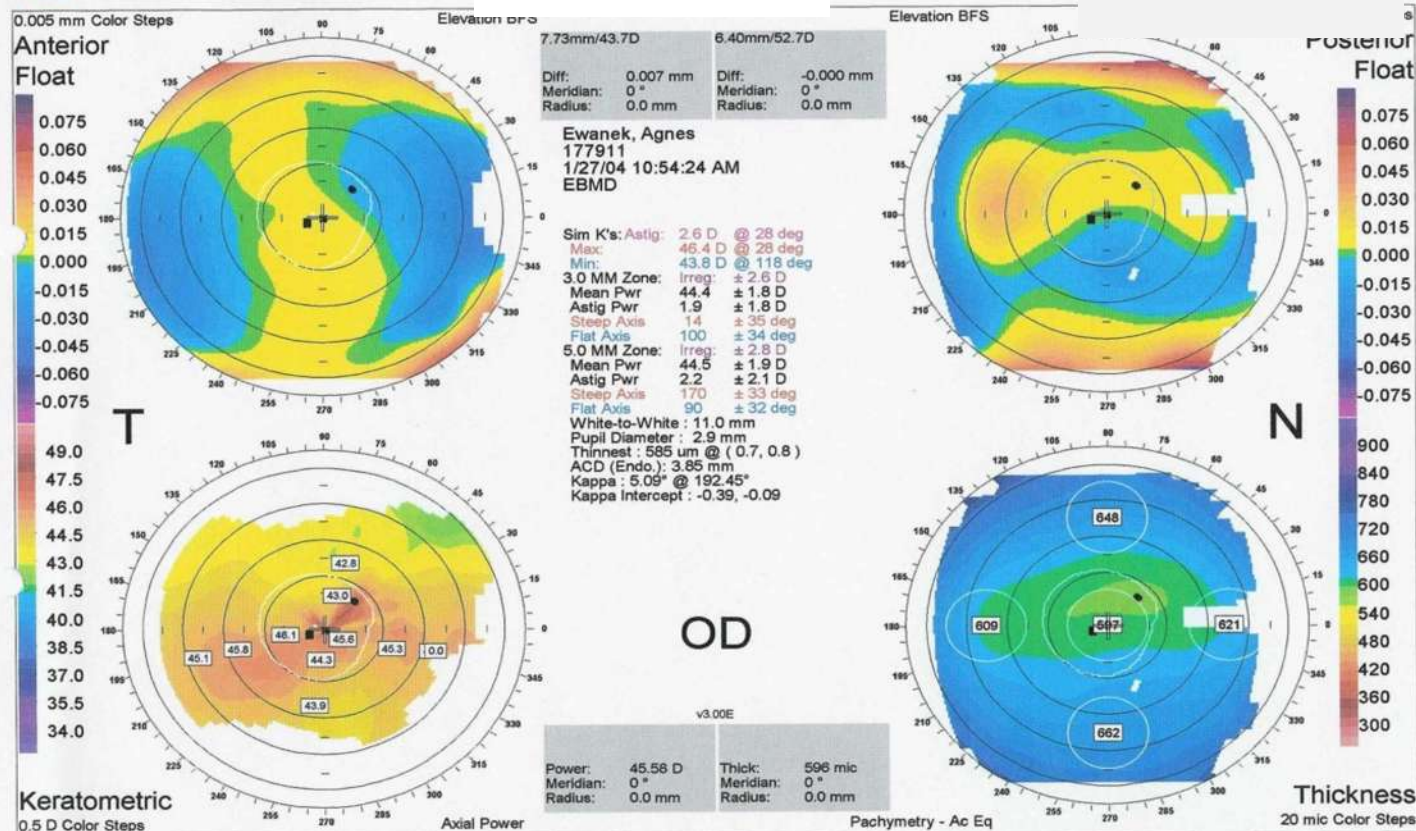
65-year-old woman

- Patient reports decreasing vision over past 6-9 months. Especially at near
- Vision 20/50 OU



Topography

Greg Caldwell, O.D.



0.005 mm Color Steps

Anterior Float

0.075
0.060
0.045
0.030
0.015
0.000
-0.015
-0.030
-0.045
-0.060
-0.075

Elevation

7.74mm/43.6D

Diff: 0.005 mm
Meridian: 0°
Radius: 0.0 mm

6.46mm/52.2D

Diff: 0.005 mm
Meridian: 0°
Radius: 0.0 mm

Ewanek, Agnes
177911
1/27/04 10:55:31 AM
EBMD

Sim K's: Astig: 2.4 D @ 164 deg
Max: 46.0 D @ 164 deg
Min: 43.6 D @ 74 deg
3.0 MM Zone: Irreg: ±1.3 D
Mean Pwr 44.6 ±0.8 D
Astig Pwr 3.1 ±1.0 D
Steep Axis 167 ±13 deg
Flat Axis 78 ±13 deg
5.0 MM Zone: Irreg: ±1.6 D
Mean Pwr 44.4 ±1.1 D
Astig Pwr 2.1 ±1.2 D
Steep Axis 167 ±20 deg
Flat Axis 77 ±20 deg
White-to-White: 11.1 mm
Pupil Diameter: 3.5 mm
Thinnest: 565 um @ (1.6, 0.4)
ACD (Endo): 3.87 mm
Kappa: 4.23° @ 1.67°
Kappa Intercept: 0.33, 0.01

OS

v3.00E

Power: 45.77 D
Meridian: 0°
Radius: 0.0 mm

Thick: 578 mic
Meridian: 0°
Radius: 0.0 mm

Elevation BFS

Posterior Float

0.075
0.060
0.045
0.030
0.015
0.000
-0.015
-0.030
-0.045
-0.060
-0.075

900
840
780
720
660
600
540
480
420
360
300

Thickness

20 mic Color Steps

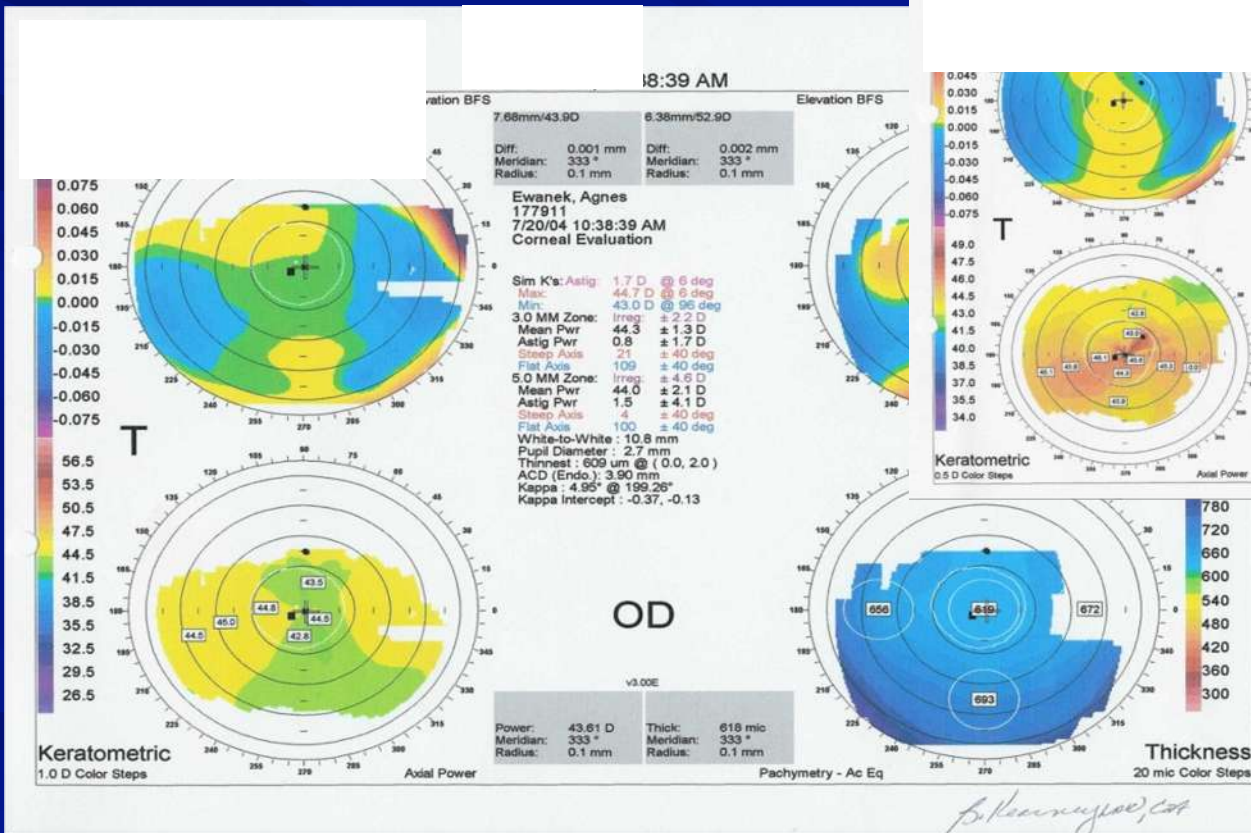
Keratometric

0.5 D Color Steps

Axial Power

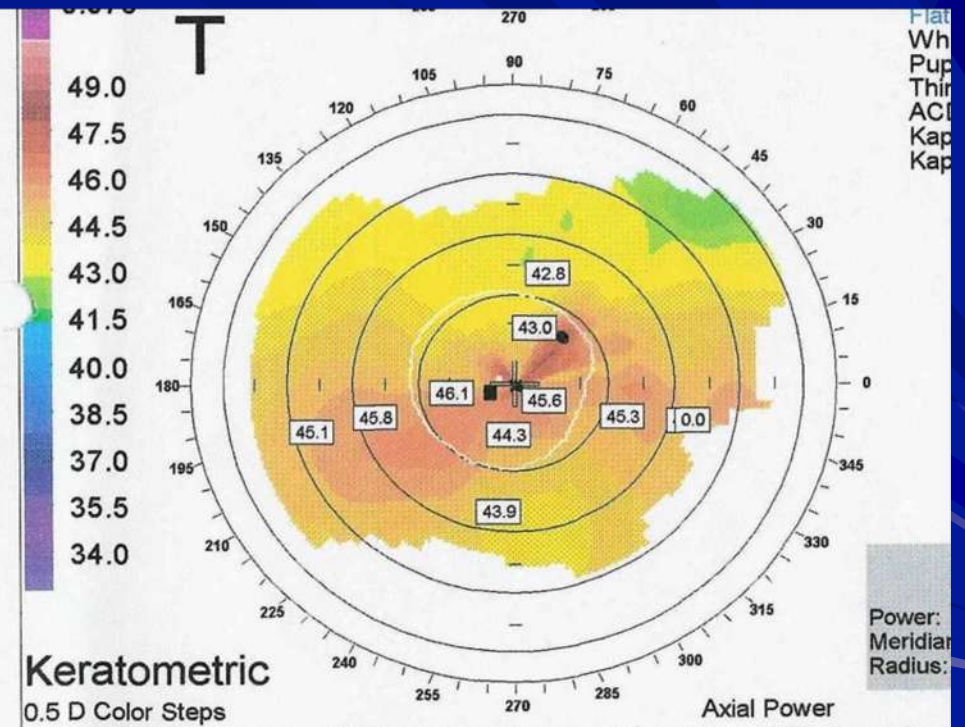
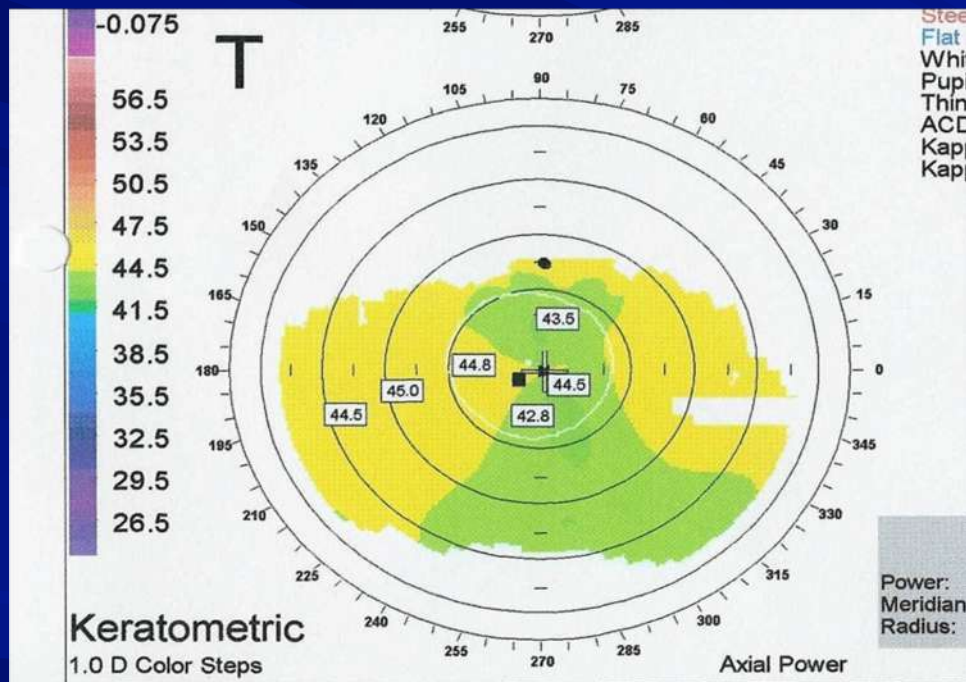
Pachymetry - Ac Eq

6 Months Later

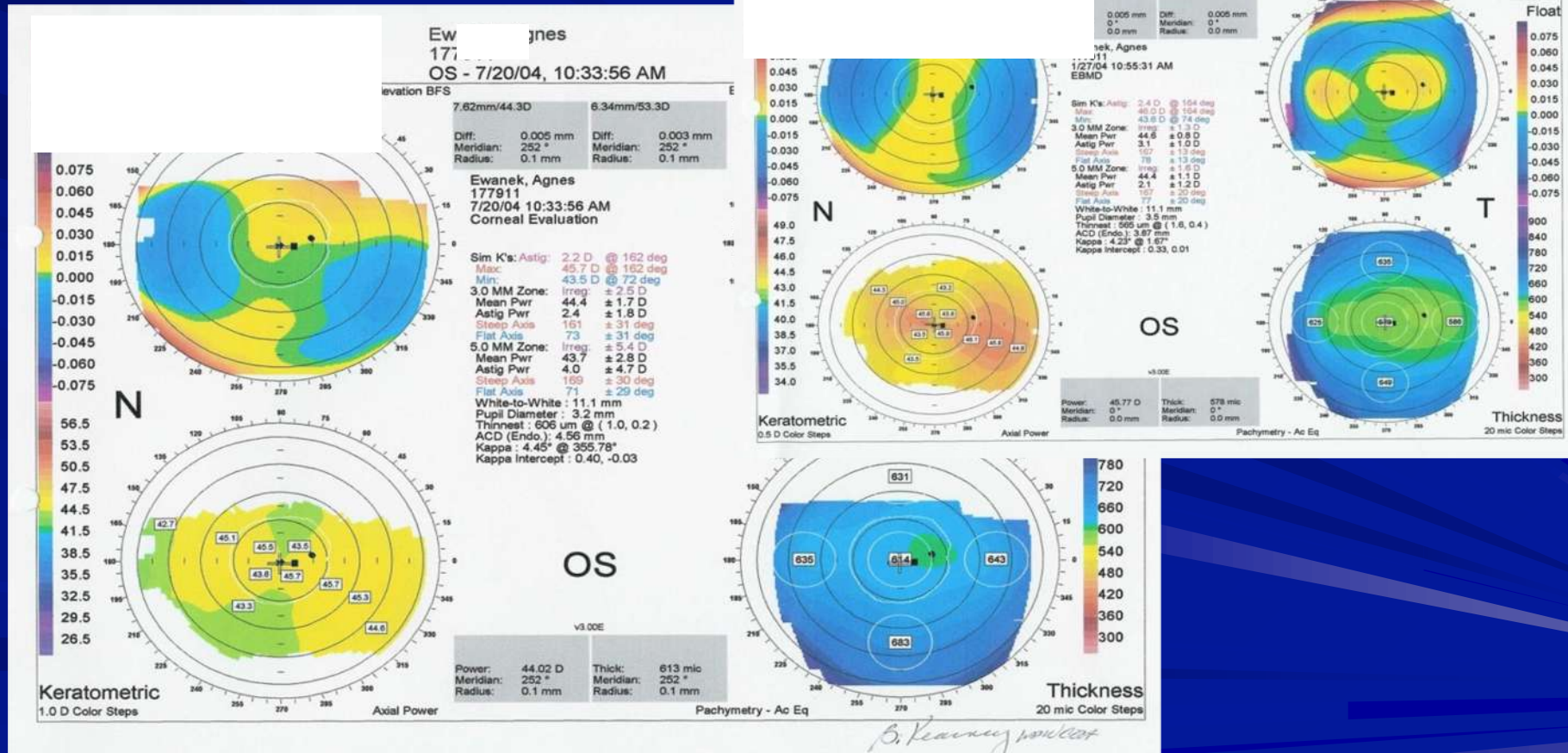


20/25 BVA

OD

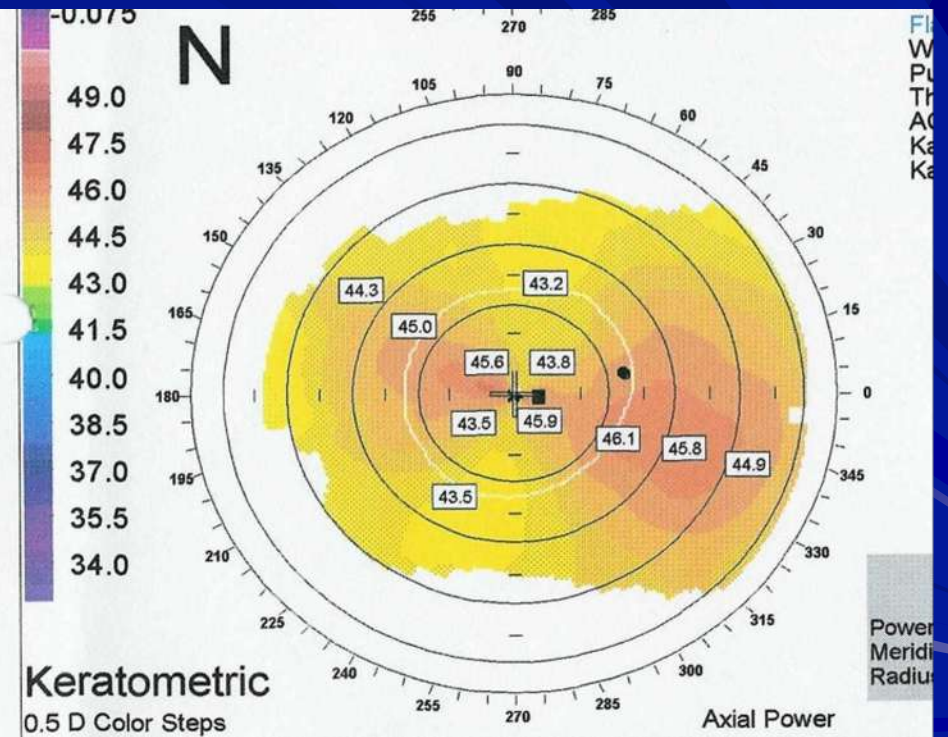
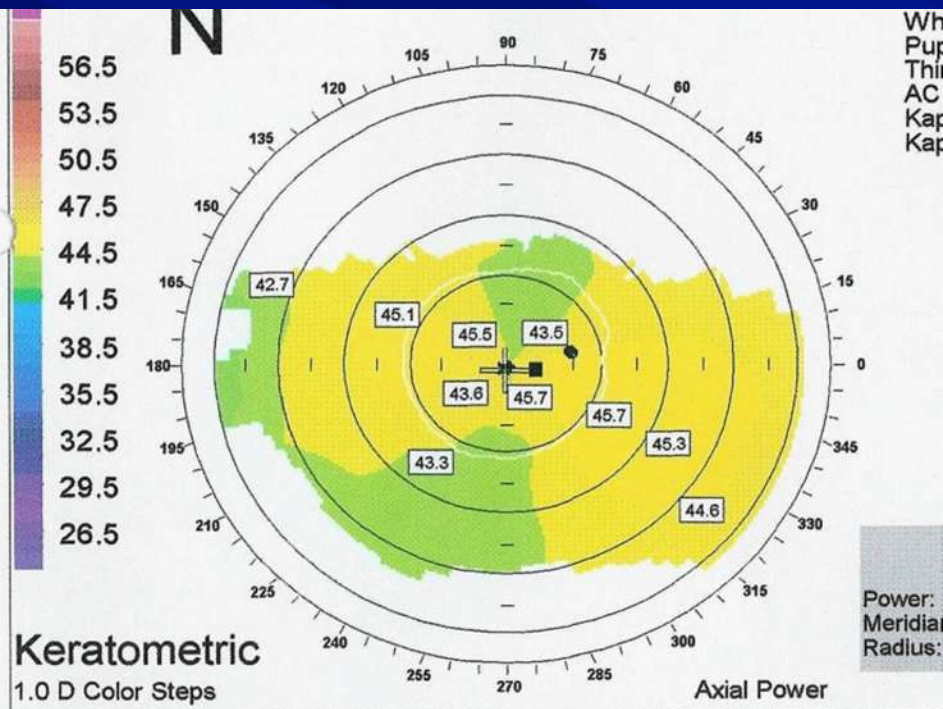


6 Months Later



20/25 BVA

OS



67-year-old man complains of vision slowly deteriorating over the past 8 months

- History of NA-ION 10 months ago OD
- Patient sees family physician for physical due to recent NA-ION
 - ★ Patient has not been to PCP for 35 years
 - ★ Patient started Cardarone™
 - ★ VA 20/80 OD 20/25 OS (9 months ago)
- VA 20/400 OD 20/200 OS (today)
- CF: severe constriction OU
- SLE: vortex corneal whorls OU

SINGLE FIELD ANALYSIS

EYE: LEFT

ID: 169143

DOB: 09-21-1936

CENTRAL 24-2 THRESHOLD TEST

FIXATION MONITOR: GAZE/BLINDSPOT

STIMULUS: III, WHITE

PUPIL DIAMETER:

DATE: 09-02-2003

FIXATION TARGET: CENTRAL

BACKGROUND: 31.5 ASB

VISUAL ACUTY:

TIME: 0157 AM

FIXATION LOSS: 1/15

STRATEGY: SITA-STANDARD

RX: +5.50 DS

DC: X

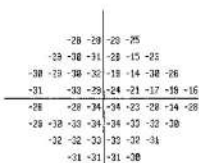
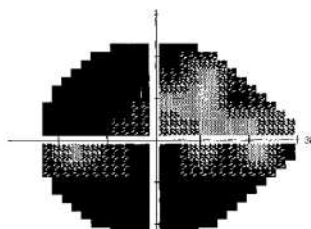
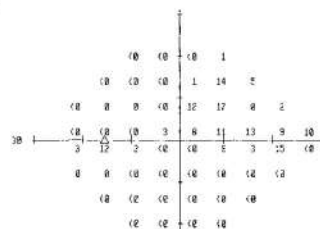
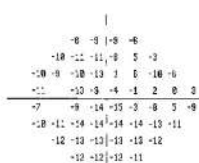
AGE: 66

FALSE POS ERRORS: 0 %

FALSE NEG ERRORS: N/A

TEST DURATION: 00:50

FOVEA: OFF

TOTAL
DEVIATIONPATTERN
DEVIATIONGHT
OUTSIDE NORMAL LIMITSMD -20.00 DS P < 0.5%
PMD 6.14 DS P < 0.5%

11 < 5%
 12 < 2%
 13 < 1%
 14 < 0.5%

© 1994-2000 HUNTER SYSTEMS
 HFA II 745-4244-1.2/2.2

SINGLE FIELD ANALYSIS

EYE: RIGHT

ID: 169143

DOB: 09-21-1936

CENTRAL 24-2 THRESHOLD TEST

FIXATION MONITOR: GAZE/BLINDSPOT

STIMULUS: III, WHITE

PUPIL DIAMETER:

DATE: 09-02-2003

FIXATION TARGET: CENTRAL

BACKGROUND: 31.5 ASB

VISUAL ACUTY:

TIME: 0158 AM

FIXATION LOSS: 4/12 X

STRATEGY: SITA-STANDARD

RX: +5.75 DS

DC: X

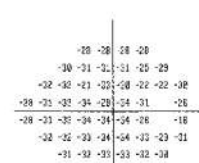
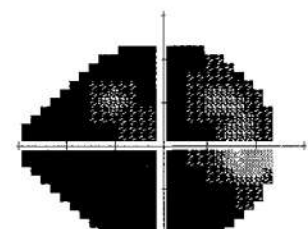
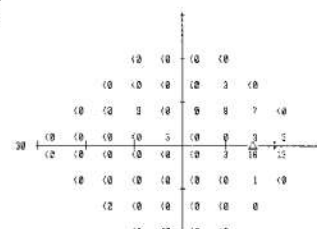
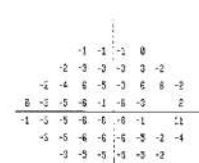
AGE: 65

FALSE POS ERRORS: 2 %

FALSE NEG ERRORS: N/A

TEST DURATION: 00:50

FOVEA: OFF

TOTAL
DEVIATIONPATTERN
DEVIATION

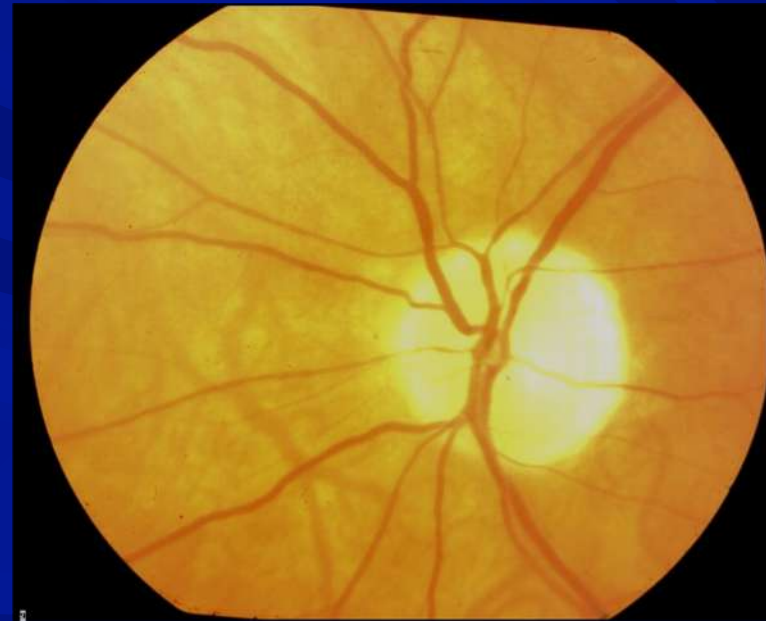
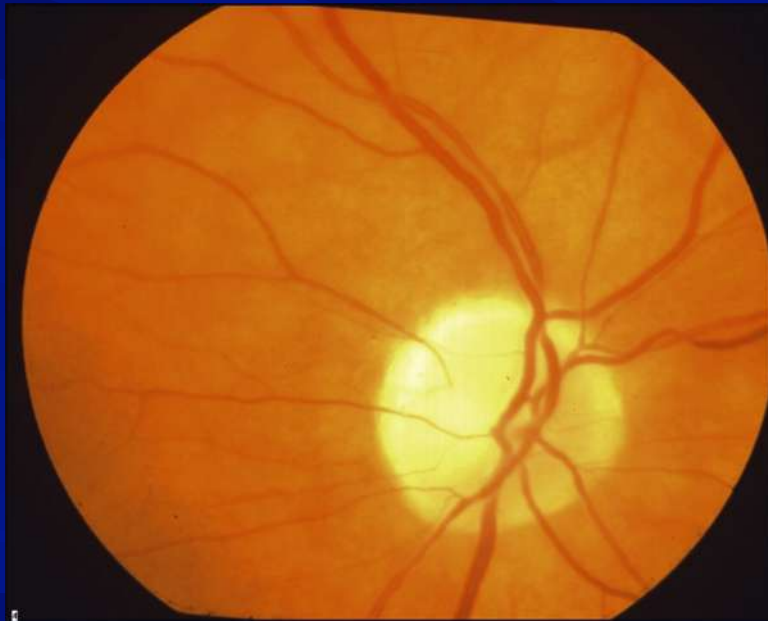
LOW PATIENT RELIABILITY
 GHT
 OUTSIDE NORMAL LIMITS

MD -30.50 DS P < 0.5%
 PMD 2.00 DS P < 0.5%

11 < 5%
 12 < 2%
 13 < 1%
 14 < 0.5%

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Amiodarone Optic Neuropathy (Toxic Optic Neuropathy)



Lanoxin™ (Digoxin)

- Anti-arrhythmic, used in CHF (+ inotrope, - chronotrope)
 - Digoxin toxicity = due to supratherapeutic levels
 - yellow or green vision
 - blurred vision
 - halos around objects

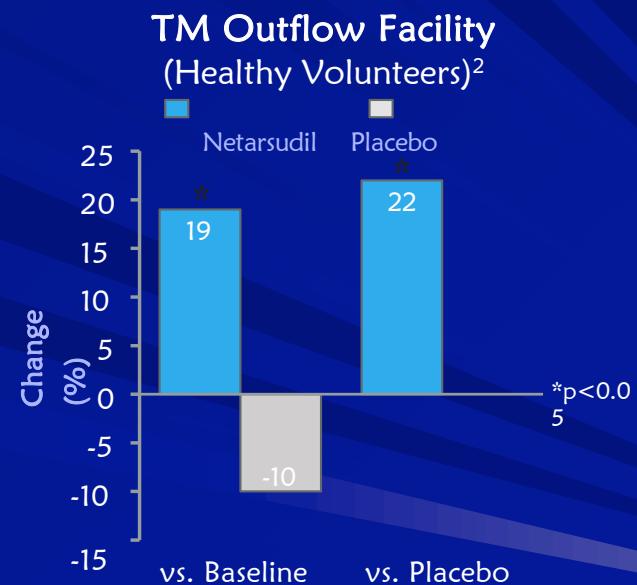
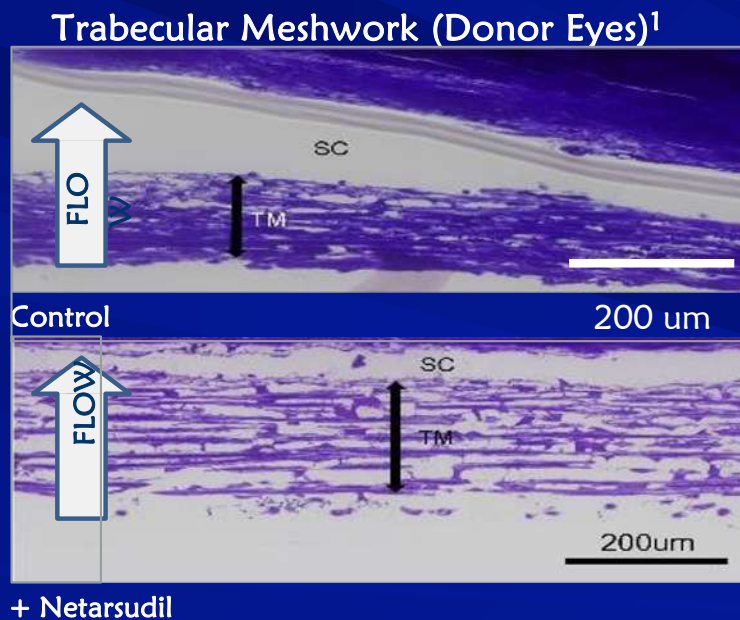
Rhopressa™ 0.02% (netarsudil ophthalmic solution)

•• Aerie Pharmaceuticals

- ★ Approved December 2017
- ★ Treatment of glaucoma or ocular hypertension
- ★ Rho kinase inhibitor
 - ☐ ROCK-NET Inhibitor
- ★ Once daily in the evening
 - ☐ Twice a day dosing is not well tolerated and is not recommended
- ★ Side Effects
 - ☐ Conjunctival hyperemia
 - ☐ Corneal verticillata
 - ☐ Conjunctival hemorrhage

Rhopressa™ 0.02% (netarsudil)

Causes Expansion of TM in Donor Eyes
Increases TM Outflow Facility in Clinic

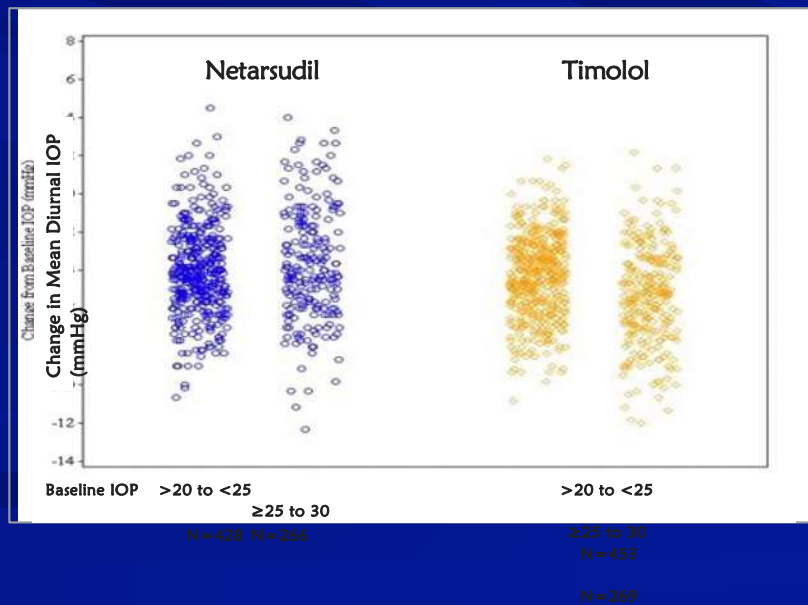


TM: Trabecular Meshwork; SC: Schlemm's Canal; Control: buffered saline solution; ESV: Episcleral Vein
1. Ren R et al. Invest Ophthalmol Vis Sci. 2016;57(14):6197-6209. 2. Sit AJ et al. Presented at AGS 2017.

Netarsudil is Similarly Effective at Baseline IOPs <25 mmHg and ≥ 25 mmHg

Pooled Analysis Rocket 1, Rocket 2, Rocket 4

Day 90: Change from Baseline IOP by Baseline
Subgroup (Pooled)



Baseline IOP >20 to <25 mmHg

	Netarsudil QD	Timolol BID
Median	-4.2	-4.3
Mean	-4.1	-4.3
Max	-10.7	-10.8

Baseline IOP ≥ 25 to <30 mmHg

	Netarsudil QD	Timolol BID
Median	-4.0	-5.3
Mean	-3.7	-5.3
Max	-12.3	-12.0

Rhopressa™ 0.02%

- No labeled contraindications for Rhopressa™
- No clinically relevant effects on vital signs
 - ★ Blood Pressure
 - 📋 Changes were generally small and not clinically relevant in both groups
 - ★ Heart Rate
 - 📋 Timolol caused statistically significant reduction in the phase 3 studies by an average of 2-3 beats per month

Conjunctival Hemorrhage was Sporadic and Severity did not Increase with Continued Dosing

Adverse Events	Netarsudil 0.02% QD	Timolol 0.5% BID
	(N=839) n (%)	(N=839) n (%)
TEAE Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
AE Resulting in Discontinuation	8 (1.0)	0

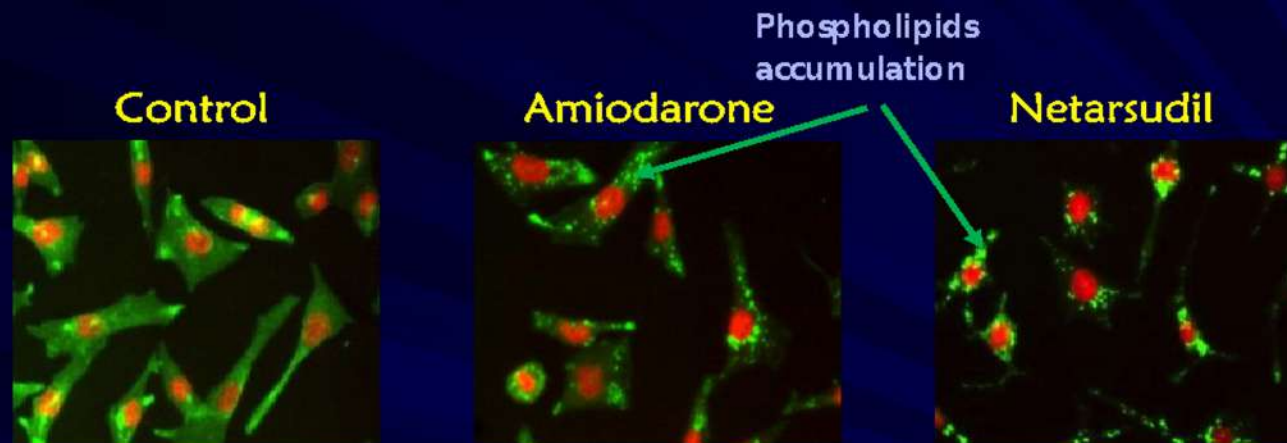
Majority 92.4% (133/144) of the conjunctival hemorrhage in netarsudil QD group was mild, 6.3% (9/144) was moderate and 1.4% (2/144) was severe
Self-resolving with continued dosing



Images were taken from netarsudil subjects
Source: Courtesy of study investigators AR-13324-CS301, -CS302

Cornea Verticillata Due to Phospholipidosis

Medications known to cause verticillata: amiodarone, chloroquine, naproxen, phenothiazine, ocular gentamicin and tobramycin*



Due to phospholipidosis where the parent drug is complexed with phospholipids in the lysosomes

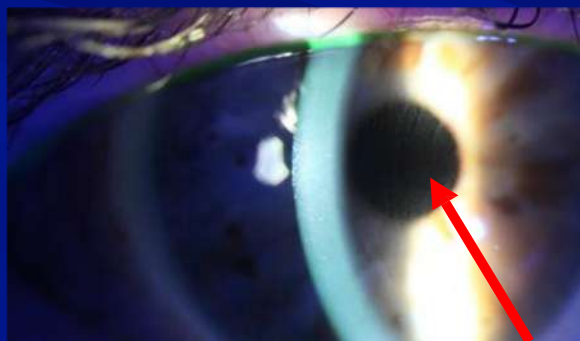
Literature review suggested it is an adaptive response by the body rather than an adverse pathology*

Data on File Based on AR-13324-IPH07

* Raizman M B et al. Surv. Ophthalmol. 2017;62:286-301

Cornea Verticillata Observed in Phase 3 Studies

- Cornea verticillata refers to a whorl-like pattern of deposits typically localized to the basal corneal epithelium
- Subjects are asymptomatic
- The onset was ~6 to 13 weeks (netarsudil QD)



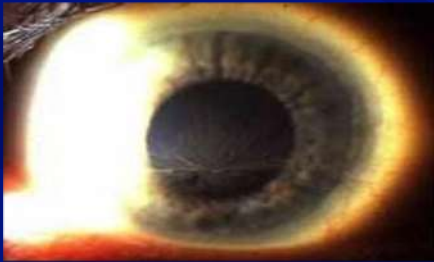
AR-13324-CS302
netarsudil QD subject



AR-13324-CS302
netarsudil BID subject

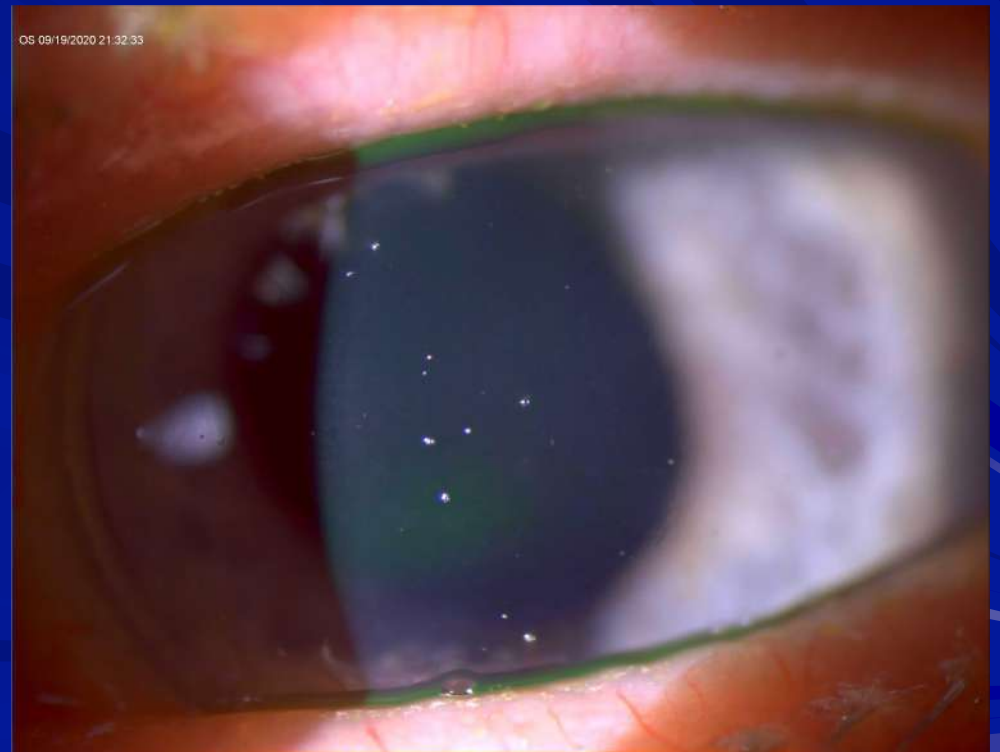
Cornea verticillata

Images were taken from netarsudil subjects
Source: Courtesy of study investigators AR-13324-CS302



My Experience

OD treated OS gtt



Summary of the Most Common Netarsudil Ocular TEAEs

Conjunctival Hyperemia

- 54.4% TEAE
- Severity did not increase with continued dosing
- Sporadic

Cornea Verticillata

- 20.9% TEAE
- Asymptomatic
- 7.4% experienced reduced visual acuity (not clear to a directly associated), all resolved after 13 weeks of D/C

Conjunctival Hemorrhage

- 17.2% TEAE
- Mild in severity and transient
- Self-resolving with continued dosing

Drugs Causing ACG – Angle Closure Glaucoma

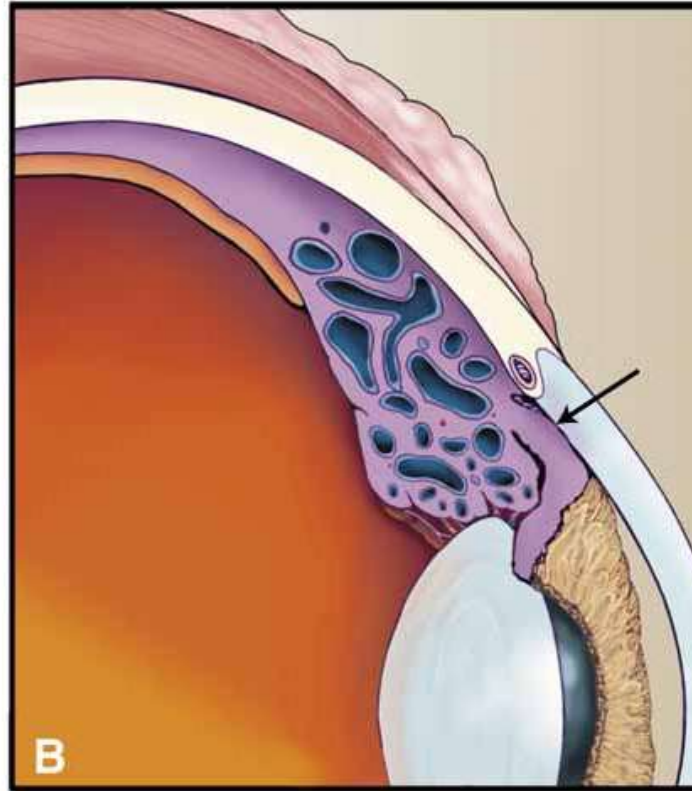
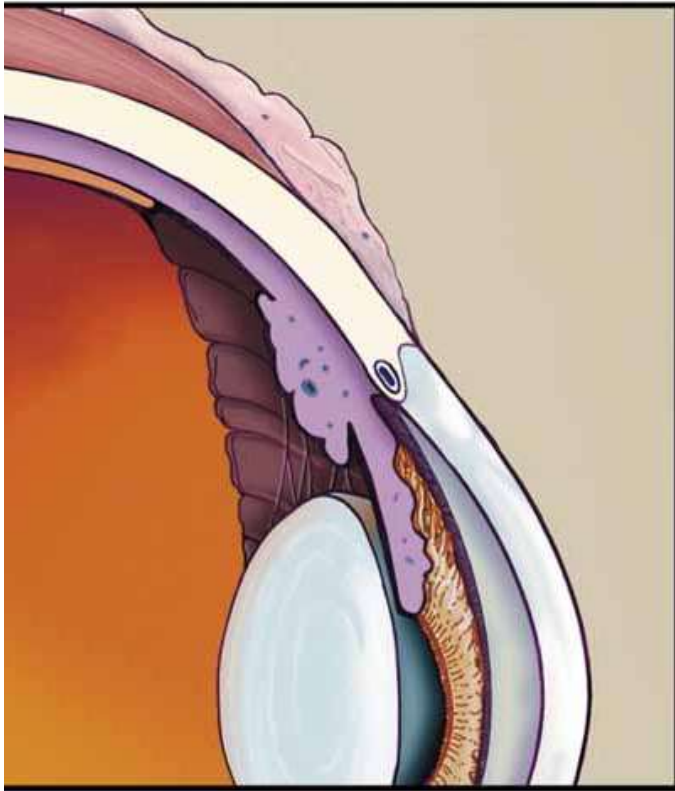
- Acetazolamide
- Hydrochlorothiazide
- Trimethoprim-sulfamethoxazole
- Indapamide
- Promethazine
- Spironolactone
- Isosorbide dinitrate
- Viagra
- Bromocriptine
- Tetracycline
- Corticosteroids
- Penicillamine
- Quinine
- Metronidazole
- Isotretinoin
- Aspirin
- Topiramate*



Ciliary Effusion

- Anterior Rotation of the Ciliary Body
 - Reduces tension on the zonules
 - Lens Thickening
 - Induces myopia
 - Iris-Lens diaphragm shifts anteriorly
 - Induces myopia by changing effectivity
 - Shallowing of Anterior Chamber
 - Potential for angle closure



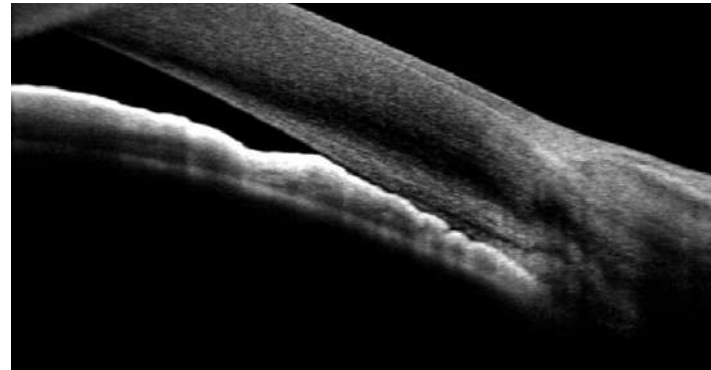
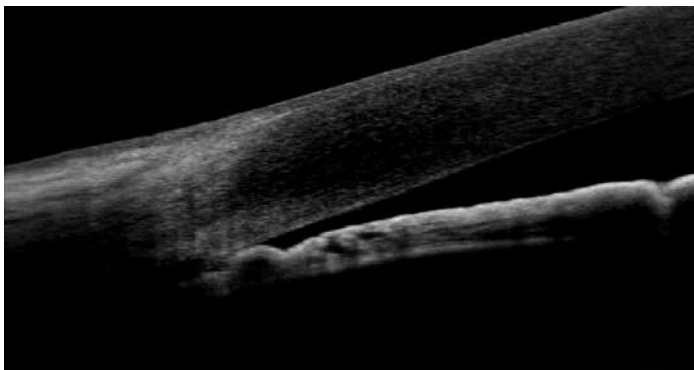




NASAL



TEMPORAL



Case

- 39 YOF
- Recently started on Topamax for migraine
- Sudden onset blurred vision and eye pain
- Formerly emmetropic, now (-) 6.00 DS
- IOP 44 mm Hg



What is the best management?

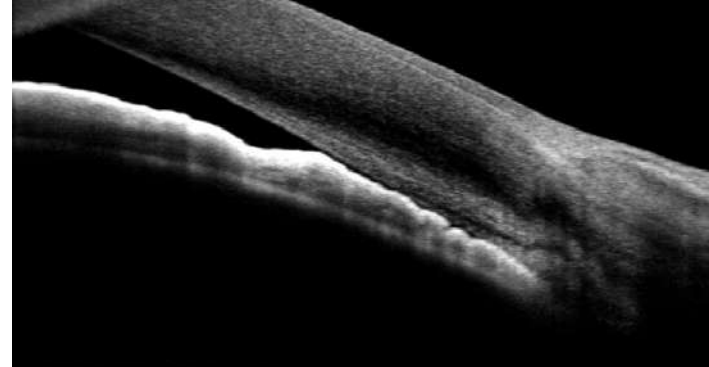
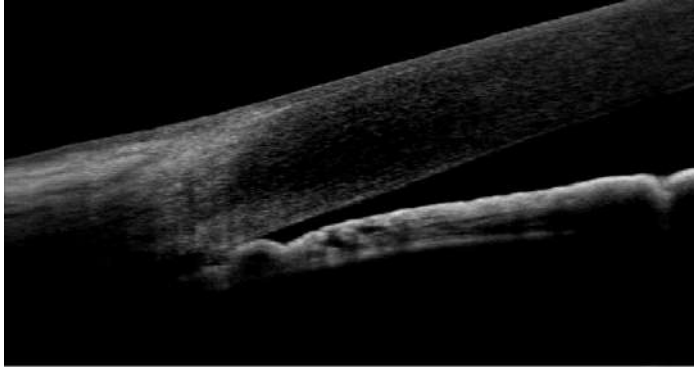
- Cycloplegic and topical steroids
- Oral Diamox
- Cosopt and Lumigan
- Immediate LPI
- I'm not sure. That's why I'm here.



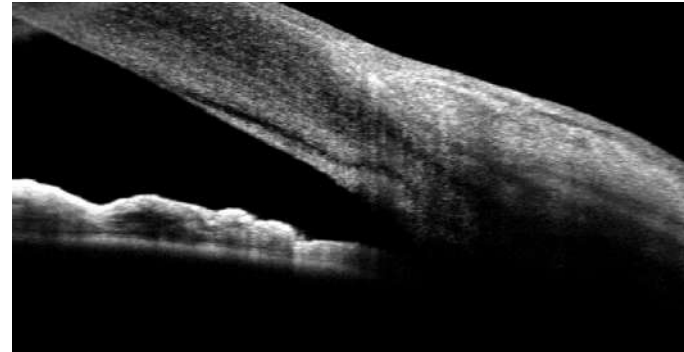
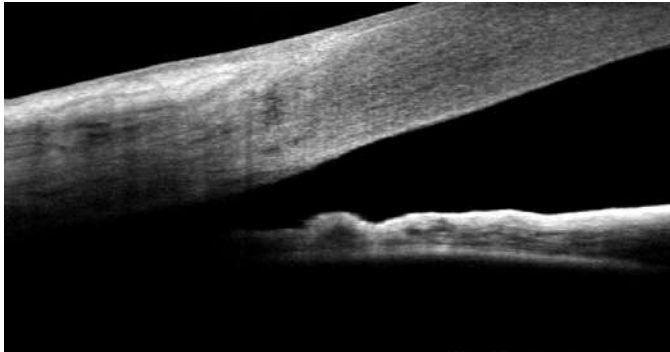
Case

- 39 YOF
- Recently started on Topamax for migraine
- Sudden onset blurred vision and eye pain
- Formerly emmetropic, now (-) 6.00 DS
- IOP 44 mm Hg
- D/C Topamax; add PF Q1H, scopolamine BID, beta blocker BID





Initial Presentation



Resolution

Choroidal Involvement in ACG

- Drug-induced choroidal expansion
- Choroidal expansion in ACG associated with shallowing of chamber
- Malignant glaucoma may not be aqueous misdirection, but poor fluid permeability and choroidal expansion
- Atropine may work by moving ciliary body and improving forward diffusional area for fluid
 - Atropine may be a better choice than pilocarpine



Toxic Optic Neuropathy

•• Causes

- ★ Ethambutol (TB)
- ★ Isoniazid
- ★ Antimicrobials
 - chloramphenicol, streptomycin, penicillamine
- ★ Halogenated hydroxyquinolones
- ★ Vigabatrin
- ★ Disulfiram
- ★ Tamoxifen
- ★ Sildenafil

•• Causes

- ★ Methanol
- ★ Heavy metals
- ★ Fumes
- ★ Solvents
- ★ Alcohol abuse
- ★ Tobacco abuse

Clinical Pearl: When you encounter a pt with these pharmaceuticals, consider and evaluate for toxic optic neuropathy (TON)

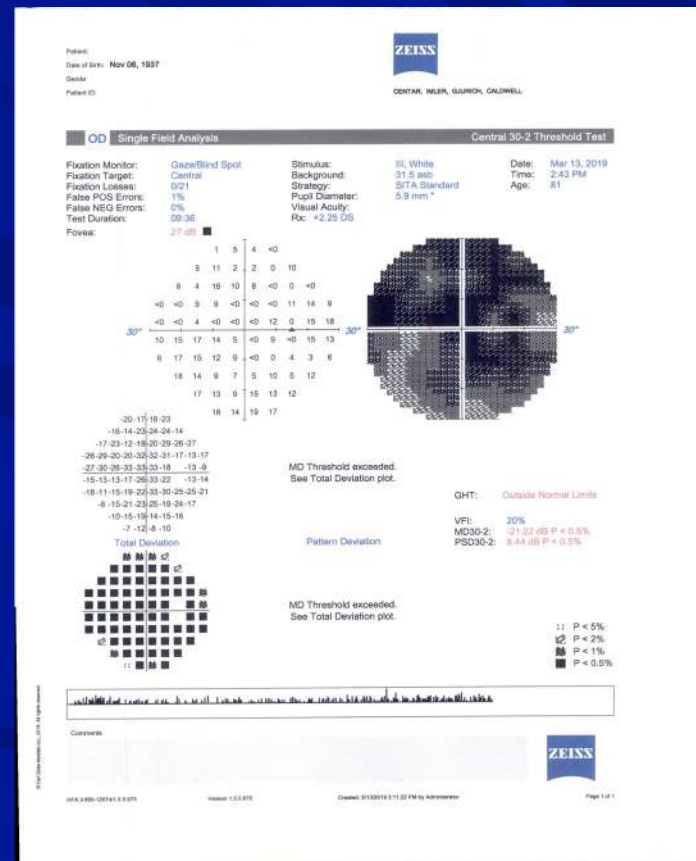
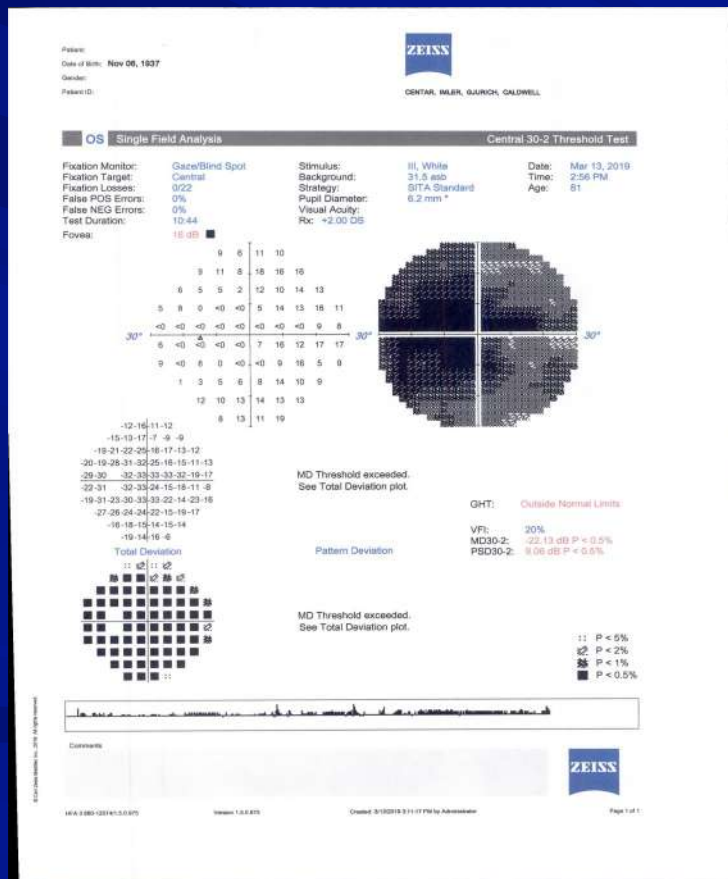
Ethambutol

- 👓 Still used in the 4-drug treatment plan for active *Mycobacterium tuberculosis* (“TB”)
 - ★ Patients will take isoniazid + rifampin + pyrazinamide + ethambutol for ABOUT 2 months
 - 📋 Organism sensitivities come back
 - 📋 Non-resistant TB = discontinuation of pyrazinamide and ethambutol
- 👓 Toxic optic neuropathy
- 👓 2 cases in the past 12 months (2019)

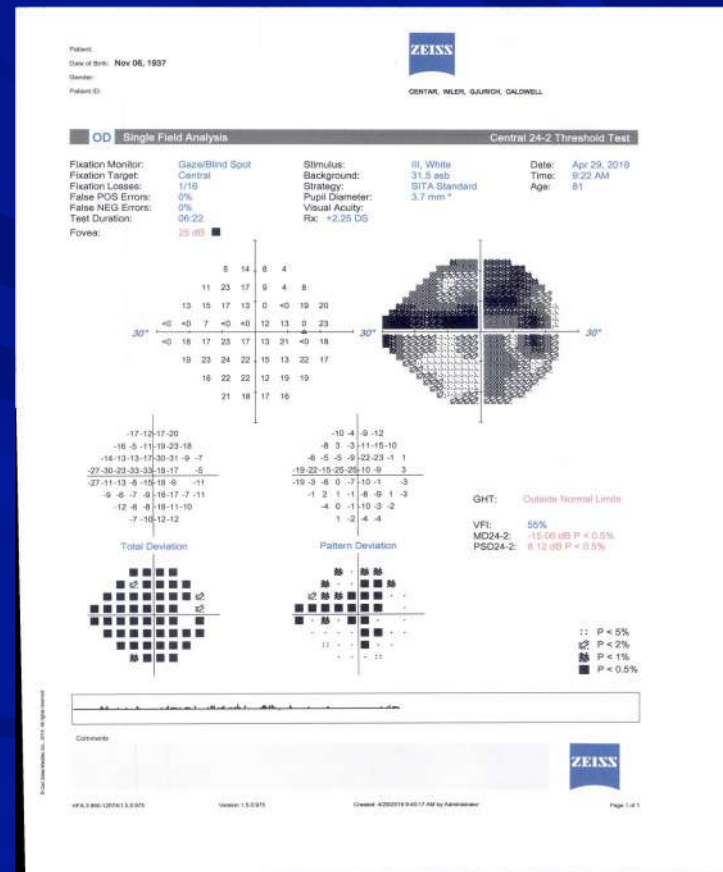
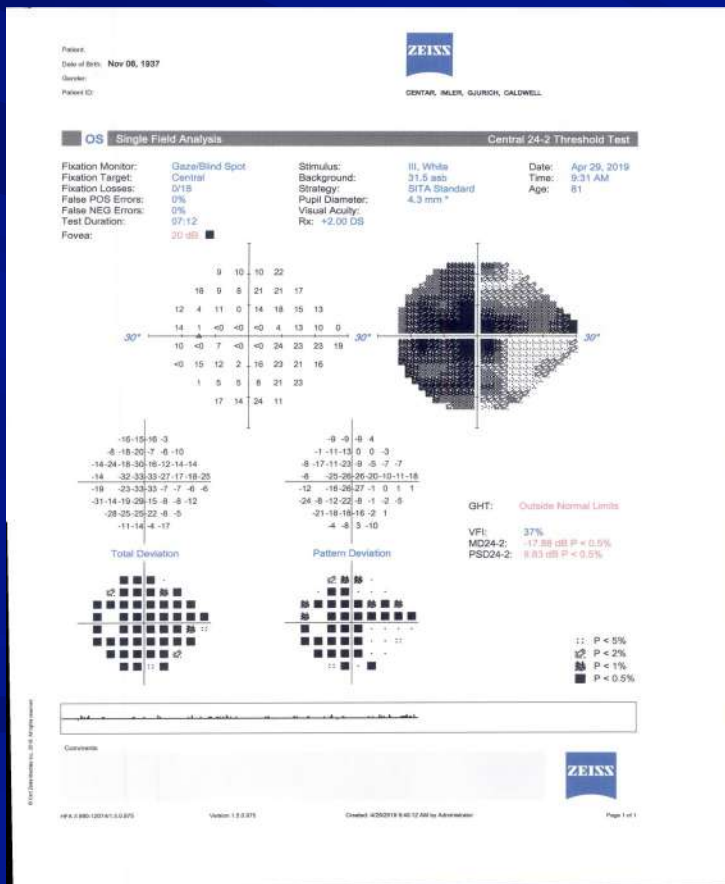
81-year-old woman

- Calls the office reporting decreased vision (3-13-19)
 - ★ Was warned vision could decrease due her medications
 - ★ Glaucoma patient
- Mycobacterium avium infection
- Ethambutol, rifampin, and azithromycin
 - ★ Ethambutol started October 2017
- Glaucoma patient
 - ★ Was on latanoprost and Rhopressa
 - ★ Had KDB
 - 📋 No glaucoma drops currently

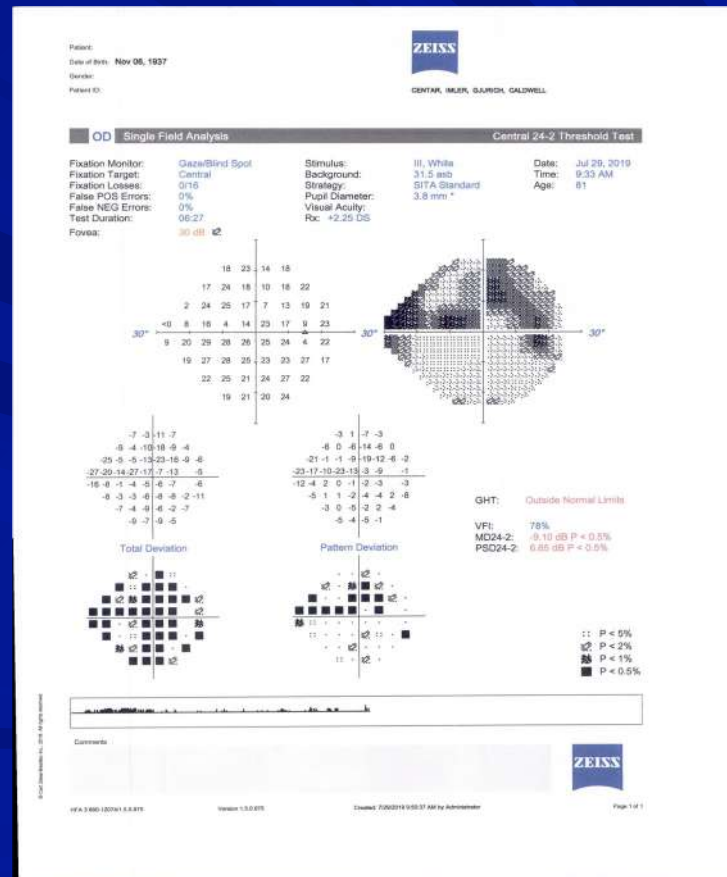
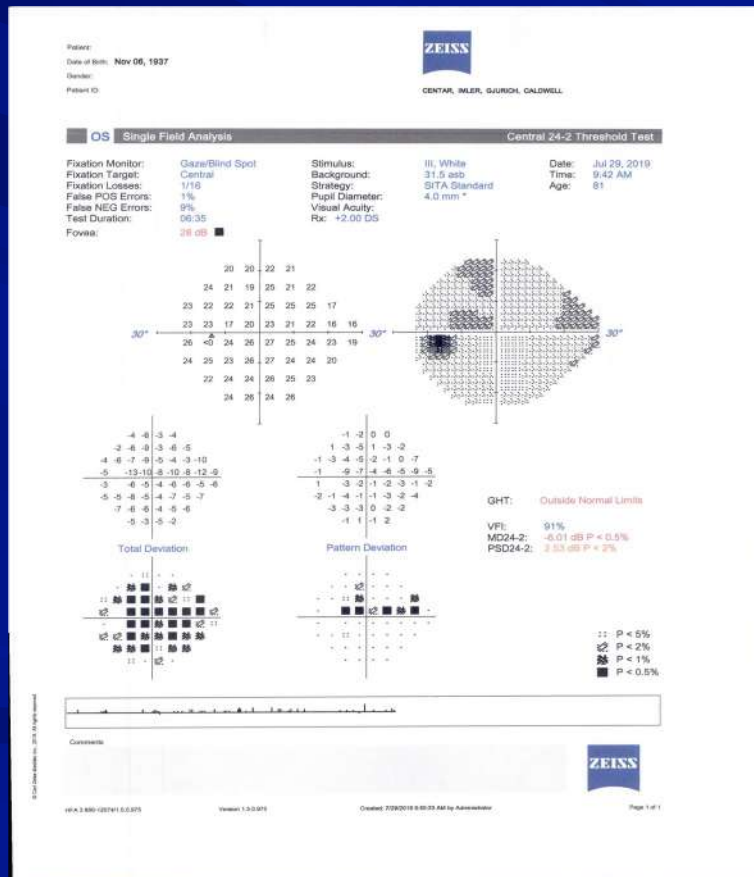
3/13/19 20/30, 20/100, 20/25



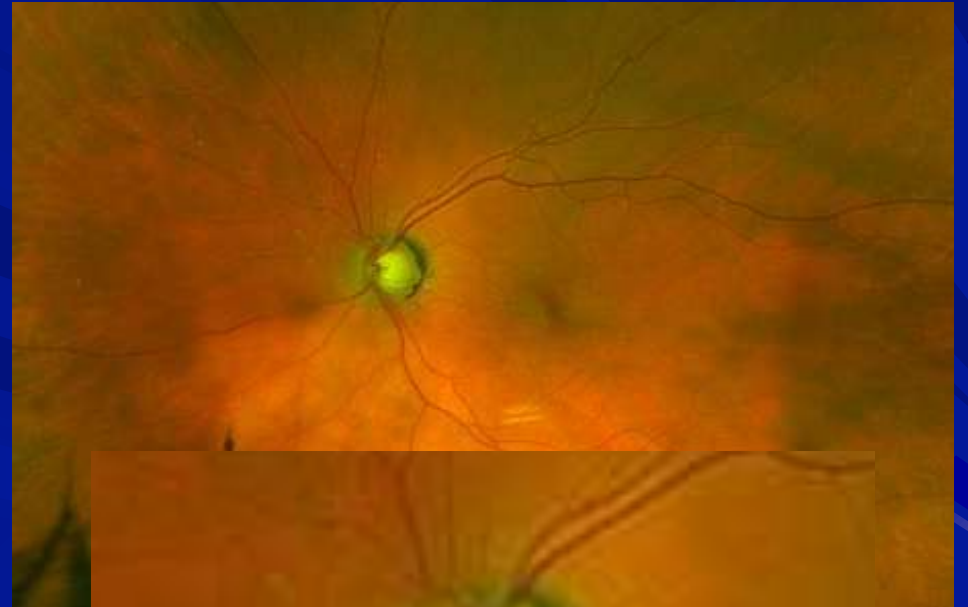
4/29/19 20/25, 20/50, 20/20



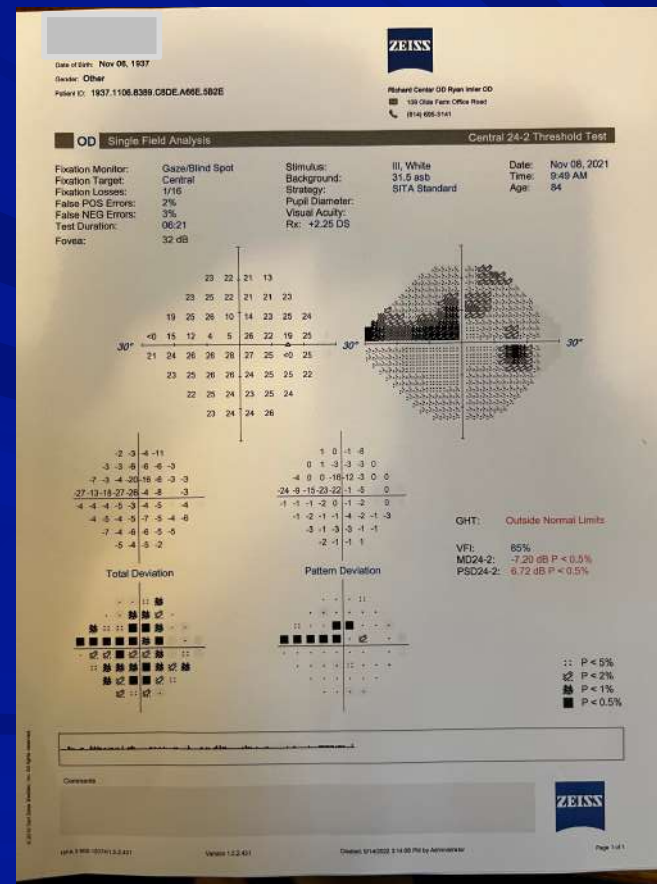
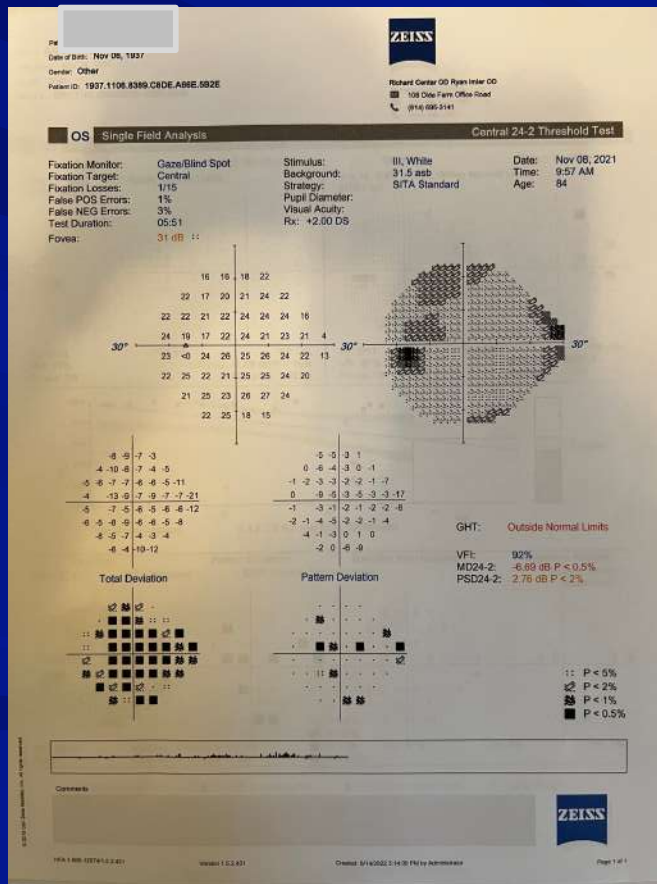
7/29/19 20/20, 20/20, 20/25, 20/20



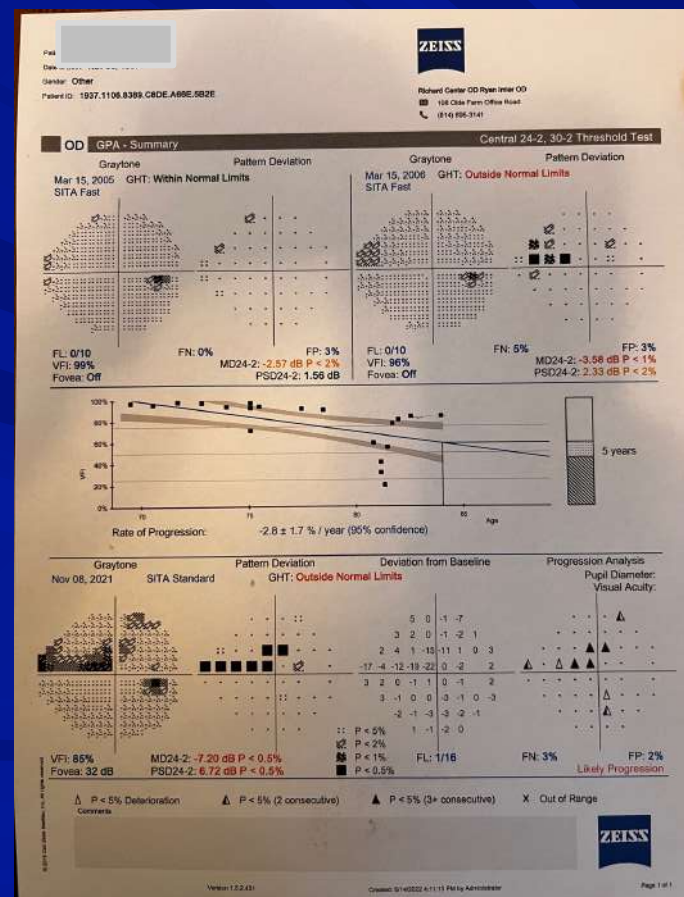
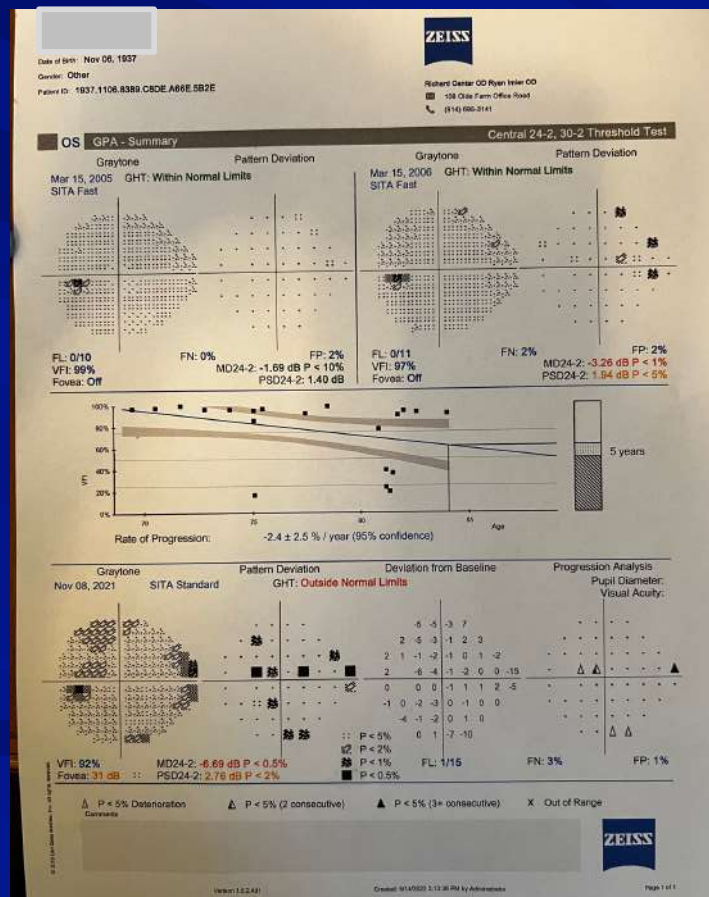
May 9, 2022



November 21, 2021



Progression thru 11-08-2021





Dupixant (dulipumab) injection

- **Atopic Dermatitis**: indicated for the treatment of adult and pediatric patients aged 6 months and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
 - ★ DUPIXENT can be used with or without topical corticosteroids
- **Asthma**: indicated as an add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma. Limitation of Use: DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.
- **Chronic rhinosinusitis with nasal polyposis (CRSwNP)**: DUPIXENT is indicated as an add-on maintenance treatment in adult patients with inadequately controlled CRSwNP.
- **Eosinophilic Esophagitis**: DUPIXENT is indicated for the treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis (EoE).

Dupixant (dulipumab) injection

Warnings and Precautions

- 🕶 **Conjunctivitis and Keratitis: (ocular warning and precautions of many)**
 - ★ Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT versus placebo, with conjunctivitis being the most frequently reported eye disorder.
 - ★ Conjunctivitis also occurred more frequently in chronic rhinosinusitis with nasal polyposis subjects who received DUPIXENT compared to those who received placebo.
 - ★ Conjunctivitis and keratitis have been reported with DUPIXENT in postmarketing settings, predominantly in atopic dermatitis patients.
 - ★ Some patients reported visual disturbances (e.g., blurred vision) associated with conjunctivitis or keratitis.
 - ★ Advise patients to report new onset or worsening eye symptoms to their healthcare provider.
 - ★ Consider ophthalmological examination for patients who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis, as appropriate.

Before and After



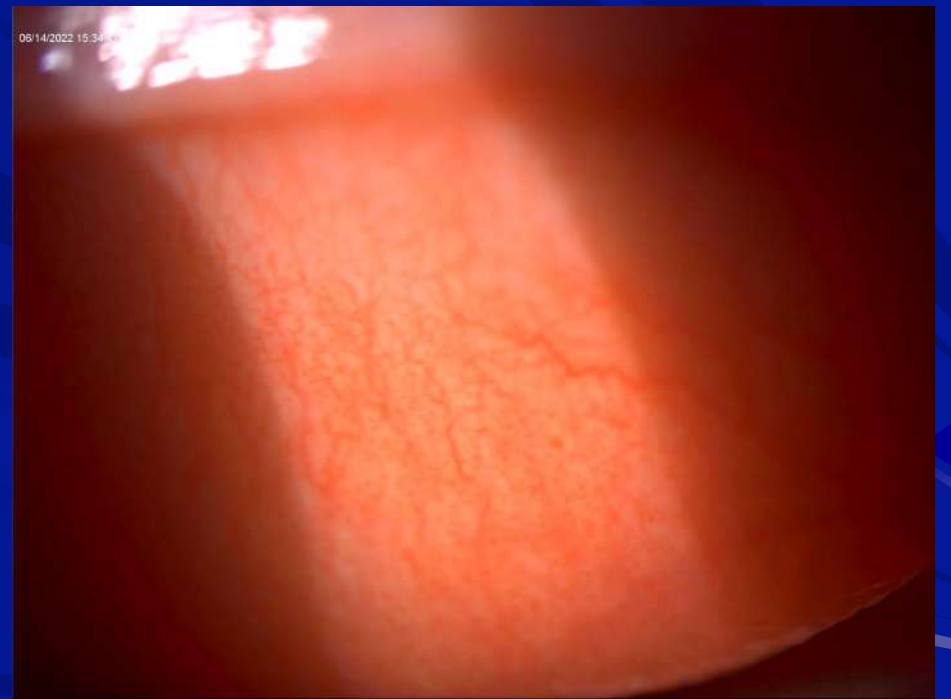
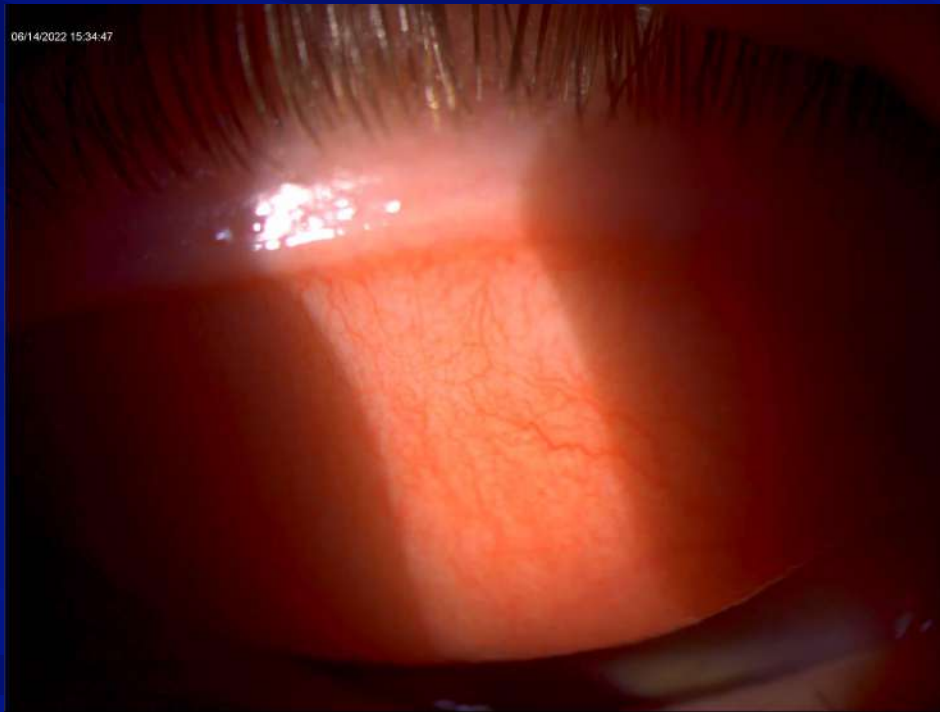
Before and After

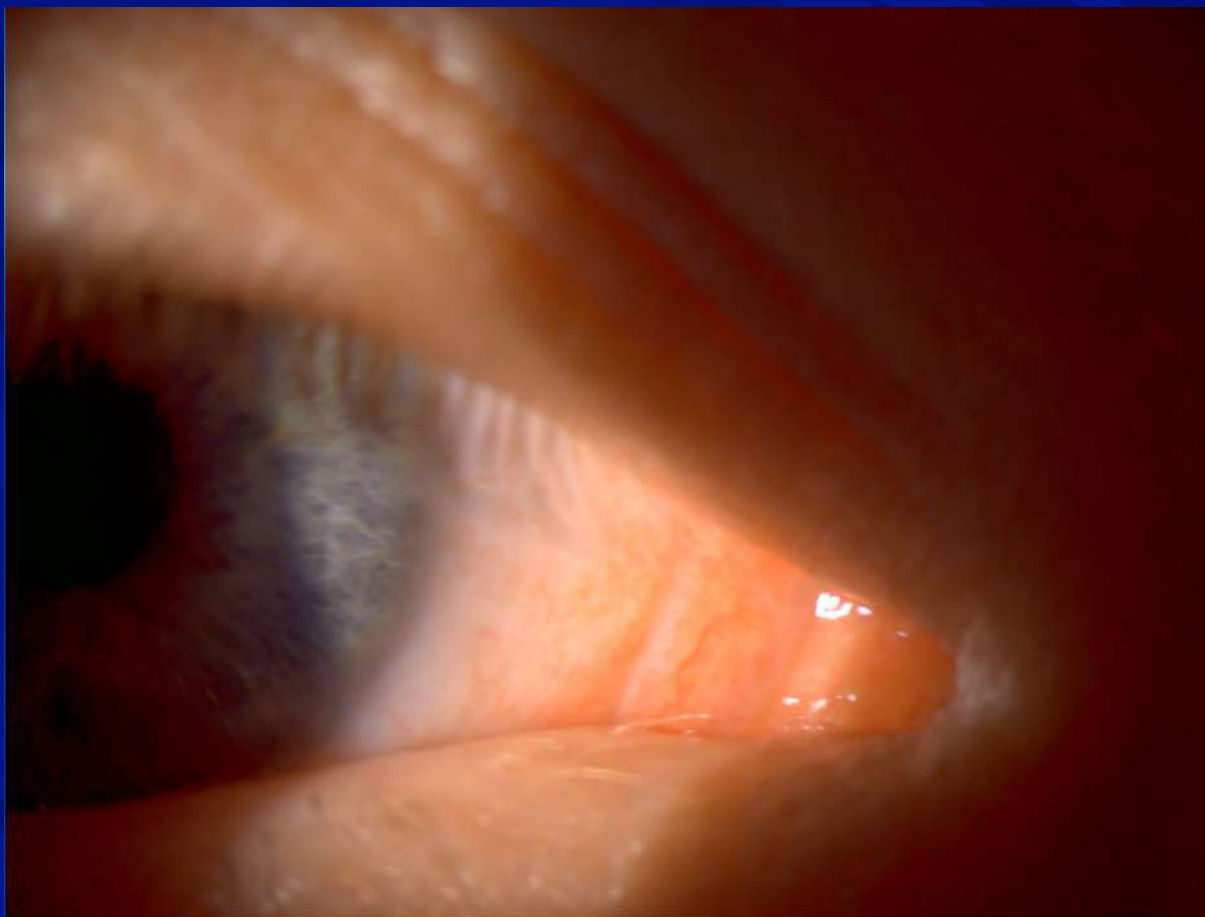


The background is a solid dark blue color. It features a series of diagonal lines in a lighter shade of blue, creating a sense of depth and movement. The lines are more prominent on the right side and fade towards the left.

Dupixant





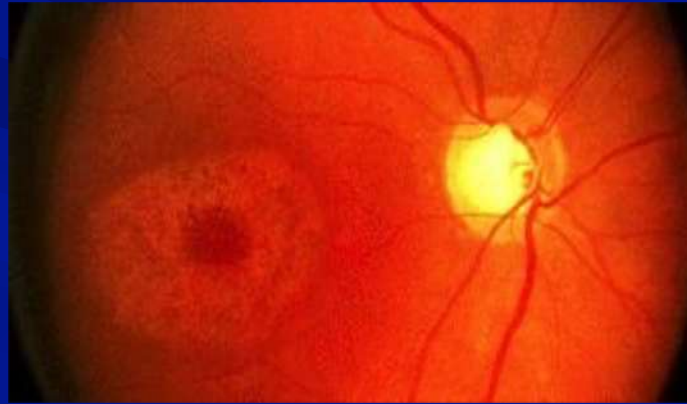


I have seen hydroxychloroquine/Plaquenil retinal toxicity in my practice:

1. Yes
2. No
3. I don't think it really happens

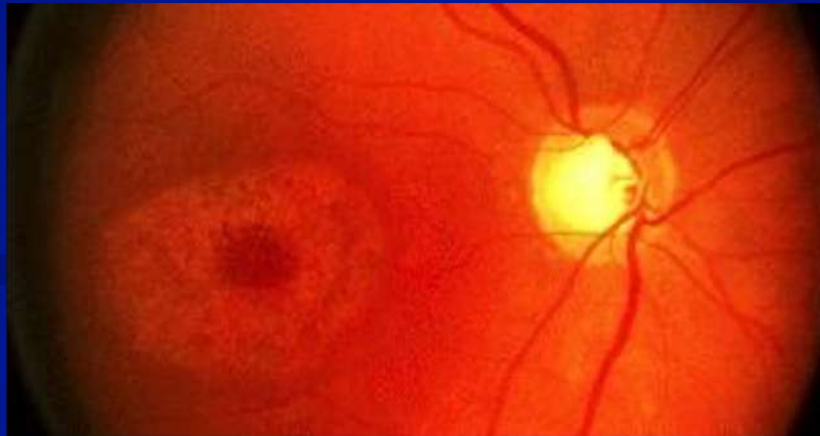


“Horse Is Out of the Barn”



Autoimmune Agents

- Treatment of rheumatologic conditions
 - ★ Rheumatoid arthritis, systemic lupus erythematosus
- Plaquenil™ (hydroxychloroquine)
 - 📋 Bull's eye maculopathy



Immunosuppressive Medications

Disease-Modifying Anti-Rheumatic Drugs (DMARDs)
Traditional Meds and Biologics

Methotrexate +/-
Hydroxychloroquine (Plaquenil™)



Tumor Necrosis Factor α Inhibitors

Adalimumab (Humira™)
Infliximab (Remicade™)
Etanercept (Enbrel™)
Certolizumab (Cimzia™)



Additional Agents

Abatacept (Orencia™)
Tocilizumab (Actemra™)
Tofacitinib (Xeljanz™)
Rituximab (Rituxan™)

Plaquenil

Hydroxychloroquine (Plaquenil) - Anti-malarial

- Ophthalmic side effects (infrequent with current dosing ranges):
 - ★ Irreversible retinal damage has been observed (“chloroquine retinopathy”).
 - ★ If there are any indications of abnormality in the color vision, visual acuity, visual field, or retinal macular areas, or any visual symptoms (eg, light flashes or streaks), d/c drug stat

Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

- Recommendations were 2002 by the American Academy of Ophthalmology
- Improved screening tools and new knowledge about prevalence of toxicity have prompt the change
 - ★ 1% after 5-7 years of use or a cumulative dose of 1000 grams (Plaquenil)
- There is no treatment for this condition
 - ★ Therefore must be caught early
- Screening for the earliest hints of functional or anatomic change
- Plaquenil toxicity is not well understood

American Academy of Ophthalmology Update

Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

Michael F. Marmor, MD,¹ Ulrich Kellner, MD,² Timothy Y. Y. Lai, MD,³ Jonathan S. Lyons, MD,⁴ William F. Mieler, MD,⁵ for the American Academy of Ophthalmology

Background: The American Academy of Ophthalmology recommendations for screening of chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy were published in 2002, but improved screening tools and new knowledge about the prevalence of toxicity have appeared in the ensuing years. No treatment exists as yet for this disorder, so it is imperative that patients and their physicians be aware of the best practices for minimizing toxic damage.

Risk of Toxicity: New data have shown that the risk of toxicity increases sharply toward 1% after 5 to 7 years of use, or a cumulative dose of 1000 g, of HCQ. The risk increases further with continued use of the drug.

Dosage: The prior recommendation emphasized dosing by weight. However, most patients are routinely given 400 mg of HCQ daily (or 250 mg CQ). This dose is now considered acceptable, except for individuals of short stature, for whom the dose should be determined on the basis of ideal body weight to avoid overdosage.

Screening Schedule: A baseline examination is advised for patients starting these drugs to serve as a reference point and to rule out maculopathy, which might be a contraindication to their use. Annual screening should begin after 5 years (or sooner if there are unusual risk factors).

Screening Tests: Newer objective tests, such as multifocal electroretinogram (mfERG), spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF), can be more sensitive than visual fields. It is now recommended that along with 10-2 automated fields, at least one of these procedures be used for routine screening where available. When fields are performed independently, even the most subtle 10-2 field changes should be taken seriously and are an indication for evaluation by objective testing. Because mfERG testing is an objective test that evaluates function, it may be used in place of visual fields. Amsler grid testing is no longer recommended. Fundus examinations are advised for documentation, but visible bull's-eye maculopathy is a late change, and the goal of screening is to recognize toxicity at an earlier stage.

Counseling: Patients should be aware of the risk of toxicity and the rationale for screening (to detect early changes and minimize visual loss, not necessarily to prevent it). The drugs should be stopped if possible when toxicity is recognized or strongly suspected, but this is a decision to be made in conjunction with patients and their medical physicians.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology* 2011;118:415-422 © 2011 by the American Academy of Ophthalmology.

Retinal toxicity from chloroquine (CQ) and its analogue, hydroxychloroquine (HCQ), has been recognized for many years. The first reports concerned long-term use of CQ for malaria, and later reports showed retinopathy after treatment of anti-inflammatory diseases.^{1,2} Chloroquine toxicity remains a problem in many parts of the world, but it is seen infrequently in the United States, where the drug has largely been replaced by HCQ for the treatment of systemic lupus erythematosus, rheumatoid arthritis, and other inflammatory and dermatologic conditions. Retinal toxicity from HCQ has a low incidence, but many thousands of individuals take this drug for medical indications.³ Toxicity from these drugs is of serious ophthalmologic concern because even after cessation of the drugs, there is little if any visual recovery, and sometimes progression of visual loss.⁴ Thus, it is imperative that ophthalmologists and other physicians be aware of this disorder and take measures to minimize its occurrence and effects.

The 2002 version of this document⁵ was prepared because different screening regimens had been proposed, which varied considerably in practicality, costs, and cost/benefit ratio. There was need for a consensus recommendation. The *Physicians' Desk Reference*, for example, recommended quarterly examinations that would represent an enormous burden on health care resources. Yet most authors concur that some screening for early toxicity is reasonable.

This revised recommendation has significant changes in light of new data on the prevalence of retinal toxicity and

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doi:10.1016/j.ophtha.2010.11.017

415

American Academy of Ophthalmology Statement

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

Michael F. Marmor, MD,¹ Ulrich Kellner, MD,² Timothy Y.Y. Lai, MD, FRCOphth,³ Ronald B. Meller, MD,⁴ William F. Mieler, MD,⁵ for the American Academy of Ophthalmology

Background: The American Academy of Ophthalmology recommendations on screening for chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy are revised in light of new information about the prevalence of toxicity, risk factors, fundus distribution, and effectiveness of screening tools.

Pattern of Retinopathy: Although the locus of toxic damage is parafoveal in many eyes, Asian patients often show an extramacular pattern of damage.

Dose: We recommend a maximum daily HCQ use of ≤ 5.0 mg/kg real weight, which correlates better with risk than ideal weight. There are no similar demographic data for CQ, but dose comparisons in older literature suggest using ≤ 2.3 mg/kg real weight.

Risk of Toxicity: The risk of toxicity is dependent on daily dose and duration of use. At recommended doses, the risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%, but it rises to almost 20% after 20 years. However, even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year.

Major Risk Factors: High dose and long duration of use are the most significant risks. Other major factors are concomitant renal disease, or use of tamoxifen.

Screening Schedule: A baseline fundus examination should be performed to rule out preexisting maculopathy. Begin annual screening after 5 years for patients on acceptable doses and without major risk factors.

Screening Tests: The primary screening tests are automated visual fields plus spectral-domain optical coherence tomography (SD OCT). These should look beyond the central macula in Asian patients. The multifocal electroretinogram (mfERG) can provide objective corroboration for visual fields, and fundus autofluorescence (FAF) can show damage topographically. Modern screening should detect retinopathy before it is visible in the fundus.

Toxicity: Retinopathy is not reversible, and there is no present therapy. Recognition at an early stage (before any RPE loss) is important to prevent central visual loss. However, questionable test results should be repeated or validated with additional procedures to avoid unnecessary cessation of valuable medication.

Counseling: Patients (and prescribing physicians) should be informed about risk of toxicity, proper dose levels, and the importance of regular annual screening. *Ophthalmology* 2016;123:1386-1394 © 2016 by the American Academy of Ophthalmology.

Revised
Again

Retinal toxicity from chloroquine (CQ) and its analogue hydroxychloroquine (HCQ) has been recognized for many years. Chloroquine toxicity remains a problem in many parts of the world, but is seen less frequently in the United States where the drug largely has been replaced by HCQ. Hydroxychloroquine is used widely for the treatment of systemic lupus erythematosus (SLE), rheumatoid arthritis, and related inflammatory and dermatologic conditions. It is now 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 retinopathy.

The American Academy of Ophthalmology recommendations for screening that were published in 2011¹ are revised in this article to account for new scientific data. The recent publication of a large demographic study has shown that toxicity is not rare among long-term users of the drug, and the risk is highly dependent on the daily dose by weight.² These data showed that real weight was better than ideal weight for calculating dose, and lower risk was achieved with doses ≤ 5 mg/kg real weight. It also has been found that the classic "bull's-eye" distribution of toxicity is infrequent in patients of Asian heritage,^{3,4} who typically show early damage in a more peripheral pattern.

Background: The American Academy of Ophthalmology recommendations on screening for chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy are revised in light of new information about the prevalence of toxicity, risk factors, fundus distribution, and effectiveness of screening tools.

Pattern of Retinopathy: Although the locus of toxic damage is parafoveal in many eyes, Asian patients often show an extramacular pattern of damage.

Dose: We recommend a maximum daily HCQ use of ≤ 6.0 mg/kg real weight, which correlates better with risk than ideal weight. There are no similar demographic data for CQ, but dose comparisons in older literature suggest using < 2.3 mg/kg real weight.

Risk of Toxicity: The risk of toxicity is dependent on daily dose and duration of use. At recommended doses, the risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%, but it rises to almost 20% after 20 years. However, even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year.

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Counseling: Patients (and prescribing physicians) should be informed about risk of toxicity, proper dose levels, and the importance of regular annual screening. *Ophthalmology* 2016;123:1386-1394 © 2016 by the American Academy of Ophthalmology

PLAQUENIL ZONE

**WITH ALL TESTING FOR PLAQUENIL
TOXICITY...FOCUS ON THE "1.0-1.5 MM RADIUS
PLAQUENIL ZONE "**

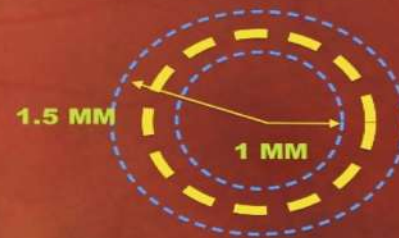
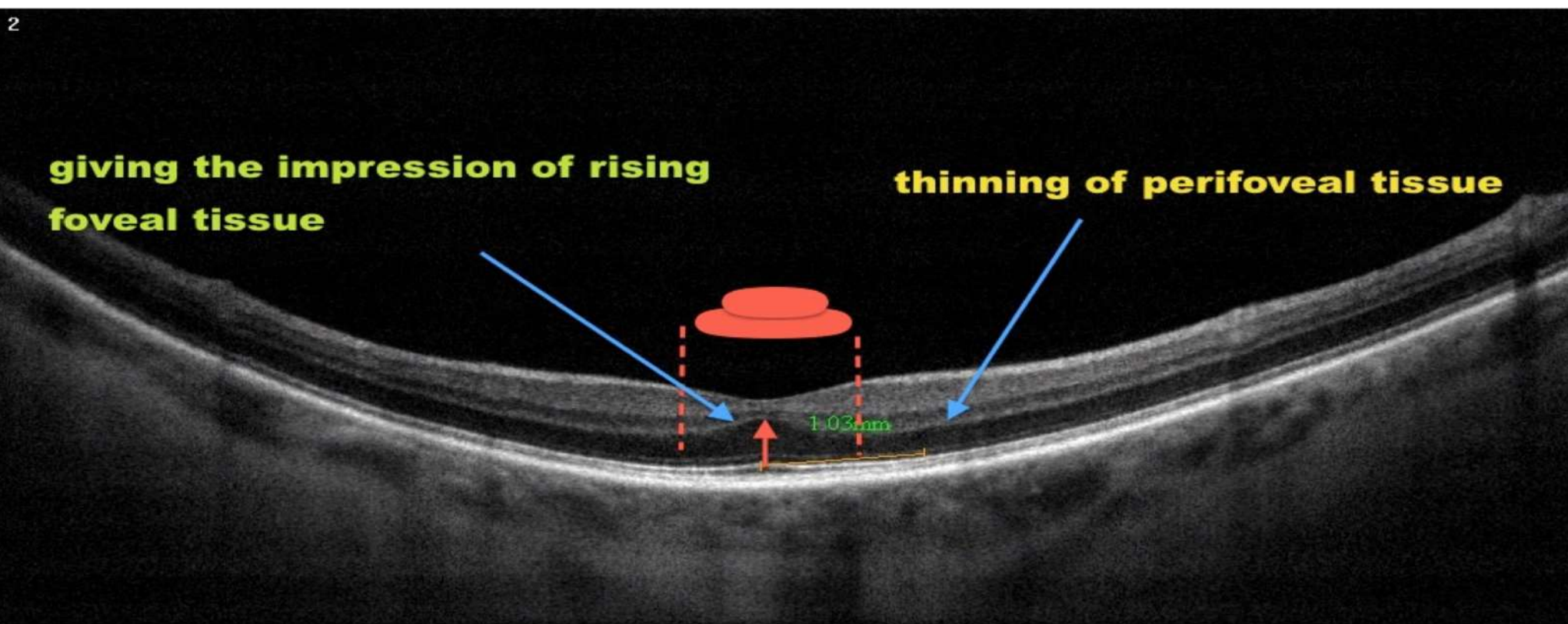


Figure 1 The flying saucer sign representing compromise of the perifoveal retinal tissue with maintenance of the foveal retinal tissue. From Chen E, Brown DM, Benz MS, et al. Spectral domain optical coherence tomography as an effective screening test for hydroxychloroquine retinopathy (the “flying saucer” sign). Clin Ophthalmol. 2010; 4: 1151–1158. Published online 2010 October 21. doi: [10.2147/OPTH.S14257](https://doi.org/10.2147/OPTH.S14257)



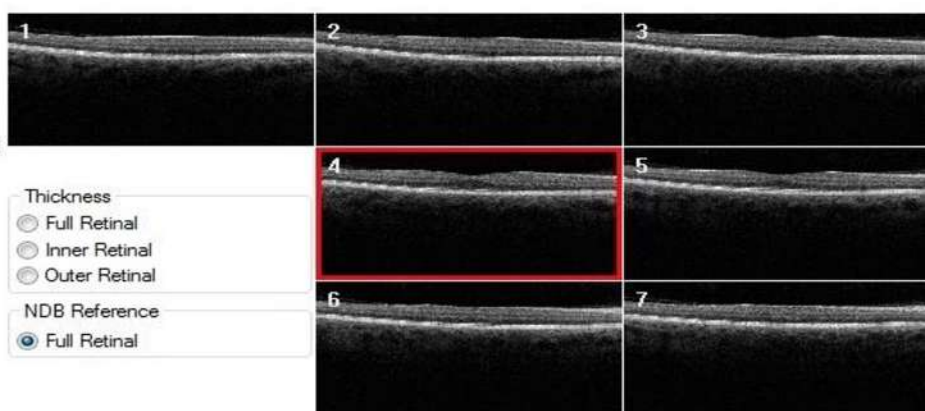
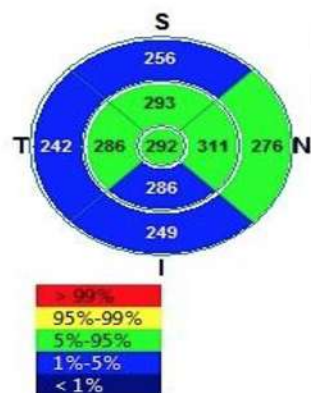
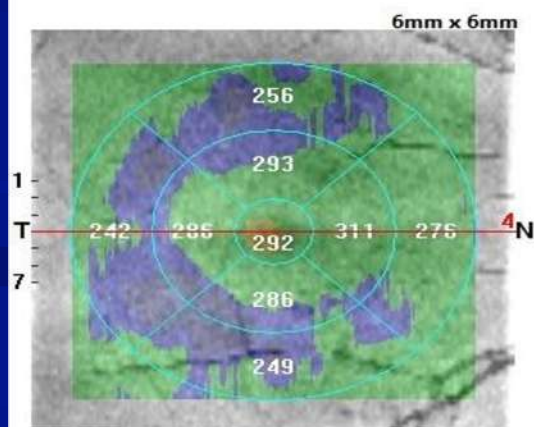
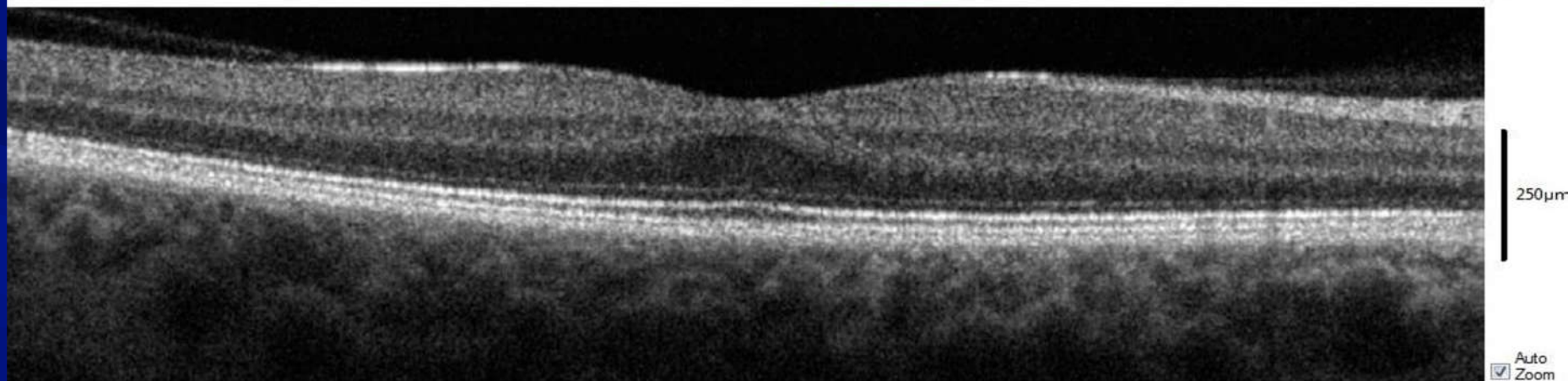
AUGUST 2014

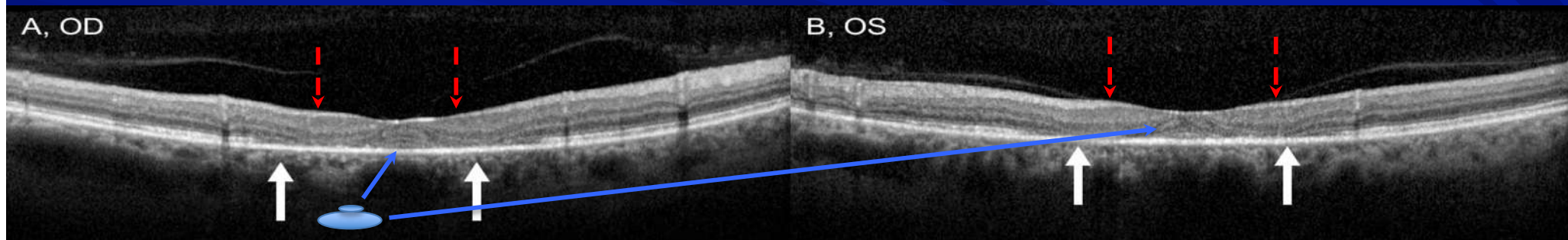
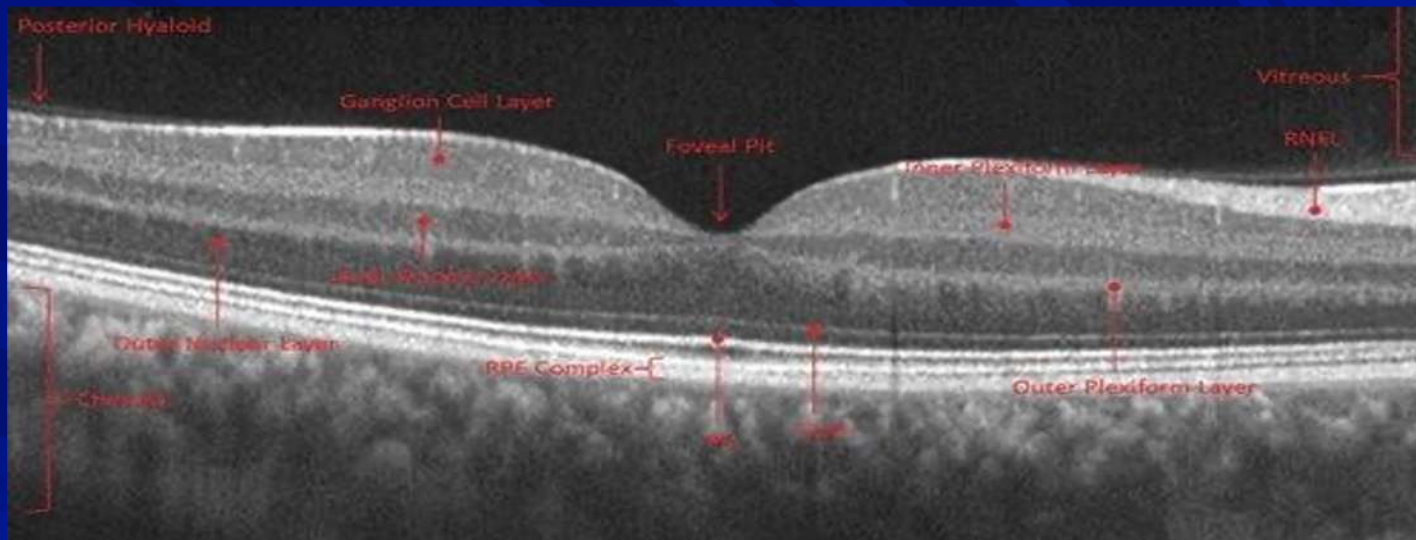
Retina Map

Scan Quality Index **Good 85**

☐ View Reproducibility

Right / OD



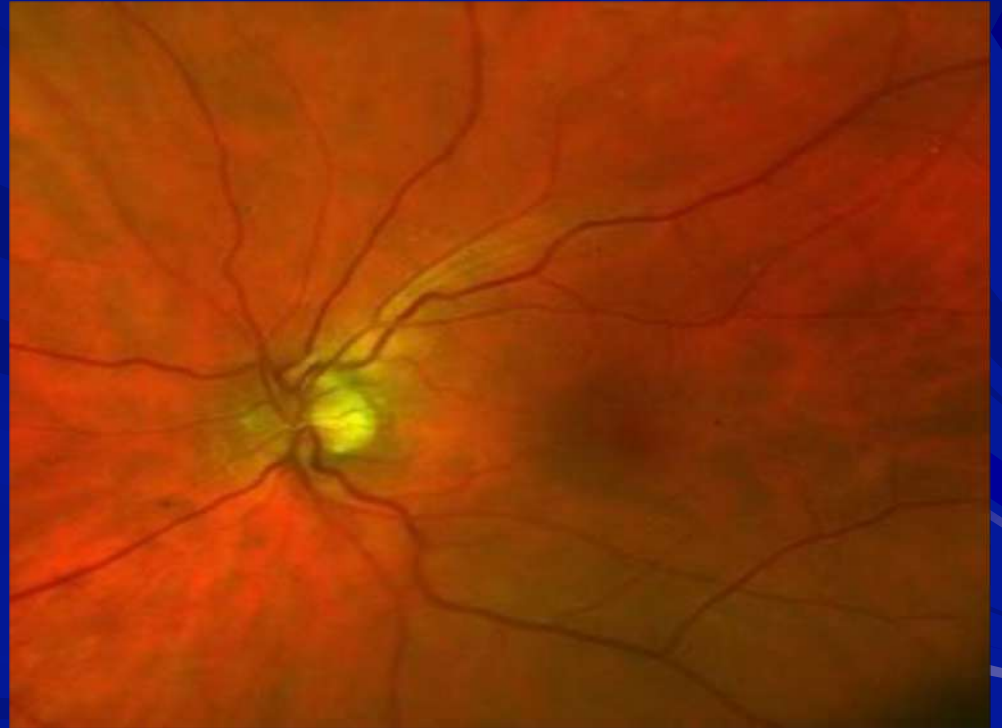


**BILATERAL COMPROMISE OF THE PIL (WHITE ARROWS)
AFTER COLLAPSE OF PERIFOVEAL RETINA (RED DASHED
ARROWS) WITH FLYING SAUCER ATTACK (BLUE ARROWS)**

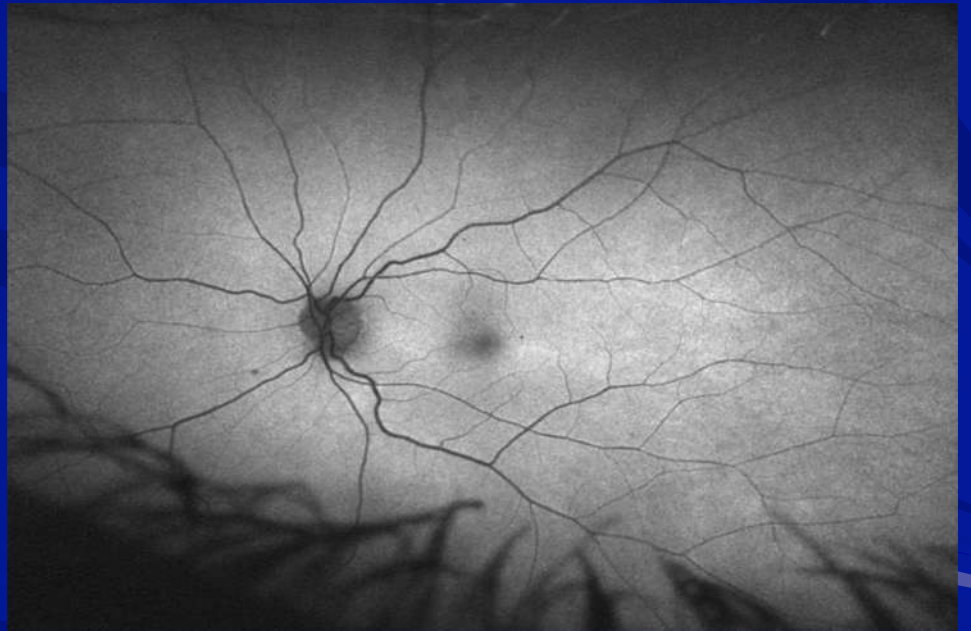
71 yo woman

- With Lupus and hypertension
- Medications:
 - ★ Clonazepam™
 - ★ Plaquenil™ 200 mg BID, 15 years
 - ★ 81 mg ASA
 - ★ Prednisone
 - ★ Losartan™
- VA 20/25 OD/OS (mild cataracts)
- Patient was told to see an ophthalmologist in 2013

2016

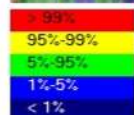
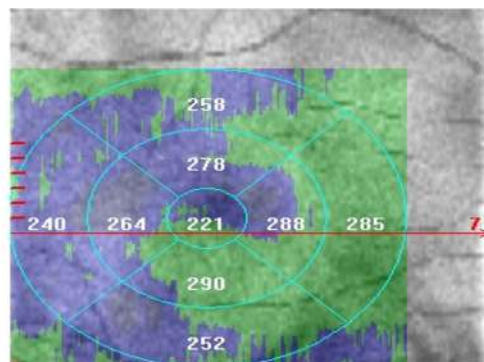


2016

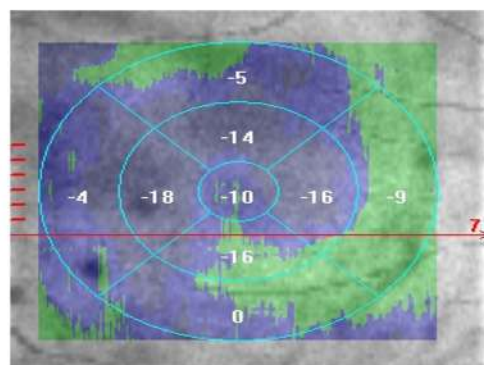


Retina Map Change Analysis

Previous Scan 10/30/2013 11:25:26



☒ Auto Zoom
☐ Show Original



Recent Scan 11/02/2016 15:10:48

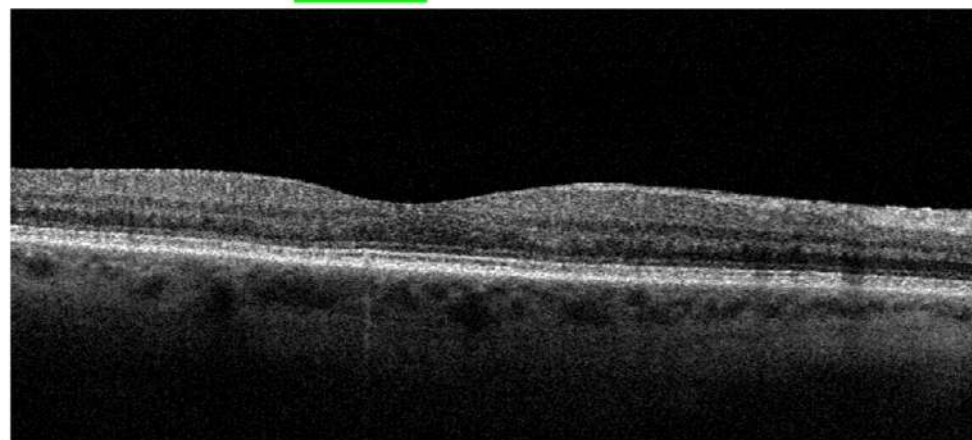
Print

Right / OD

Scan Quality Index

Good 66

6.00 x 6.00 Scan Size (mm)



250µm

Thickness

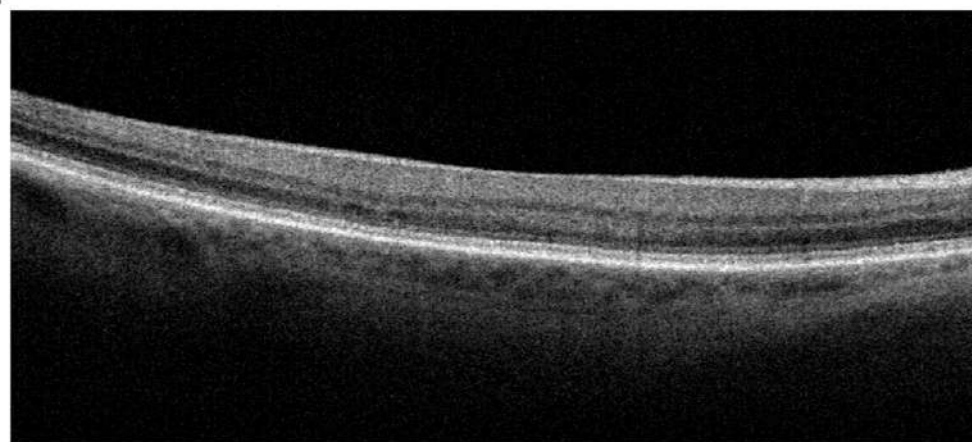
☐ Full Retinal

☐ Inner Retinal

☐ Outer Retinal

NDB Reference

☒ Full Retinal



Scan Quality Index

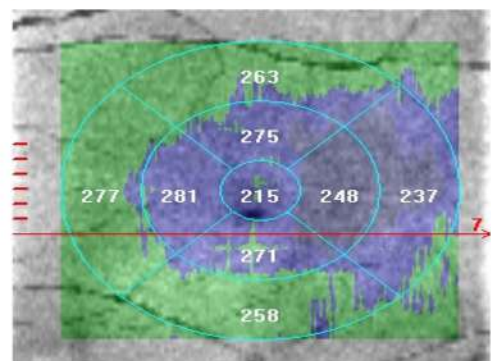
Good 61

OU Report

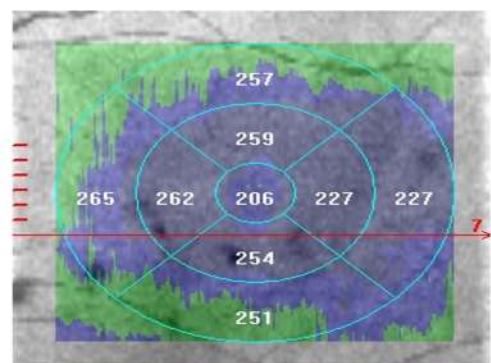
optovue

Retina Map Change Analysis

Previous Scan 10/30/2013 11:27:07



- ☒ Auto Zoom
- ☒ Show Original



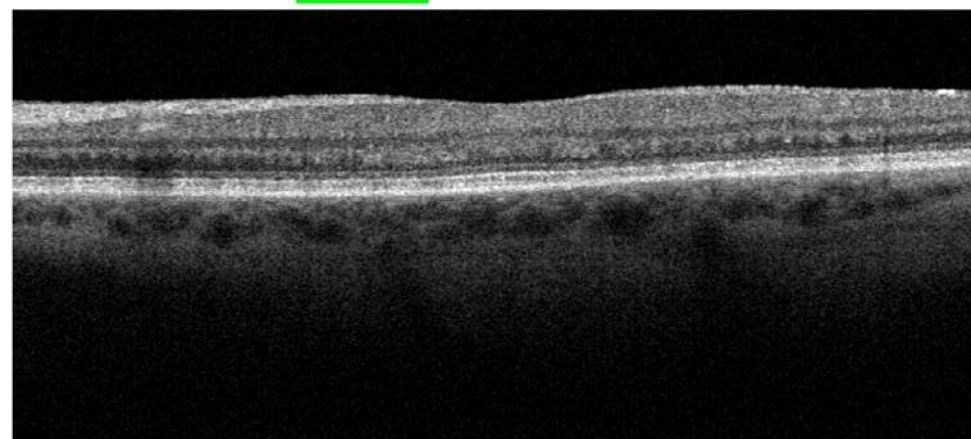
Recent Scan 11/02/2016 15:11:15

Print

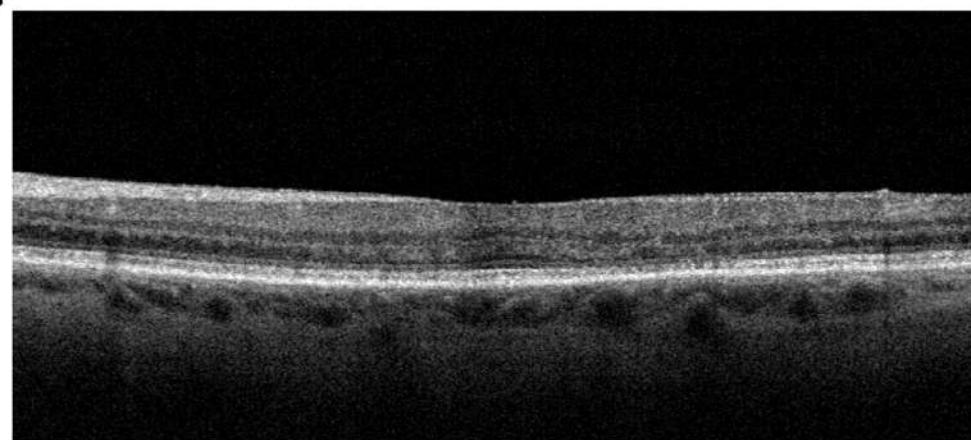
Scan Quality Index

Good 77

Left / OS
6.00 x 6.00 Scan Size (mm)



Thickness
☐ Full Retinal
☐ Inner Retinal
☐ Outer Retinal
 NDB Reference
☒ Full Retinal



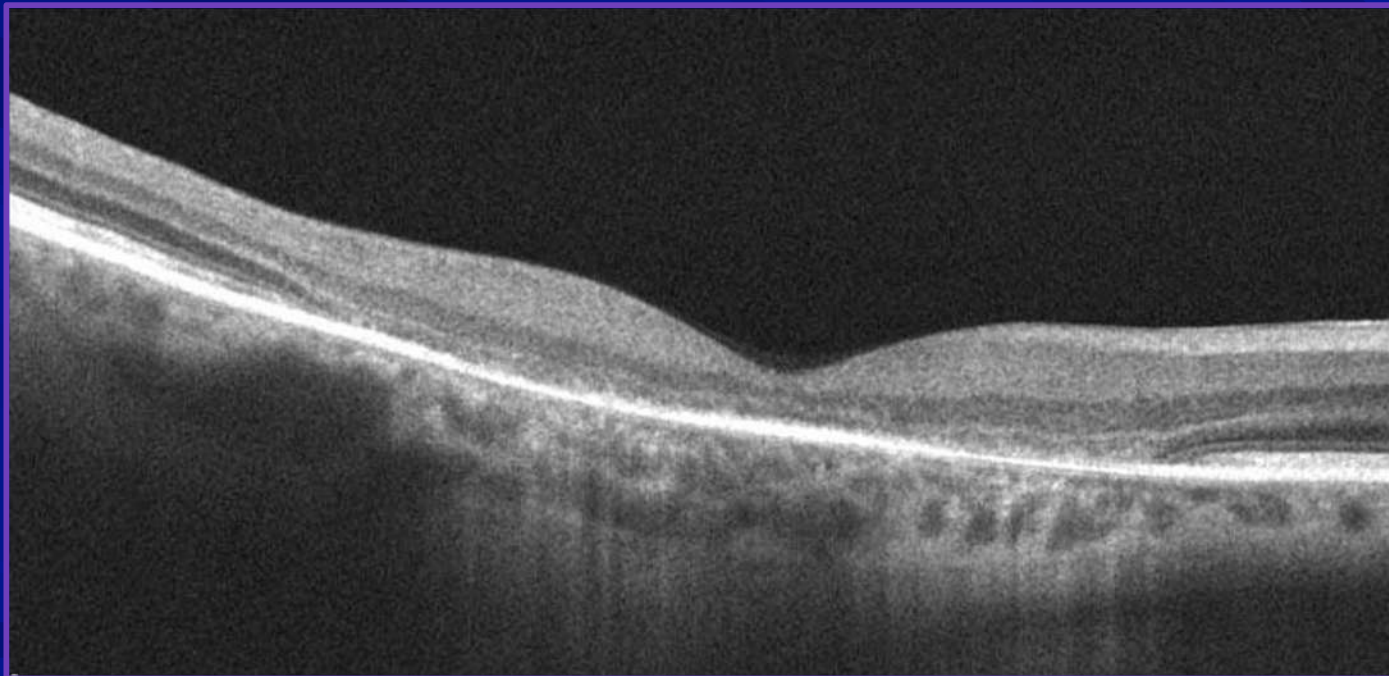
Scan Quality Index

Good 65

OU Report

optovue

Plaquenil Toxicity



Courtesy of Joe Shovlin, OD, FAAO



an Date: 7/5/2011
an Time: 4:53 PM
chnician: Operator, Citrus
nal Strength: 10/10

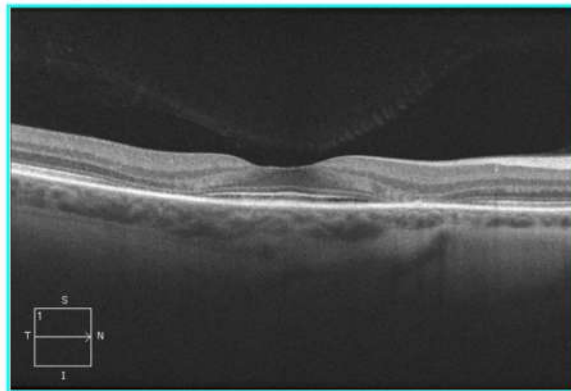
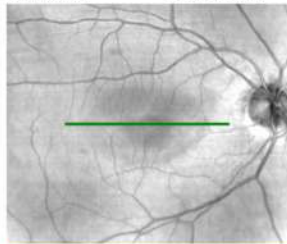
CZM

D 5 Line Raster

OD ☒ OS ☐

:0 mm

Length: 6 mm



Comments

Doctor's Signature

SW Ver 5.1.1.6
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Page 1 of 1

Plaquenil Toxicity

Courtesy of Joe Shovlin, OD, FAAO

ID: 3483799
DOB: 7/16/1951
Gender: Female
Doctor:
Exam Date: 3/14/2012
Exam Time: 3:13 PM
Technician: Operator, Cirrus
Signal Strength: 7/10

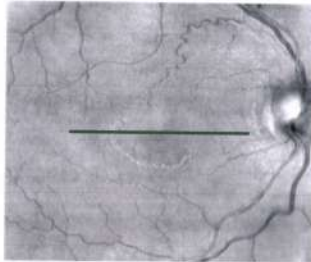
CZMI



High Definition Images: HD 5 Line Raster

OD ☒ OS ☐

Scan Angle: 0° Spacing: 0 mm Length: 6 mm



Comments

↓ photoreceptor

Plaque use

Doctor's Signature

SW Ver: 5.1.1.6
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Page 1 of 1

ID: 3483799
DOB: 7/16/1951
Gender: Female
Doctor:
Exam Date: 3/14/2012
Exam Time: 3:15 PM
Technician: Operator, Cirrus
Signal Strength: 8/10

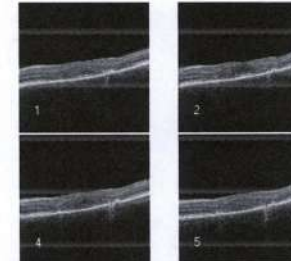
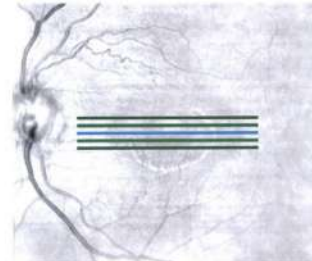
CZMI



High Definition Images: HD 5 Line Raster

OD ☐ OS ☒

Scan Angle: 0° Spacing: 0.25 mm Length: 6 mm



Comments

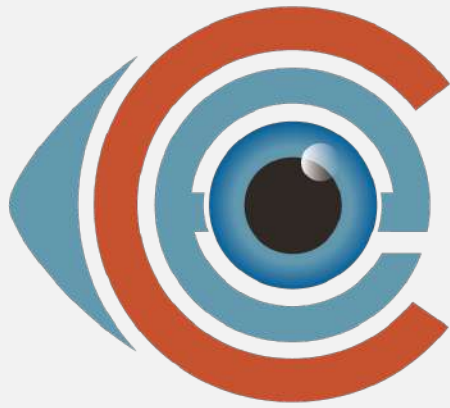
↓ photoreceptor

Plaque use

Doctor's Signature

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Courtesy of Joe
Shovlin, OD,
FAAO



Optometric
Education
Consultants

Thank you! Questions?

Complications of Pharmaceutical
Every Optometrist Should Know!

Greg Caldwell, OD, FAAO

