Optometric Education Consultants

Complications of Pharmaceuticals Every Optometrist Should Know!

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Sunday, June 27, 2021

Disclosures- Greg Caldwell, OD, FAAO

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- Lectured for: Alcon, Allergan, Aerie, BioTissue, Kala, Maculogix, Optovue
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  - Boiron: honorarium, webinar/speaker
- Has not received any assistance from any commercial interest in the development of this course

Financial Obligations

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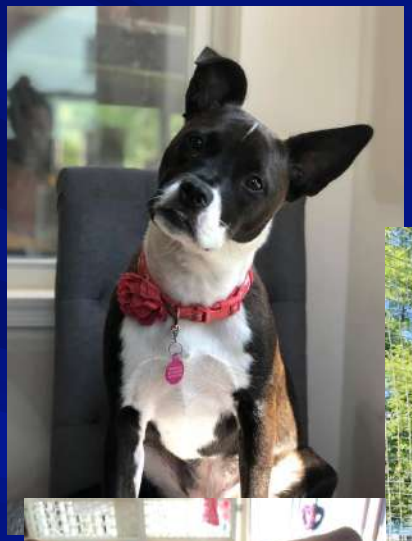


Text a Question/Comment

Greg Caldwell

814-931-2030

Course Description

- Optometrists use topical and oral (systemic) pharmaceuticals for the treatment of a variety of ocular conditions in patient care
- Comparably, systemic medicines are used to treat numerous conditions by various practitioners in the healthcare system
- These treatments or pharmaceutical agents have the potential to produce ocular adverse side effects and systemic complications
- This course will discuss the complications and adverse events that every optometrist should know
- This presentation will immediately aid in everyday patient care

Antibiotics

- Fluoroquinolones
  - ★ Levaquin™ (levofloxacin)
  - ★ Cipro™ (ciprofloxacin)
    - Tendon rupture
    - Retinal detachment
      - 1 in 2,500 will experience (compared to 1 in 1,000 who will experience tendinitis)

IN THE JOURNALS PERSPECTIVE

Oral fluoroquinolone not associated with retinal detachment

Choi SY, et al. PLOS One. 2018;doi:10.1371/journal.pone.0195563.
Primary Care Optometry News, December 2018

Oral administration of fluoroquinolone was not associated with the increased risk of developing rhegmatogenous retinal detachment, but patients with exposure to the therapy for 91 to 180 days had a modest association, according to a nested case control study.

Researchers used data from the Korean National Health Insurance National Sample Cohort (KNHIS-NSC) from 2002 to 2013.

SEE ALSO

Oral fluoroquinolones not associated with retinal…

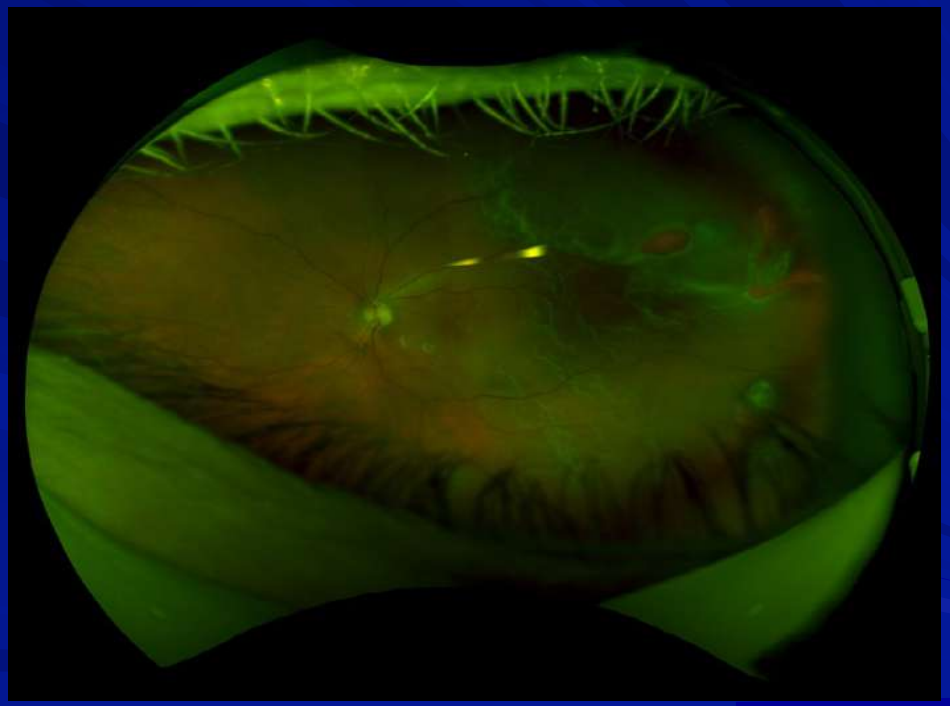
Young woman presents with nonresponding conjunctivitis

Higher doses of sildenafil citrate can lead to…

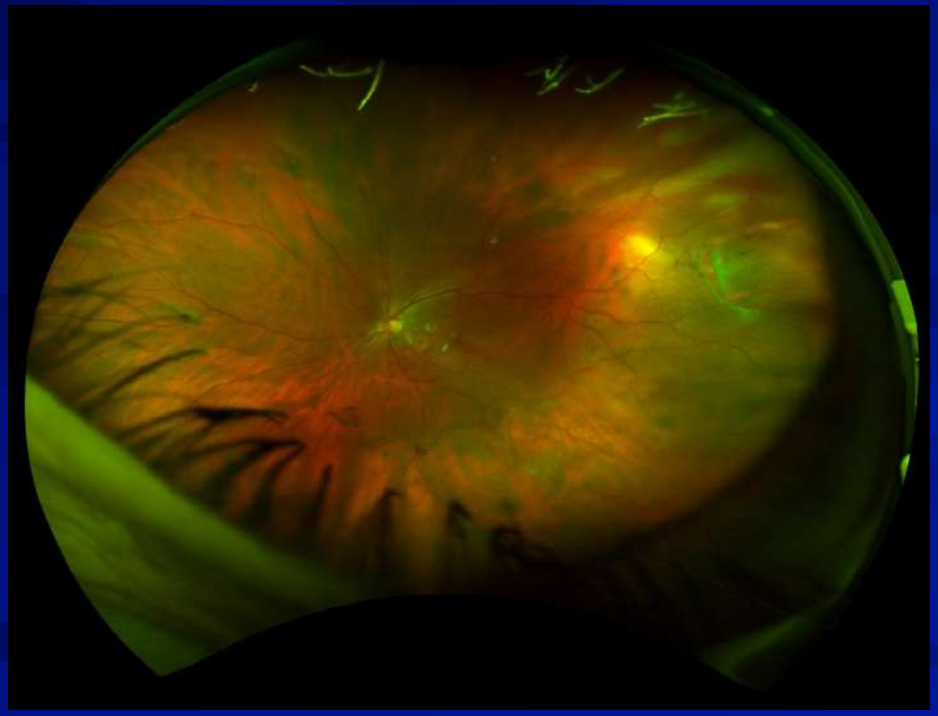
Subjects who visited an ophthalmologist were included in the cohort, and researchers defined cases as subjects who underwent surgery for rhegmatogenous retinal detachment (RRD). Controls, who did not undergo surgery for RRD, were matched by sex, age group and cohort entry data.

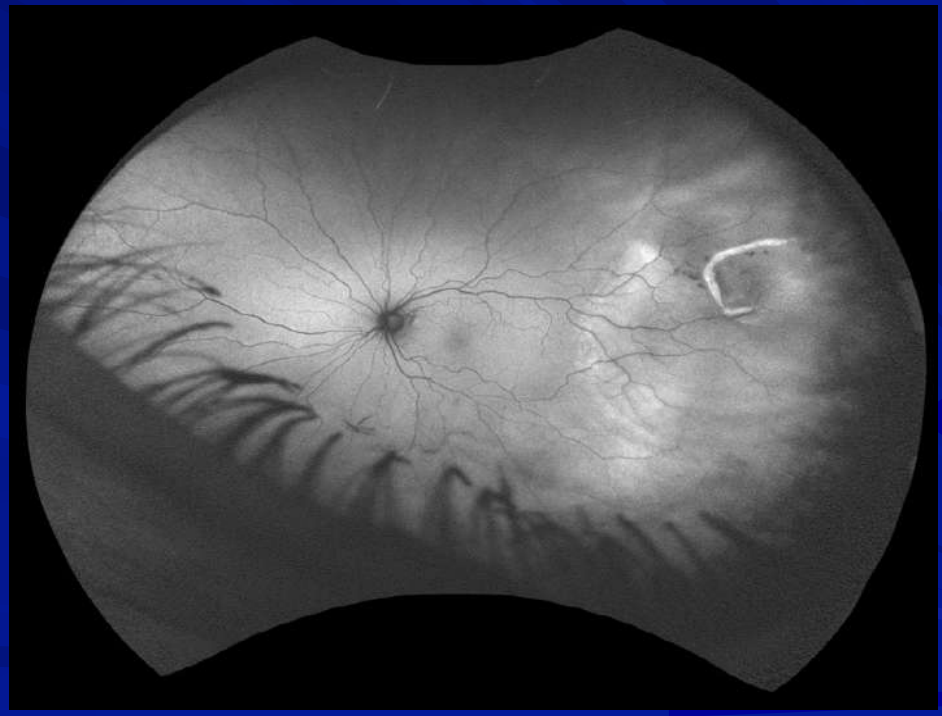
A total of 1,151 subjects in the case group and 11,470 subjects in the control group, were included.

Antibiotic Fluoroquinolones Dropless Cataract Surgery



Antibiotic Fluoroquinolones Dropless Cataract Surgery

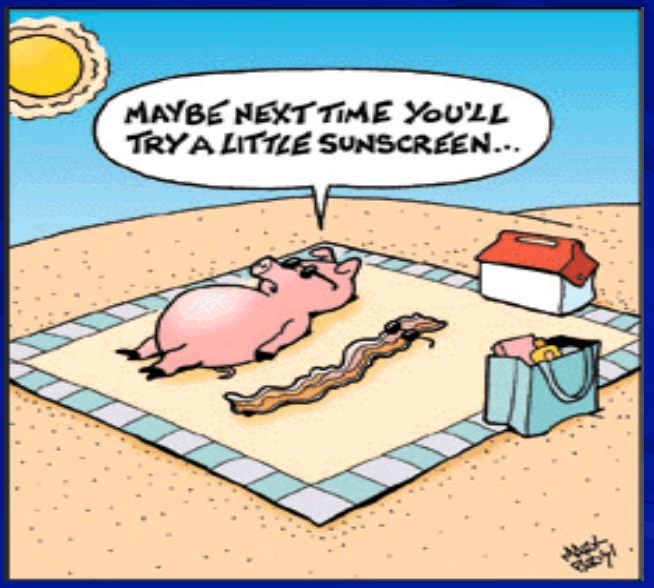




Antibiotics (anti-inflammatory)
Adverse Drug Reactions

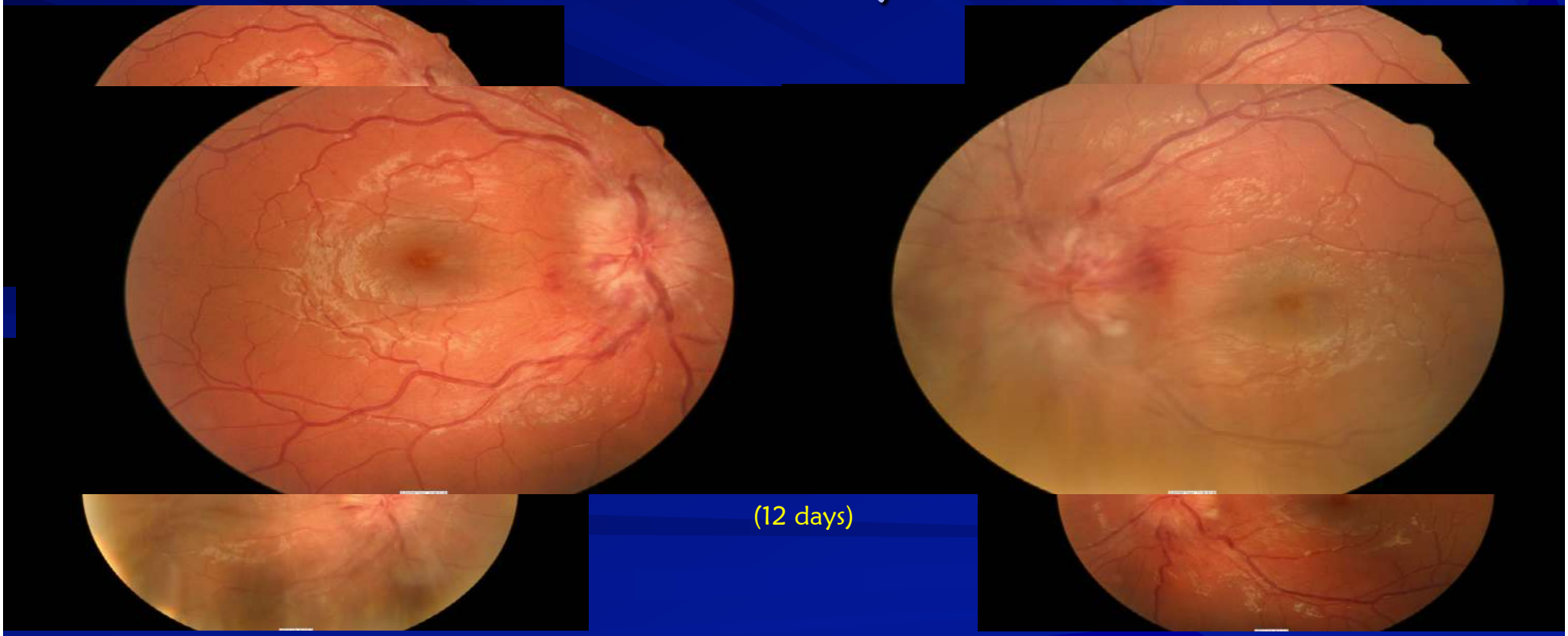
- Tetracycline analogs
  - Doxycycline
  - Minocycline

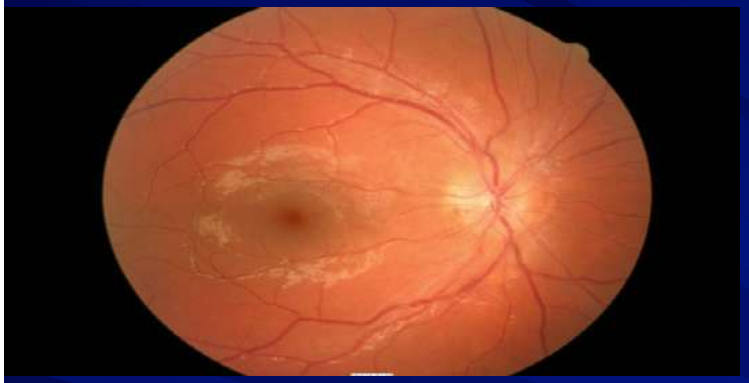
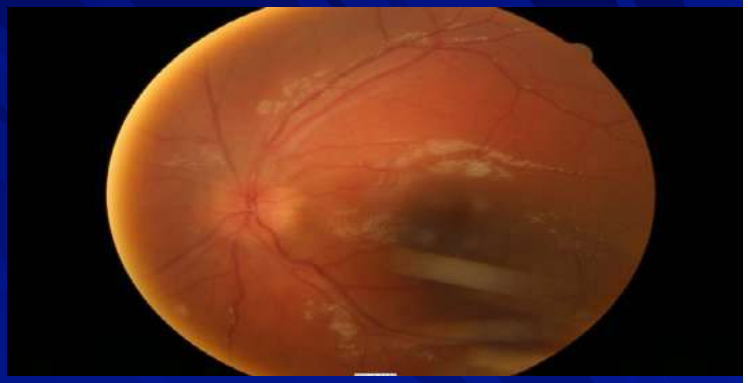
- Enhanced photosensitivity
- Avoid in children and pregnancy (Category D), and in breastfeeding women
  - Stained teeth
  - Small incisors
- Enhances the effects of
  - Coumadin
    - Comment on antibiotic drug interactions…
  - Digoxin
- Idiopathic intracranial hypertension
  - Pseudotumor cerebri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



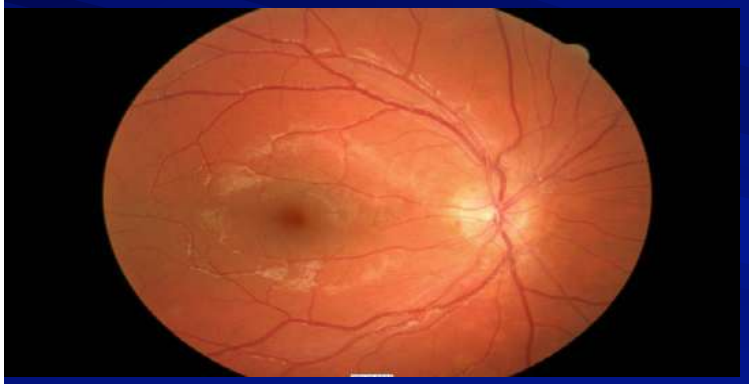
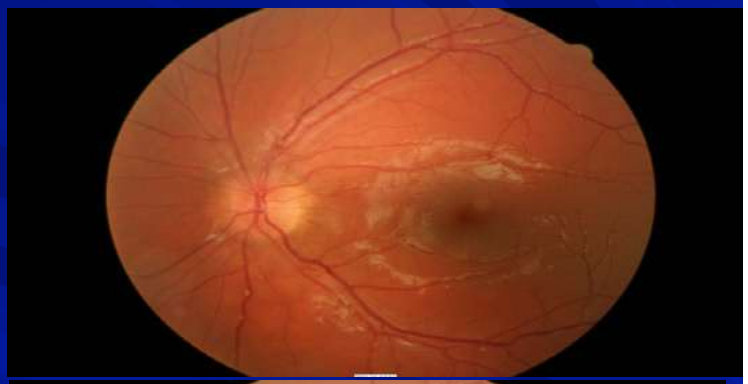
Benign intracranial hypertension

"It's not rare if it's in your chair"

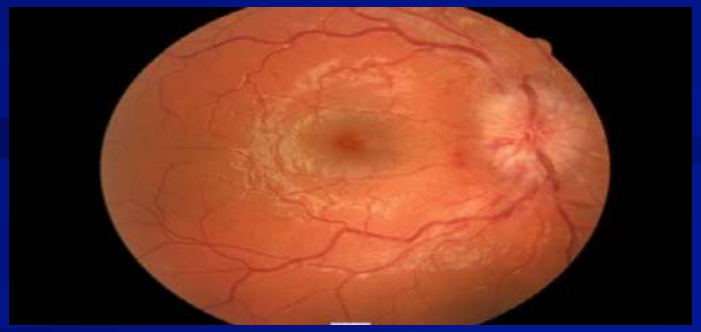
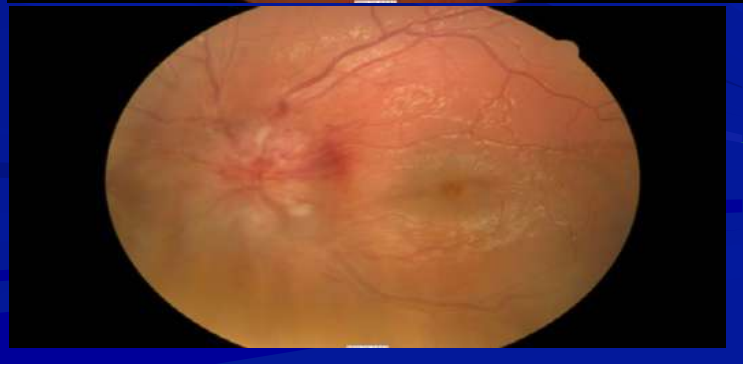


9-13-2010
(25 days)

10-6-2010
(48 days)

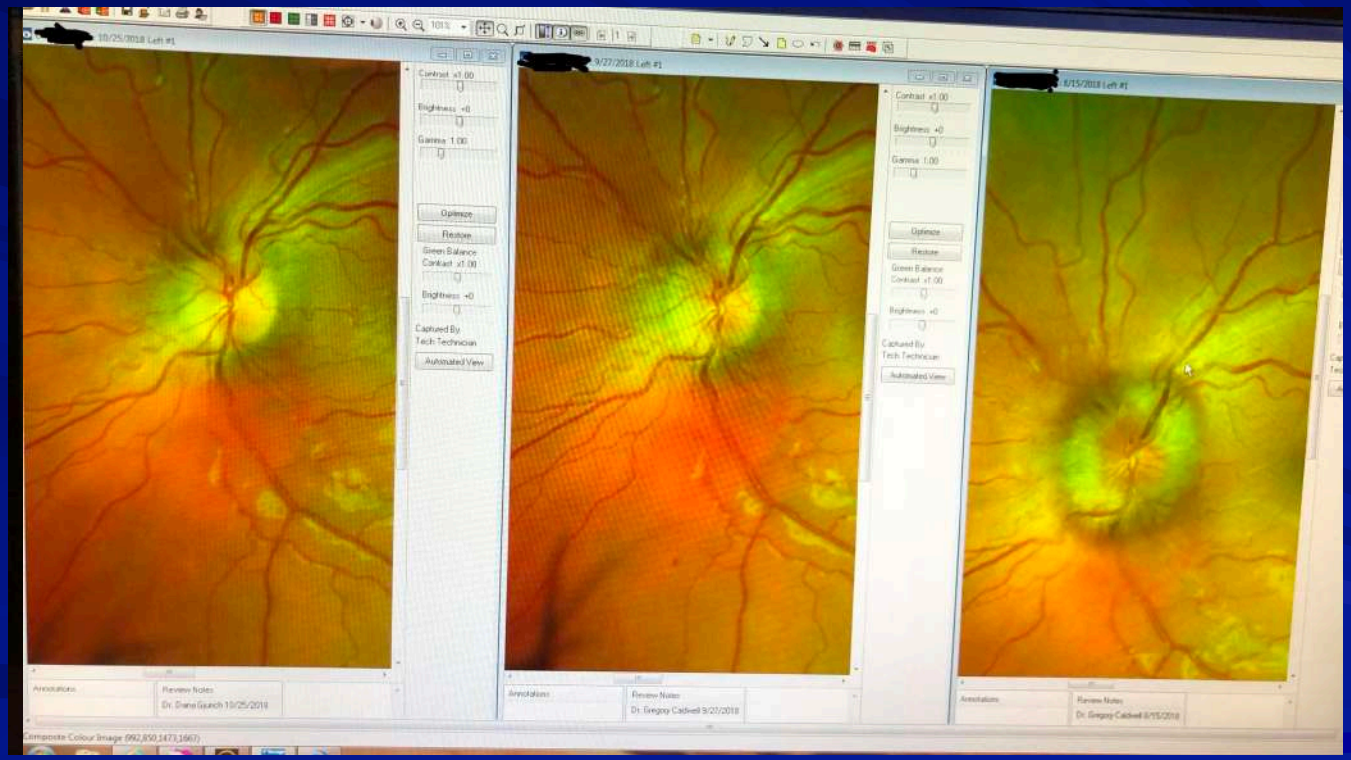



8-19-2010

PTC VS. IIH (THANKS DR. JOE SOWKA)

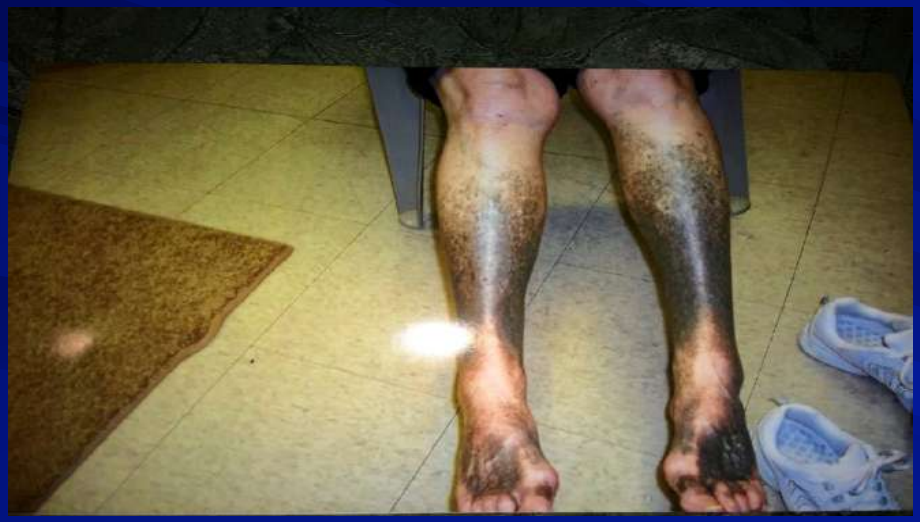
- **Pseudotumor Cerebri (PTC)**
  - Increased intracranial pressure in the absence of an intracranial mass lesion
  - Many causative agents have been identified
- **Idiopathic Intracranial Hypertension (IIH)**
  - Increased intracranial pressure without an identifiable cause
  - Young, obese females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

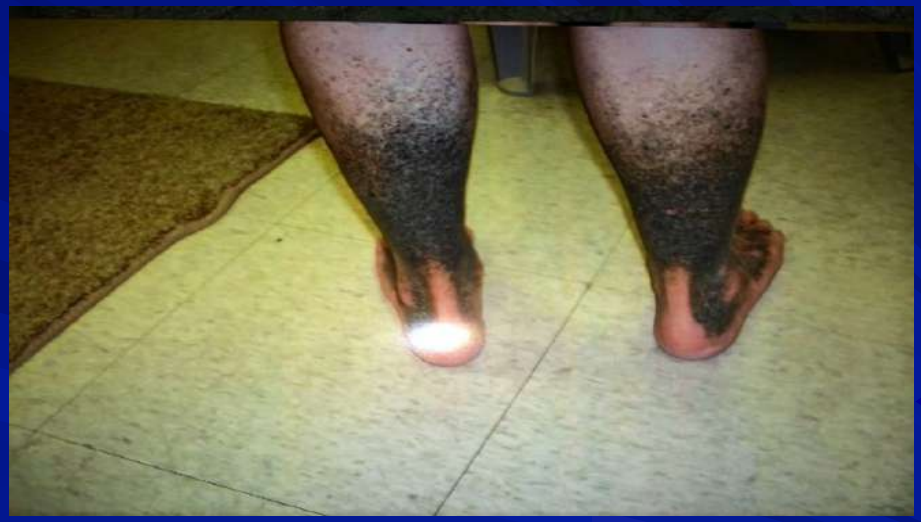
Minocycline Optic Nerve Edema



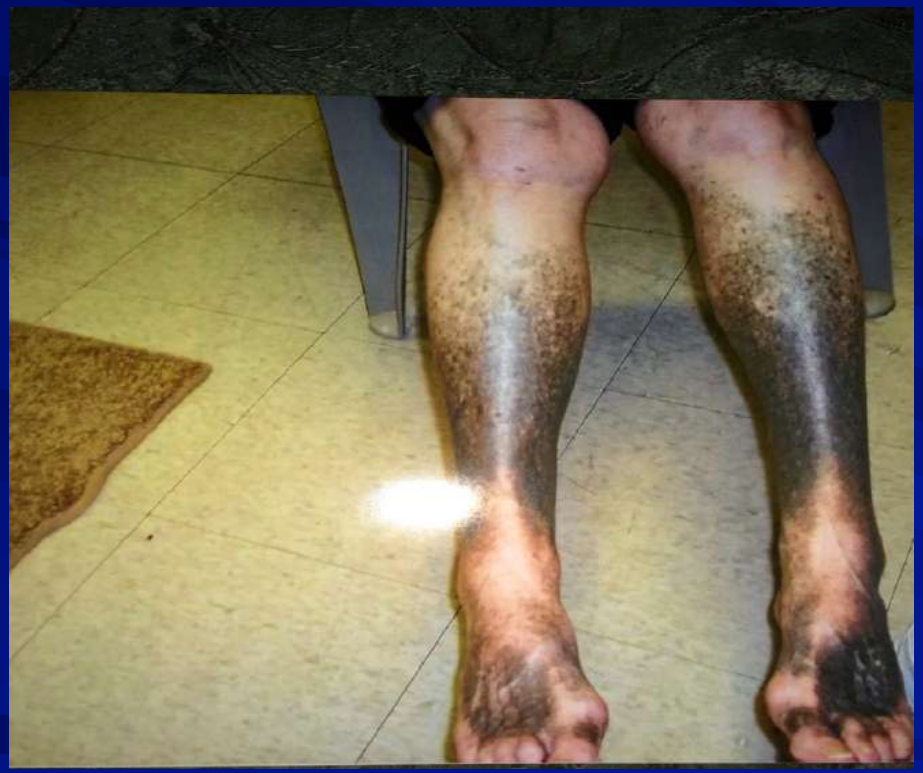
Minocycline Optic Nerve Edema

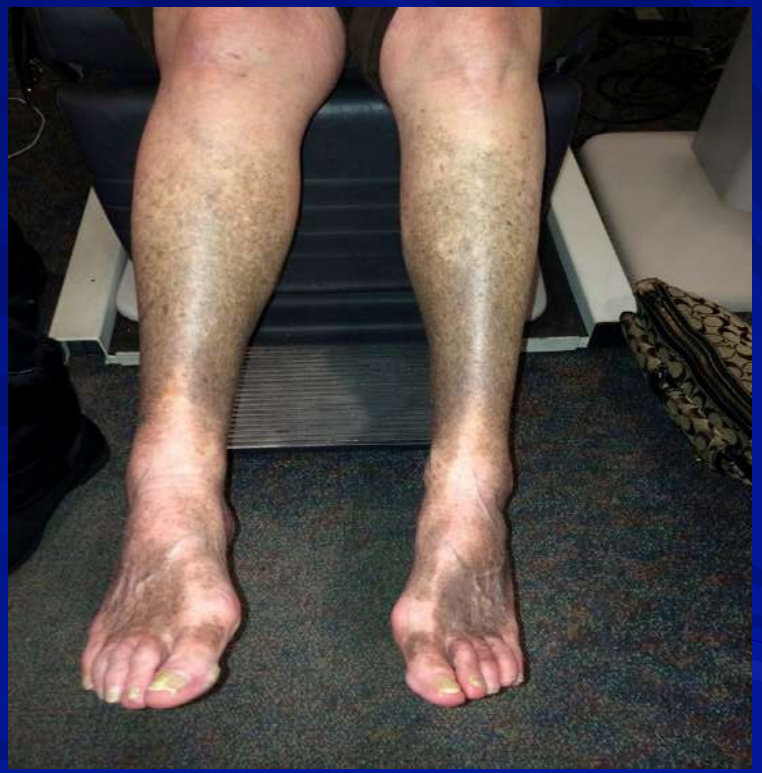
OMG



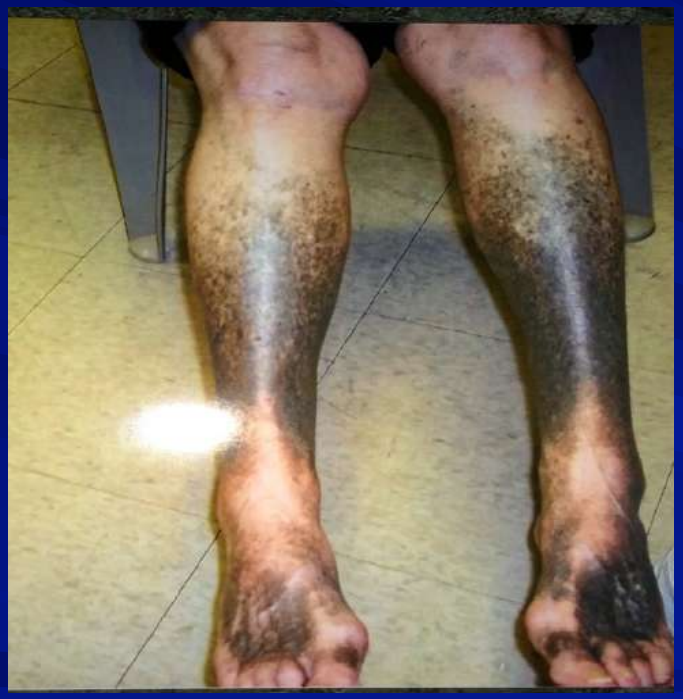


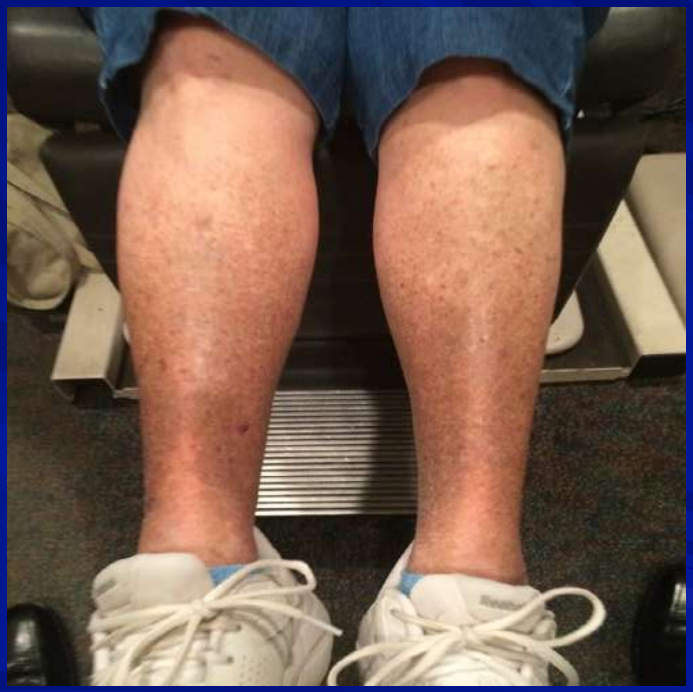
6 Months Later





1 Year Later





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

- Treatment of CHF and/or hypertension
  - Coreg™ (Carvedilol)
    - Alpha1/beta 2 blocker

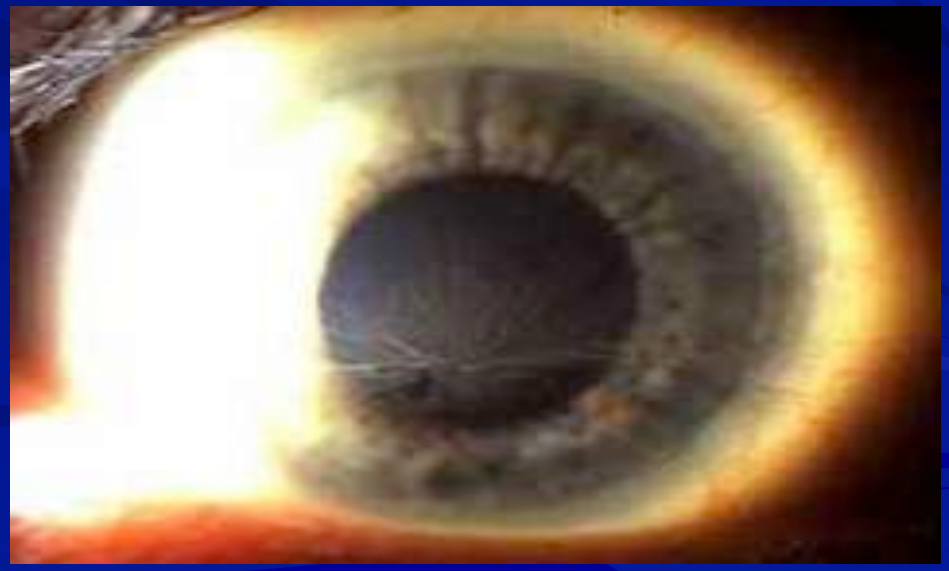
- Treatment of refractory hypertension:
  - Hytrin™ (Terazosin)
    - Alpha 1 blocker

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?

Anti-arrhythmics

- Treatment of cardiac arrhythmia
  - ★ Cordarone™ (amiodarone)
    - Corneal deposits
    - Optic neuritis

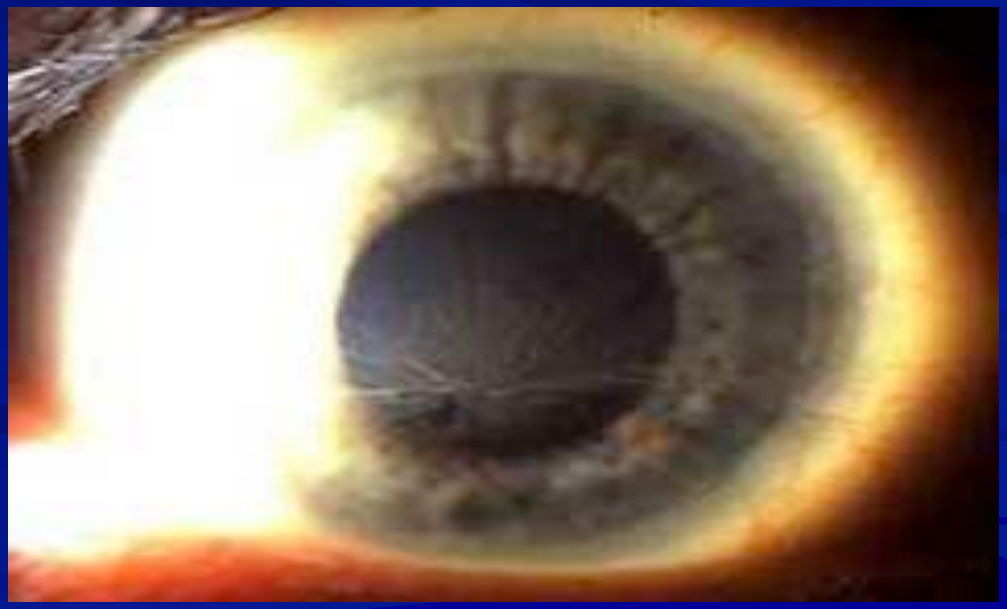


Stages

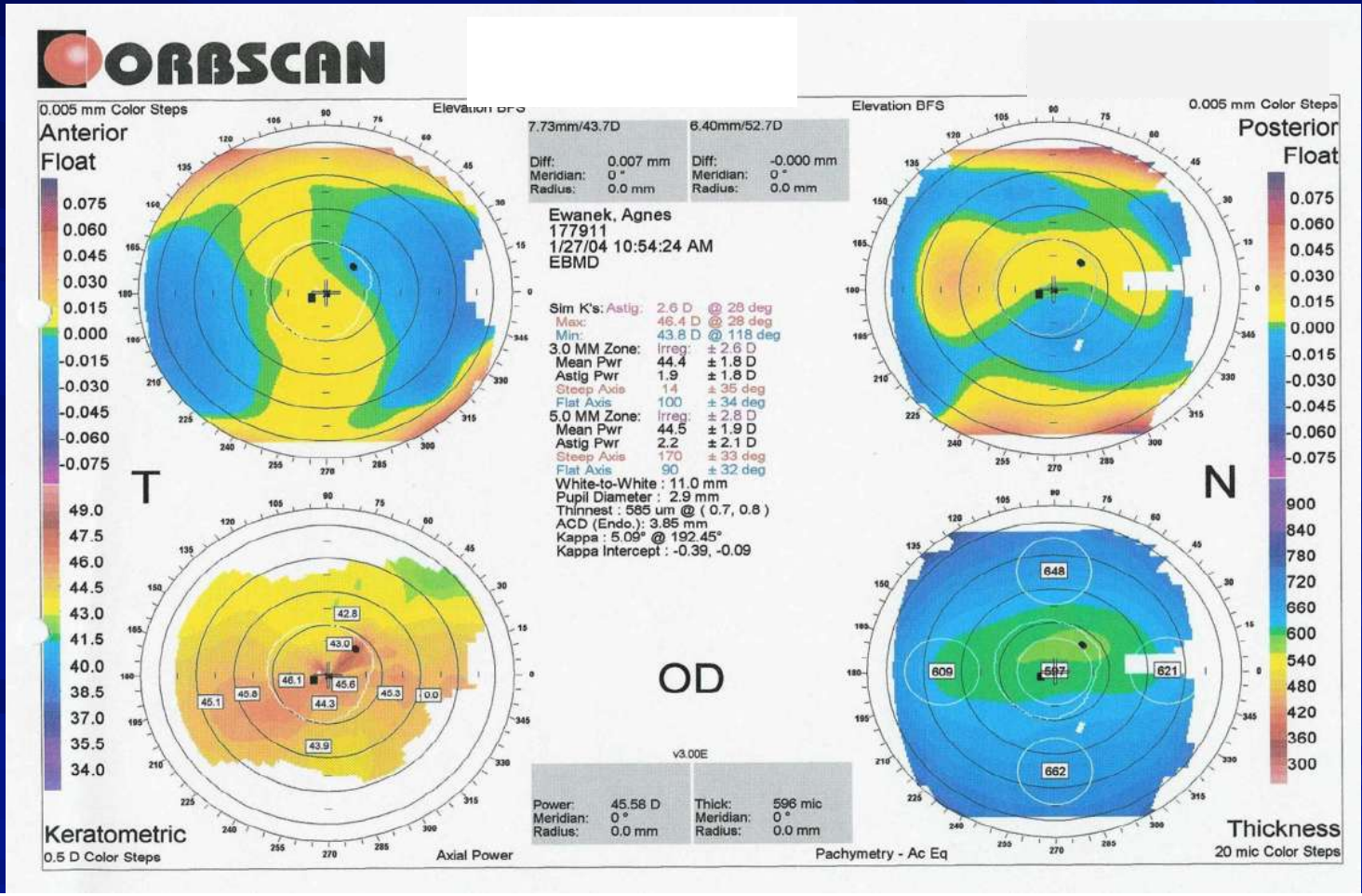
Grade I	Punctate opacities in a horizontal linear pattern in the inferior cornea
Grade II	More aligned deposits in a linear pattern that extend into the inferior pupillary margin toward the limbus
Grade III	Increased numbers of branching patterns in the inferior pupillary area into the visual axis
Grade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


ORBSCAN
0.005 mm Color Steps
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6.40mm/52.7D
Diff: -0.000 mm
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Radius: 0.0 mm
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EBMD
Sim K's: Astig: 2.6 D @ 28 deg
Max: 46.4 D @ 28 deg
Min: 43.8 D @ 118 deg
3.0 MM Zone: Irreg: ± 2.6 D
Mean Pwr 44.4 ± 1.8 D
Astig Pwr 1.9 ± 1.8 D
Steep Axis 14 ± 35 deg
Flat Axis 100 ± 34 deg
5.0 MM Zone: Irreg: ± 2.8 D
Mean Pwr 44.5 ± 1.9 D
Astig Pwr 2.2 ± 2.1 D
Steep Axis 170 ± 33 deg
Flat Axis 90 ± 32 deg
White-to-White : 11.0 mm
Pupil Diameter : 2.9 mm
Thinnest : 585 um @ (0.7, 0.8)
ACD (Endo.): 3.85 mm
Kappa : 5.09° @ 192.45°
Kappa Intercept : -0.39, -0.09
OD
v3.00E
Power: 45.58 D
Meridian: 0 °
Radius: 0.0 mm
Thick: 596 mic
Meridian: 0 °
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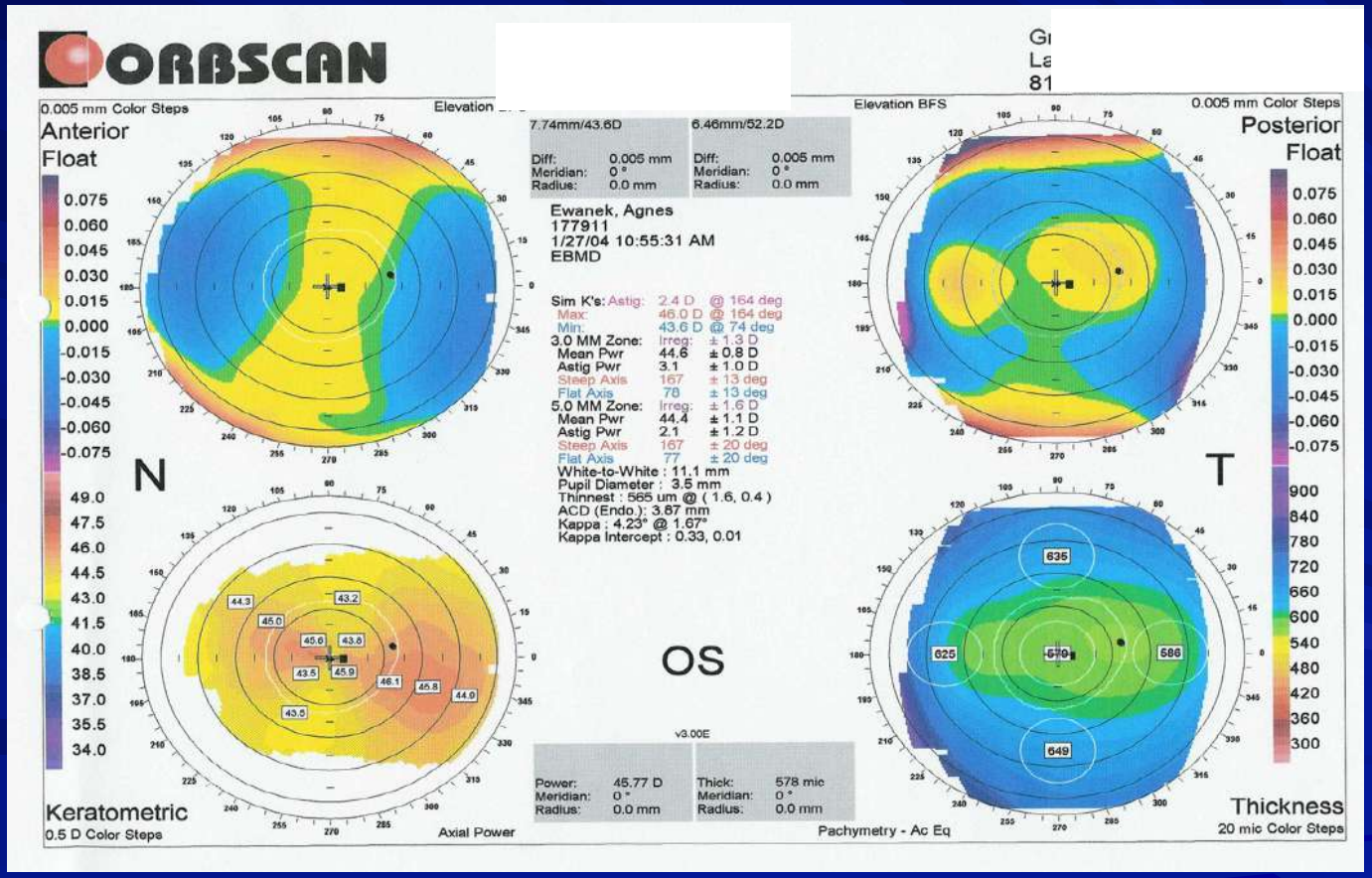
Thickness
20 mic Color Steps
Pachymetry - Ac Eq

Topography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6.46mm/52.2D
Diff: 0.005 mm
Meridian: 0 °
Radius: 0.0 mm
Ewanek, Agnes
177911
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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
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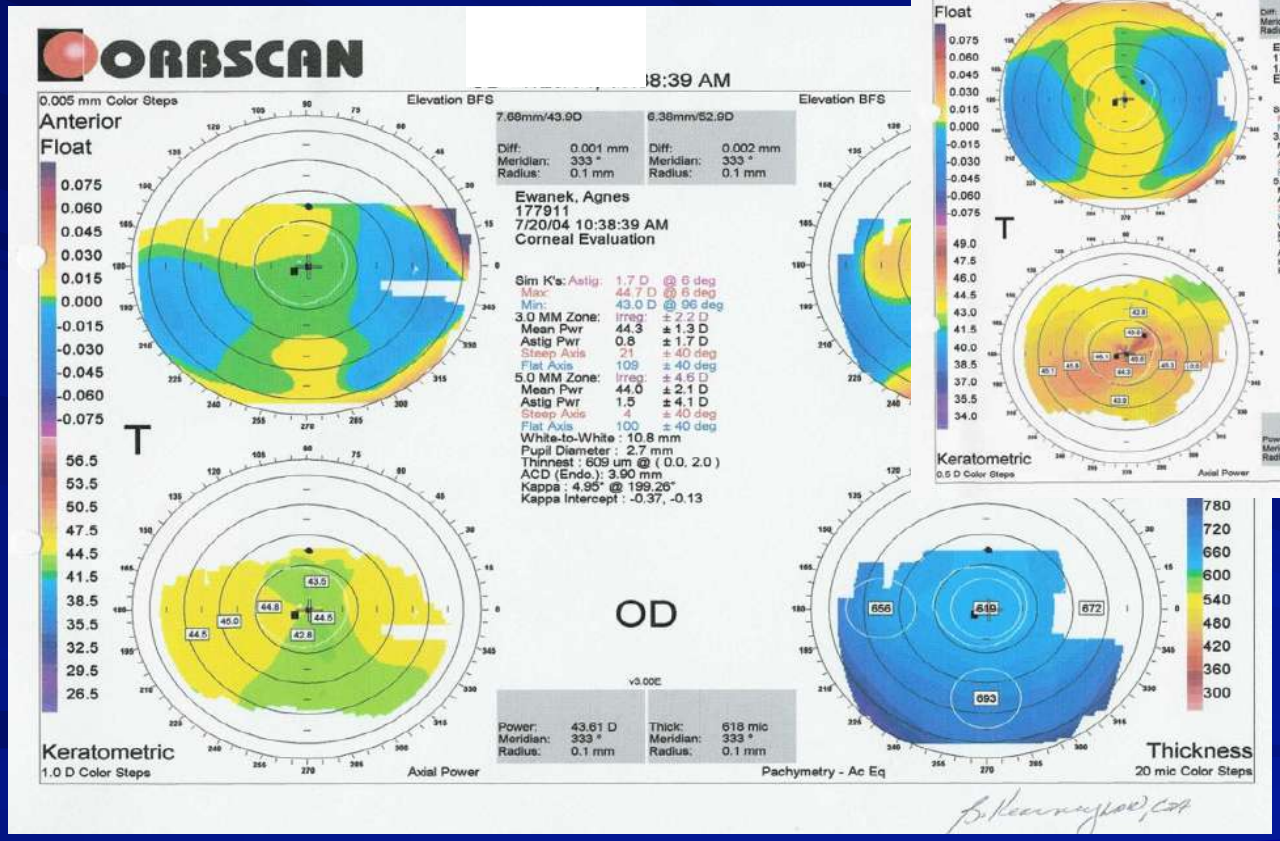
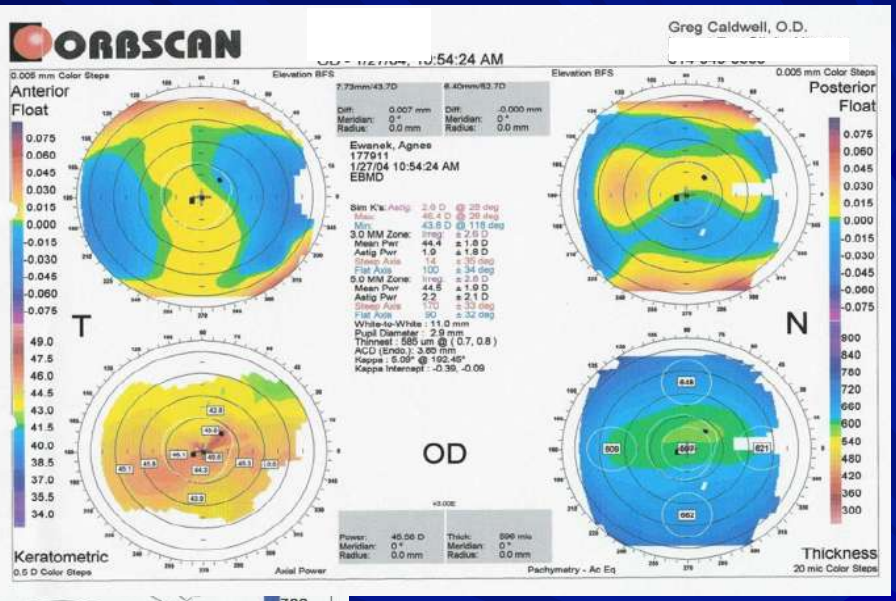
Pachymetry - Ac Eq

6 Months Later





20/25 BVA

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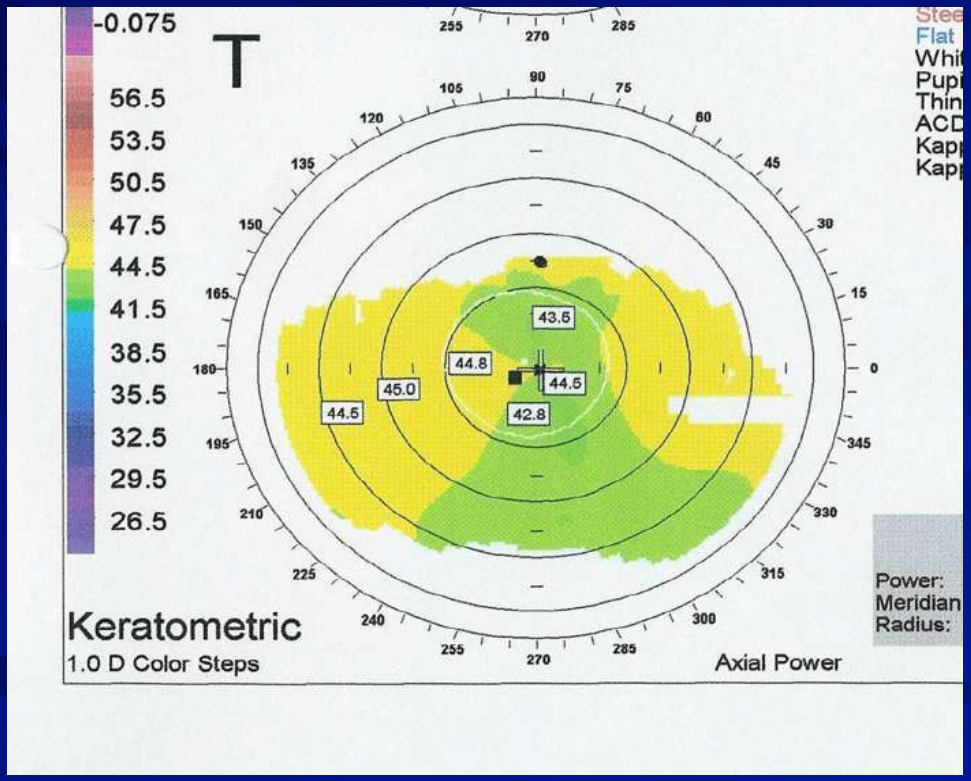
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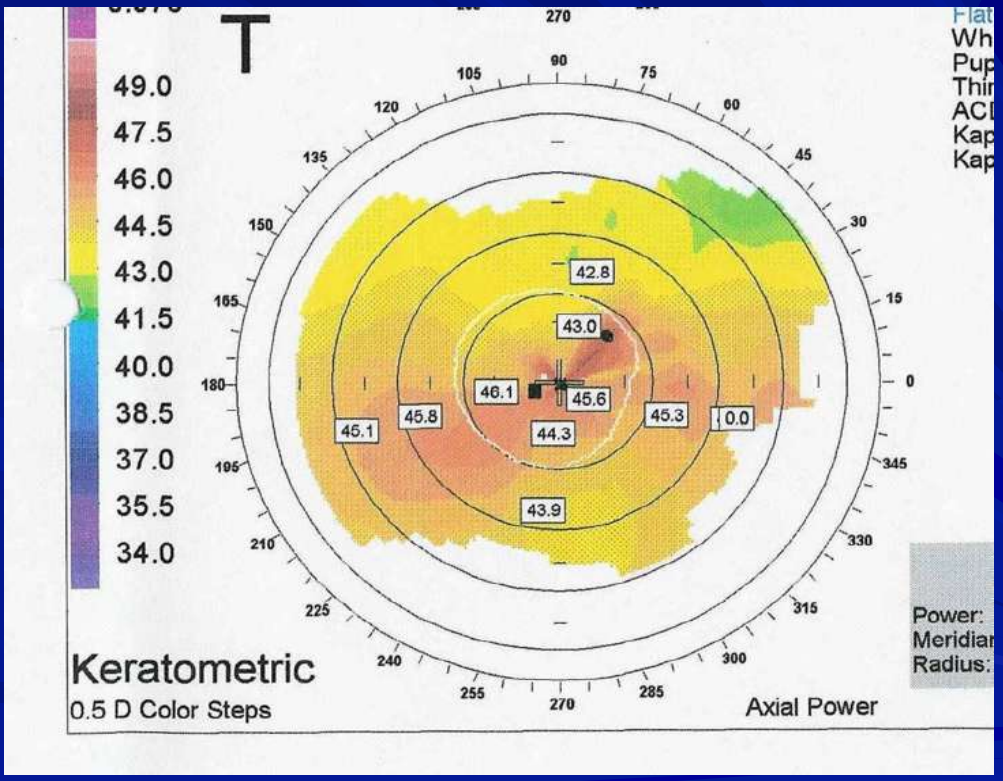
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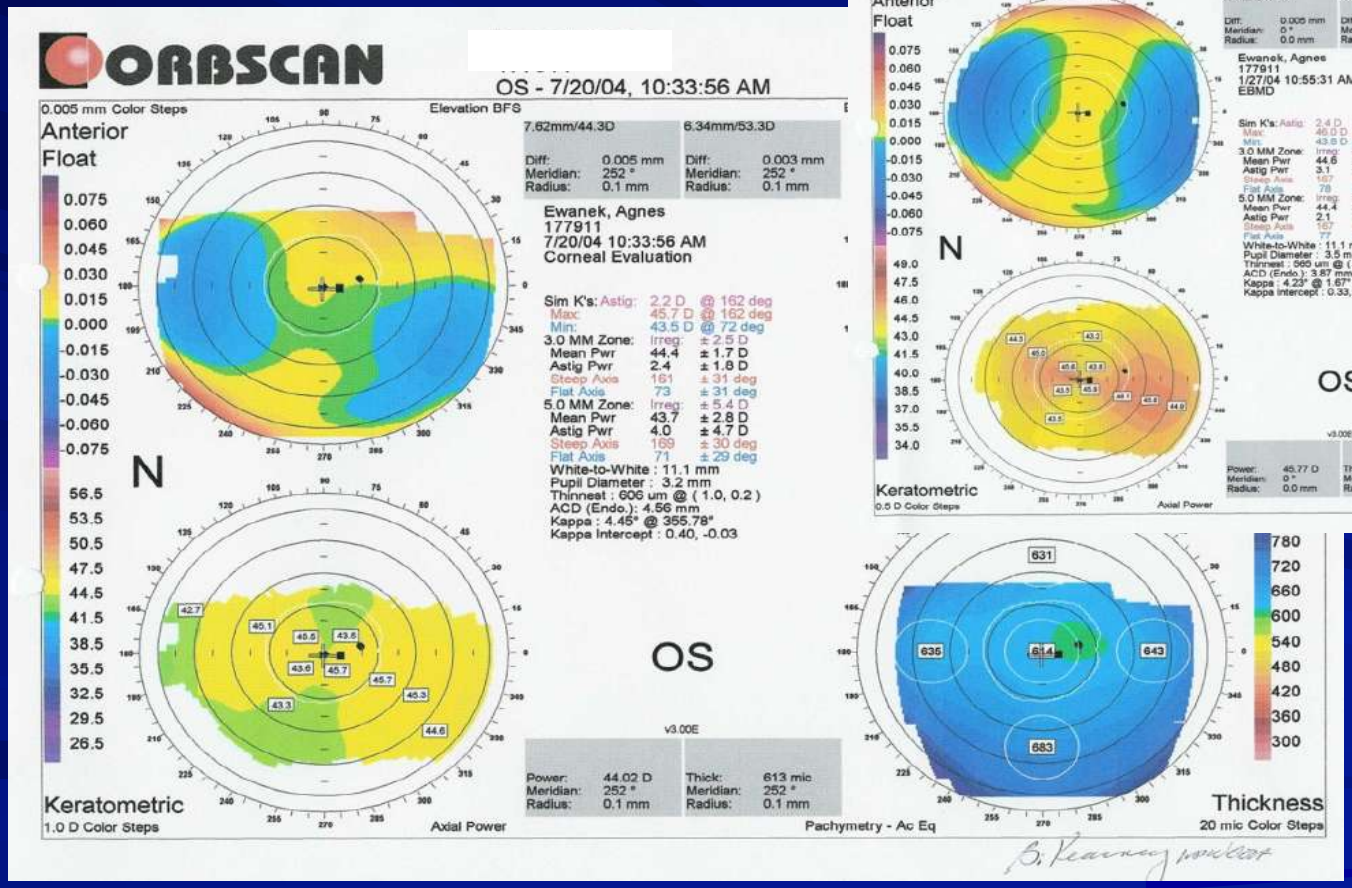

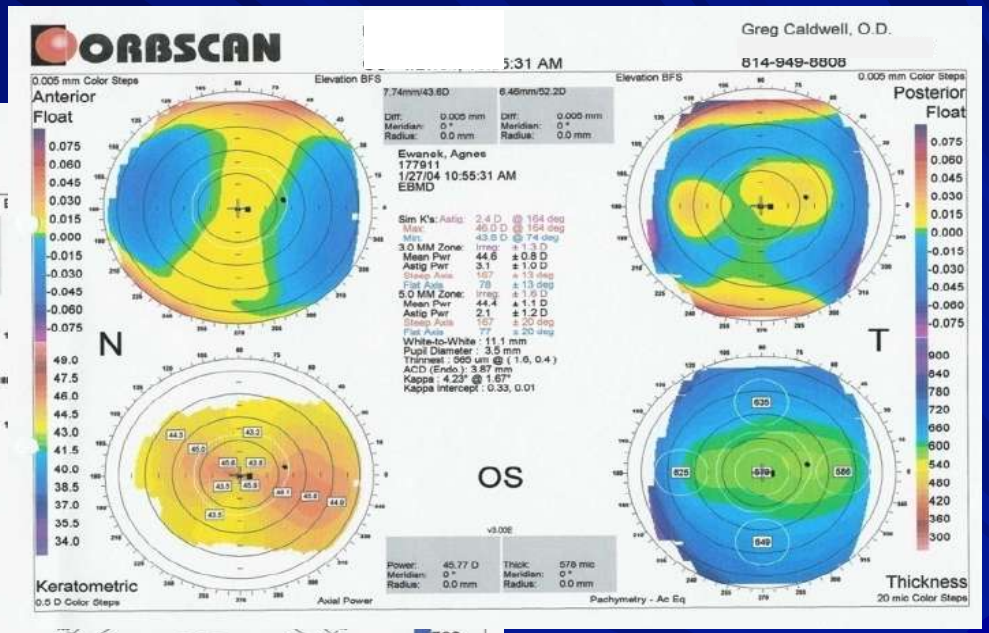

20/25 BVA

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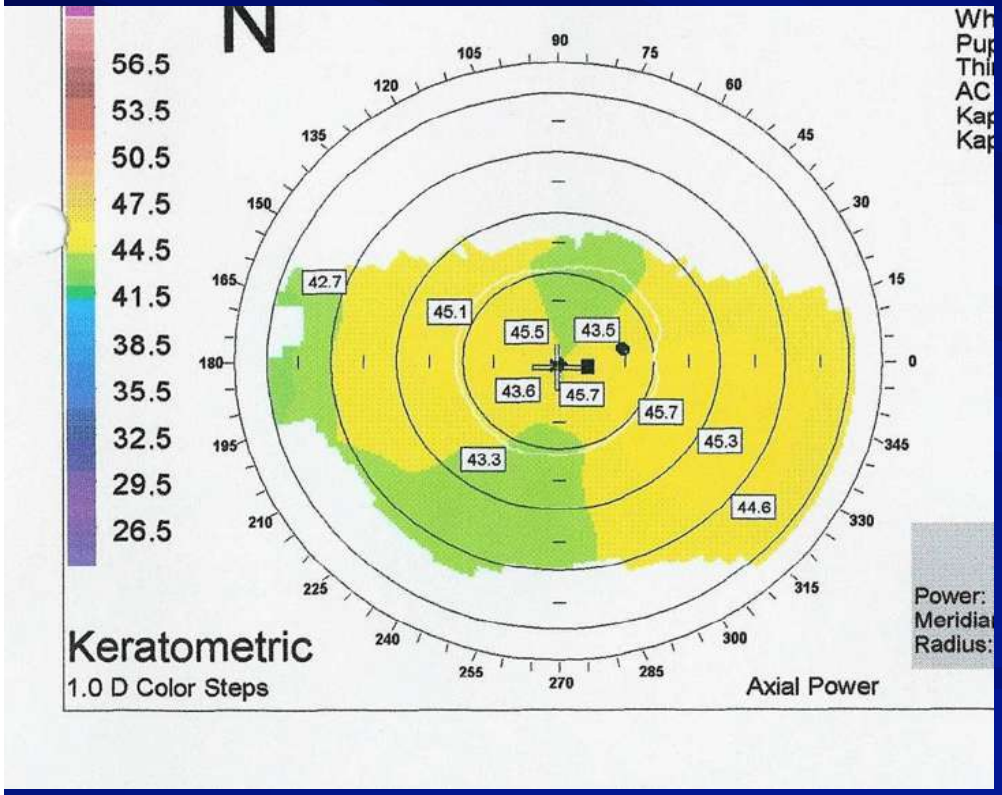
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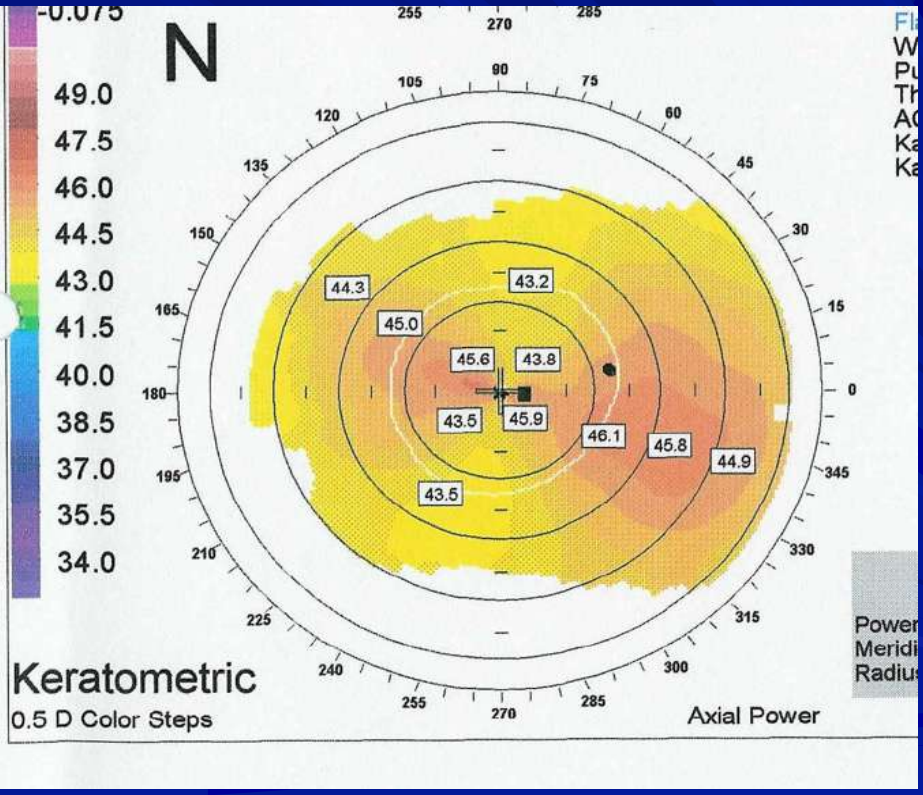
Axial Power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Keratometric
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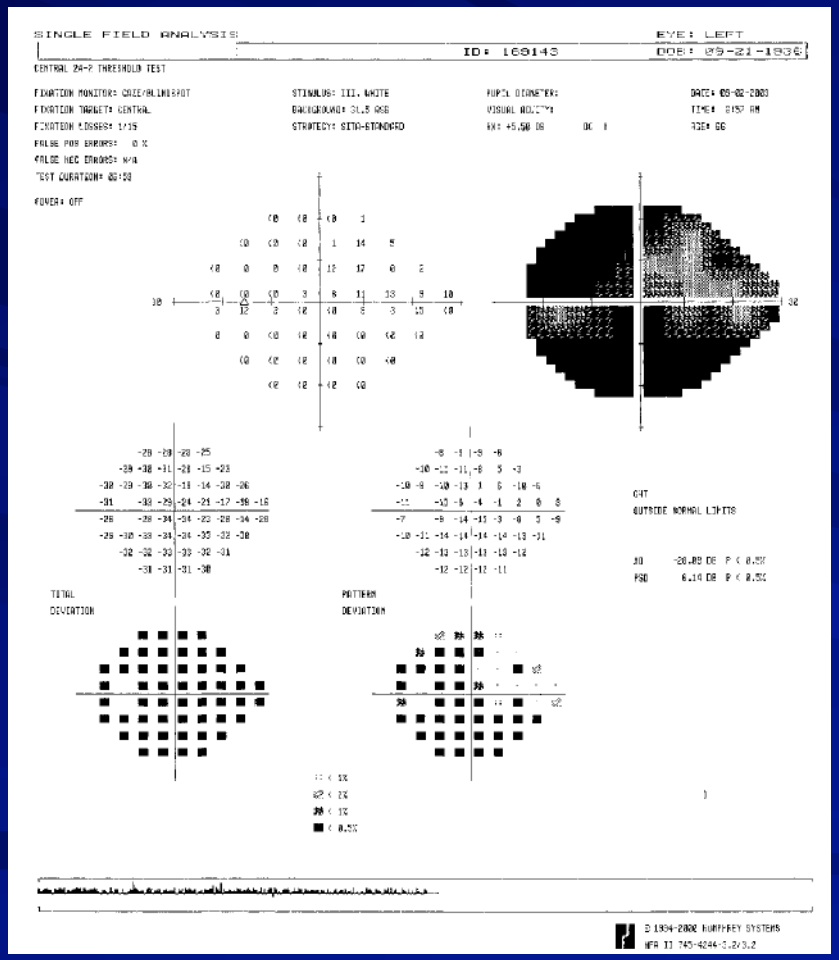
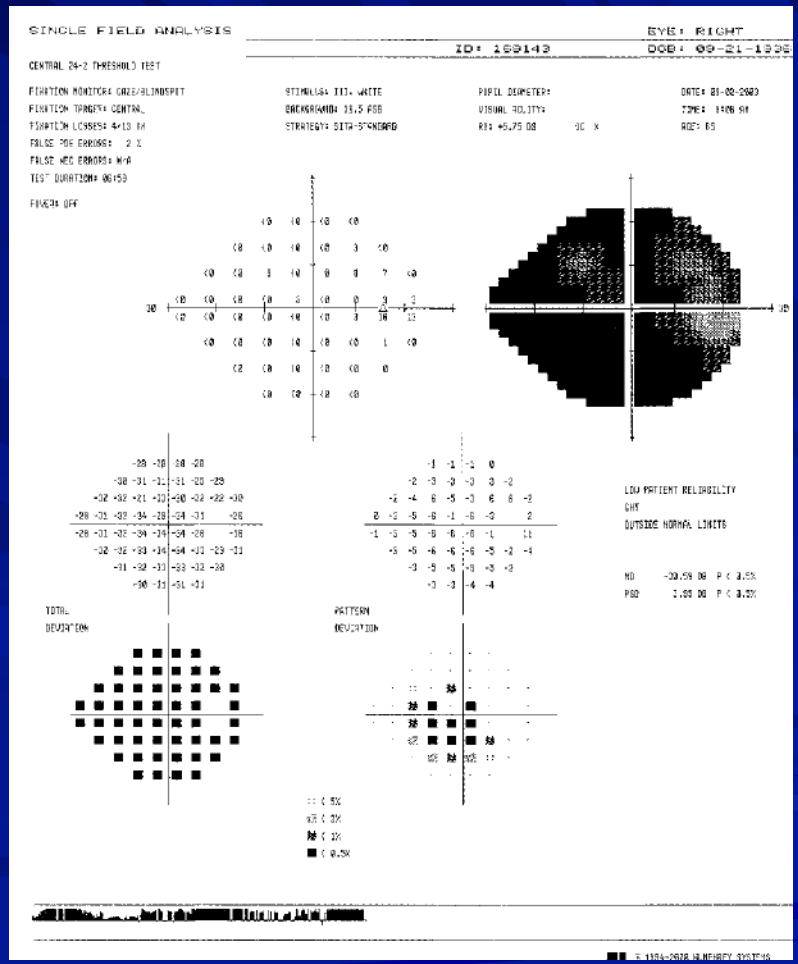
Axial Power

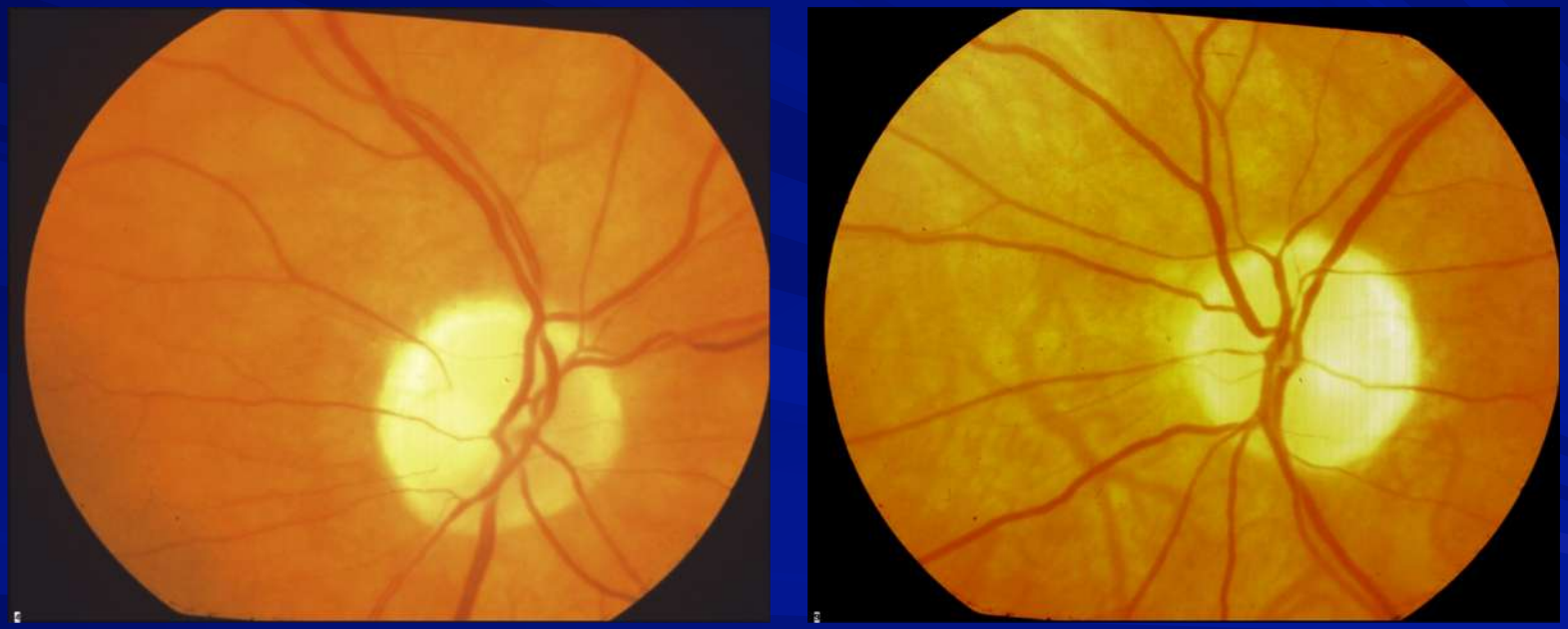
67 year old man complains of vision slowly deteriorating over the past 8 months

- 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/BLIND SPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 1/15
FALSE POS ERRORS: 0 %
FALSE NEG ERRORS: N/A
TEST DURATION: 06:50
STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-STANDARD
PUPIL DIAMETER:
VISUAL ACUITY:
RX: +5.50 DS
DATE: 09-02-2003
TIME: 8:57 AM
AGE: 66
FOVEA: OFF
TOTAL DEVIATION
PATTERN DEVIATION
GHT
OUTSIDE NORMAL LIMITS
MD -20.89 DB P < 0.5%
PSD 6.14 DB P < 0.5%
< 5%
< 2%
< 1%
< 0.5%
© 1994-2002 HUMPHREY SYSTEMS
REF II 745-4244-3.2/3.2


SINGLE FIELD ANALYSIS
EYE: RIGHT
ID: 169143
DOB: 09-21-1936
CENTRAL 24-2 THRESHOLD TEST
FIXATION MONITOR: GAZE/BLINDSPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 4/13
FALSE POS ERRORS: 2 %
FALSE NEG ERRORS: N/A
TEST DURATION: 06:53
STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-STANDARD
PUPIL DIAMETER:
VISUAL ACUITY:
RX: +5.75 DS
DATE: 01-09-2003
TIME: 8:06 AM
AGE: 65
FOVEA: OFF
TOTAL DEVIATION
PATTERN DEVIATION
LOW PATIENT RELIABILITY
GHT
OUTSIDE NORMAL LIMITS
MD -20.59 DB P < 0.5%
PSD 1.88 DB P < 0.5%
< 5%
< 2%
< 1%
< 0.5%

Amiodarone Optic Neuropathy
(Toxic Optic Neuropathy)



Rhopressa™ 0.02% (netarsudil ophthalmic solution)

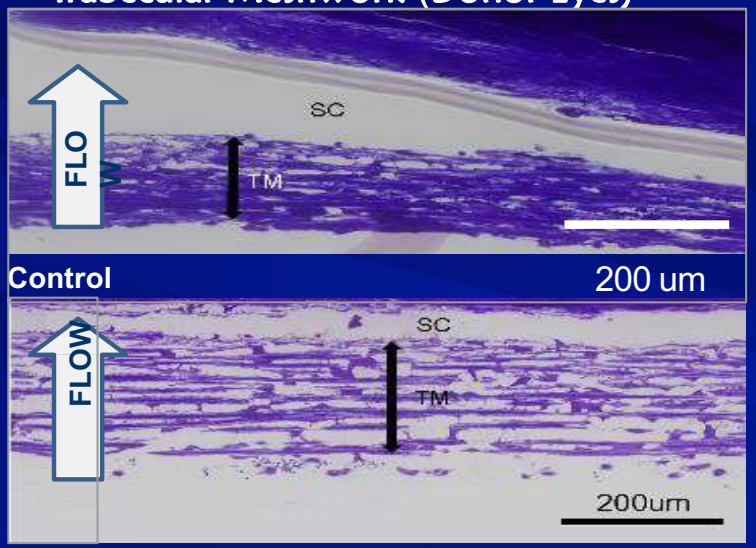
- Aerie Pharmaceuticals
  - Approved December 2017
  - Treatment of glaucoma or ocular hypertension
  - Rho kinase inhibitor
    - ROCK-NET Inhibitor
  - Once daily in the evening
    - Twice a day dosing is not well tolerated and is not recommended
  - Side Effects
    - Conjunctival hyperemia
    -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

Rhopressa™ 0.02% (netarsudil)

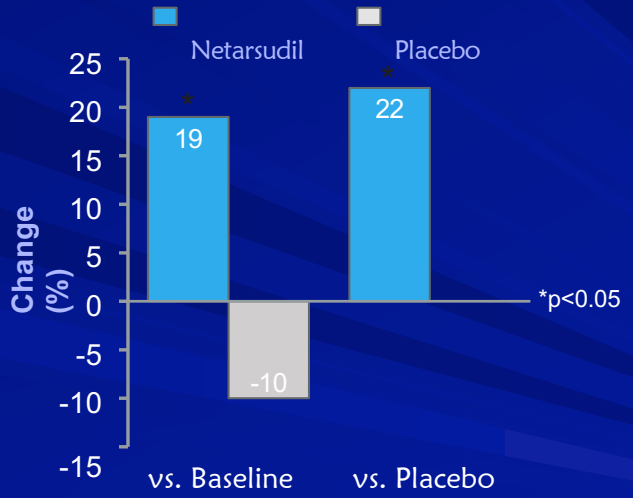
Causes Expansion of TM in Donor Eyes

Increases TM Outflow Facility in Clinic

Trabecular Meshwork (Donor Eyes)[1]



TM Outflow Facility (Healthy Volunteers)[2]



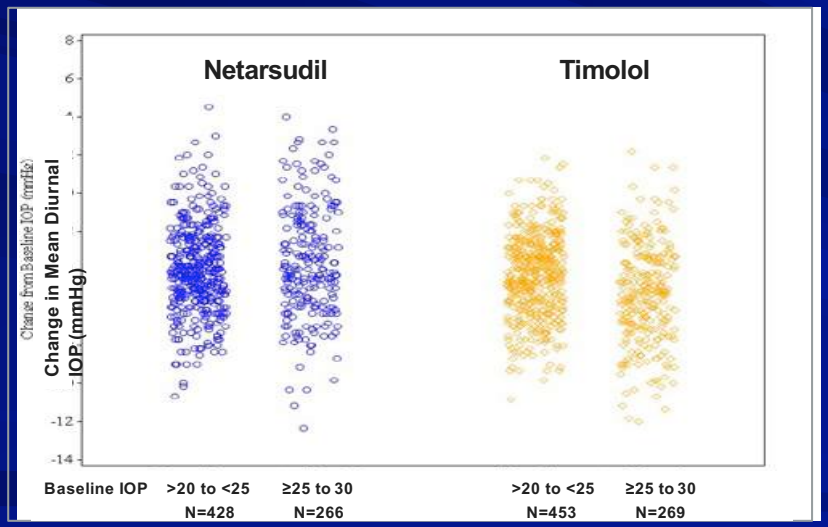
TM: Trabecular Meshwork; SC: Schlemm's Canal; Control: buffered saline solution; ESV: Episcleral Vein

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

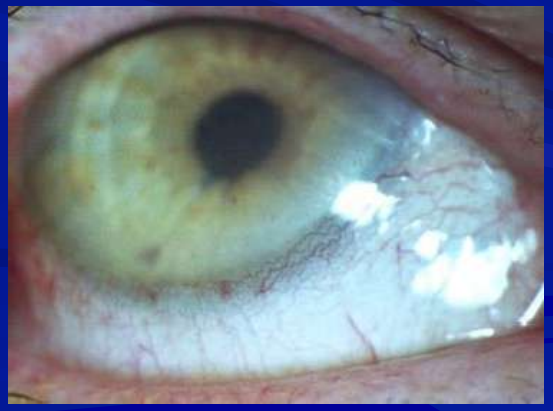
1. RHOPRESSA® (netarsudil ophthalmic solution) 0.02% Prescribing Information. 2. Khouri et al. Association for Research in Vision and Ophthalmology oral presentation 2017 [E-abstract 2461].

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

Adverse Events	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (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

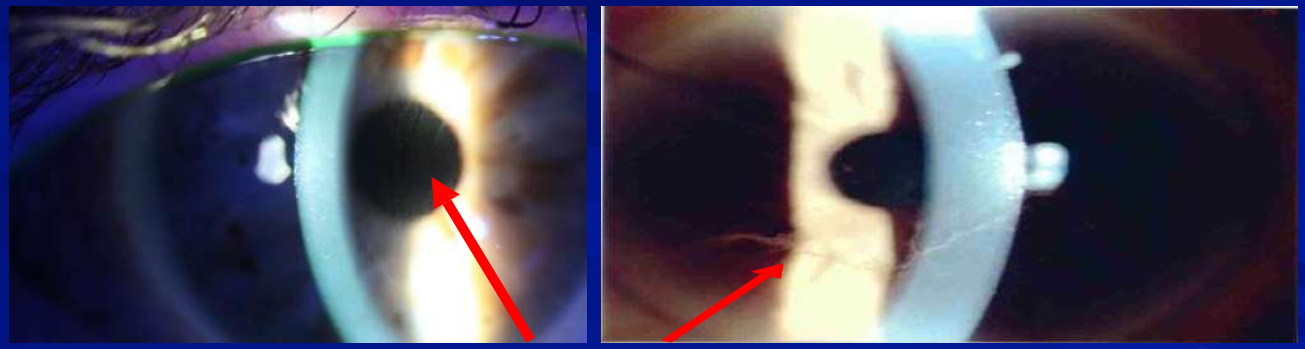
Literature review suggested it is an adaptive response by the body rather than an adverse pathology*

Data on File Based on AR-13324-IPH07

* Raizman MB 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)



Cornea verticillata

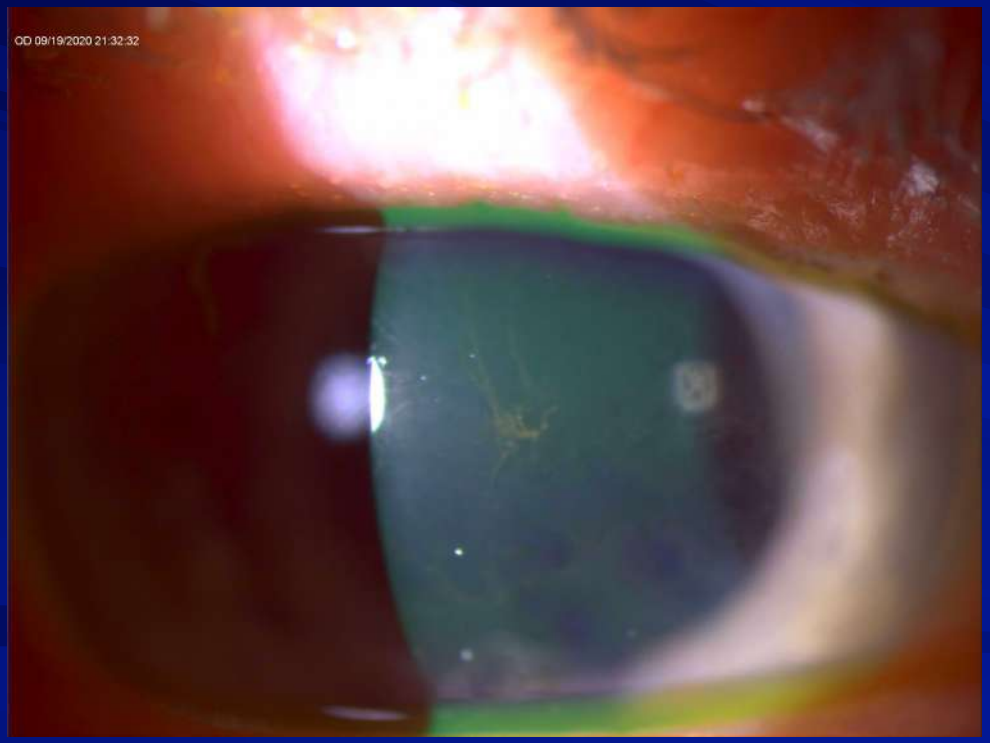
AR-13324-CS302
netarsudil QD subject

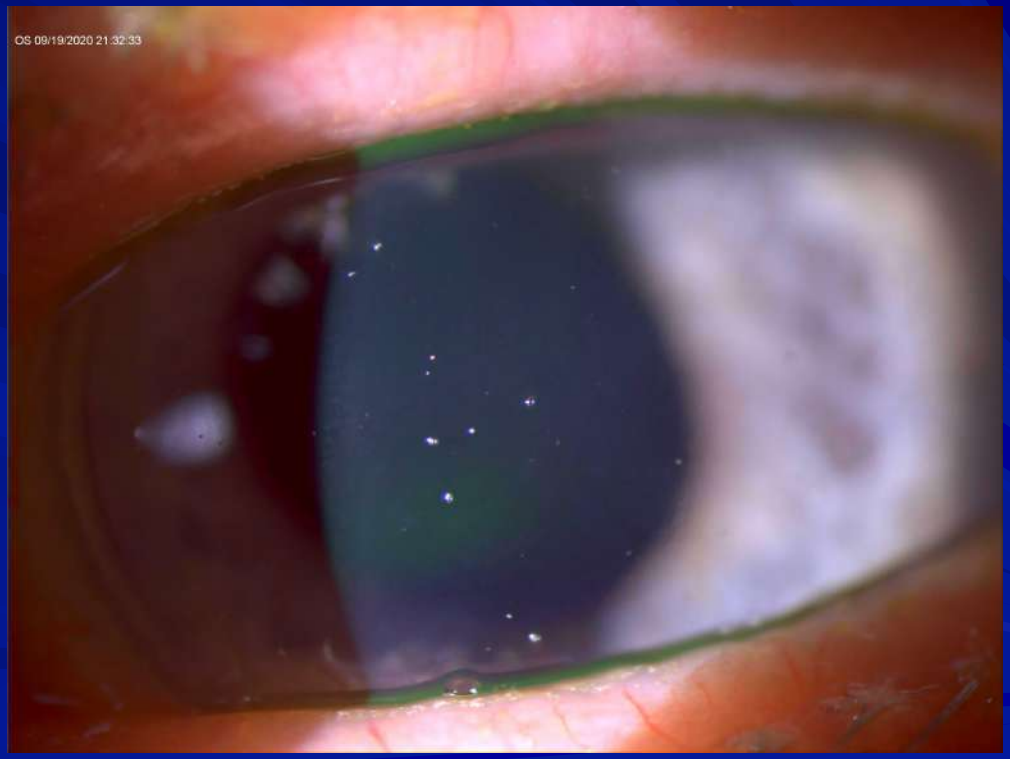
AR-13324-CS302
netarsudil BID subject

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

My Experience

OD treated OS gtts

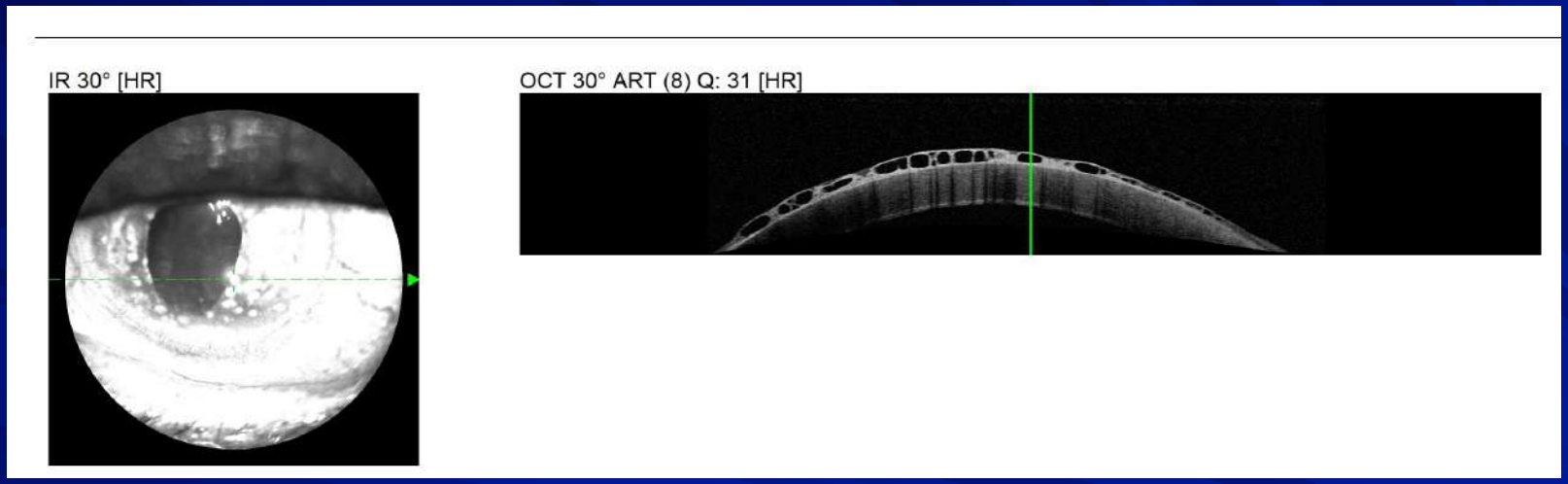




Summary of the Most Common Netarsudil Ocular TEAEs

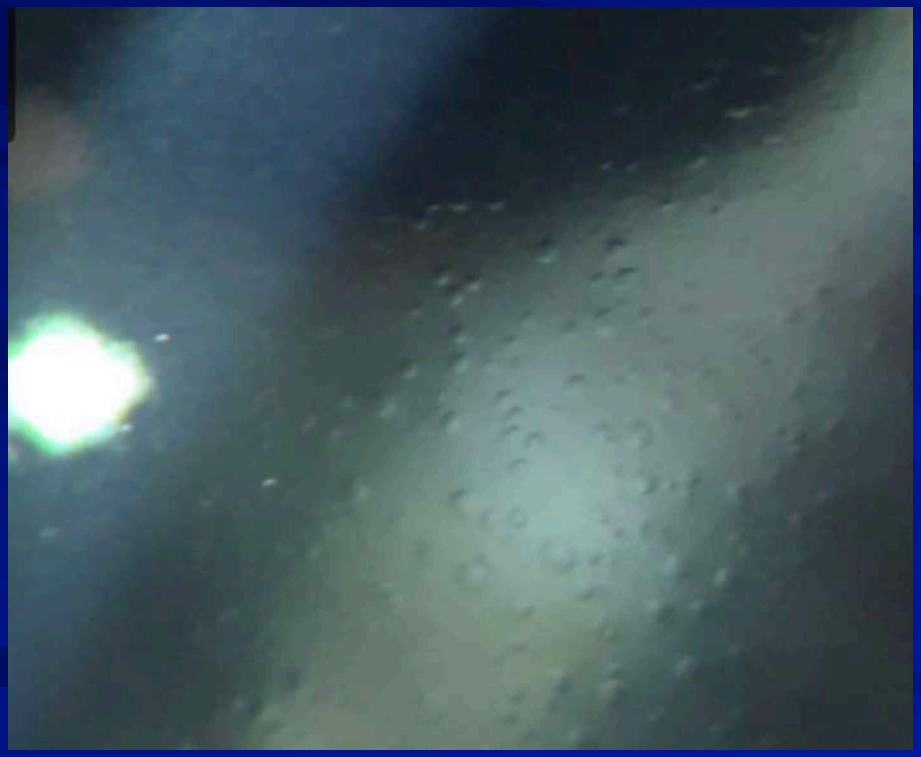
Conjunctival Hyperemia	Cornea Verticillata	Conjunctival Hemorrhage
• 54.4% TEAE • Severity did not increased with continued dosing • Sporadic	• 20.9% TEAE • Asymptomatic • 7.4% experienced reduced visual acuity • Not clear to a directly associated • All resolved after 13 weeks of D/C	• 17.2% TEAE • Mild in severity and transient • Self-resolving with continued dosing

Honeycomb Epithelial Edema Associated With Rho Kinase Inhibition



- Thank you, Charles McBride, O.D., Beaverton, OR (12-23-2020 OGS – Google Groups)
- Sample of Rocklatan yesterday to lower his IOP of 46mmHg
- IOP today was 34
- Didn't measure corneal thickness
- The eye is blind and pretty sure it is neovascular glaucoma
- He's not been seen in three years and recently relocated from Missouri

Honeycomb Epithelial Edema Associated With Rho Kinase Inhibition
Graft Patient



Thank you! Joe Shovlin, OD, FAAO

CannaBinoiDs (CBD)

Effect of Sublingual Application of Cannabinoids on Intraocular Pressure: A Pilot Study

Ileana Tomida, MD, Augusto Azuara-Blanco, MD, PhD,* Heather House, BSc,† Maggie Flint, BSc,‡ Roger G. Pertwee, DPhil, DSc,§ and Philip J. Robson, MD†*

Purpose: The purpose of this study was to assess the effect on intraocular pressure (IOP) and the safety and tolerability of oromucosal administration of a low dose of delta-9-tetrahydrocannabinol (Δ-9-THC) and cannabidiol (CBD).

Patients and Methods: A randomized, double-masked, placebo-controlled, 4 way crossover study was conducted at a single center, using cannabis-based medicinal extract of Δ-9-THC and CBD. Six patients with ocular hypertension or early primary open angle glaucoma received a single sublingual dose at 8 AM of 5 mg Δ-9-THC, 20 mg CBD, 40 mg CBD, or placebo. Main outcome measure was IOP. Secondary outcomes included visual acuity, vital signs, and psychotropic effects.

Results: Two hours after sublingual administration of 5 mg Δ-9-THC, the IOP was significantly lower than after placebo (23.5 mm Hg vs. 27.3 mm Hg, $P = 0.026$). The IOP returned to baseline level after the 4-hour IOP measurement. CBD administration did not reduce the IOP at any time. However, the higher dose of CBD (40 mg) produced a transient elevation of IOP at 4 hours after administration, from 23.2 to 25.9 mm Hg ($P = 0.028$). Vital signs and visual acuity were not significantly changed. One patient experienced a transient and mild panic-like reaction after Δ-9-THC administration.

Conclusions: A single 5 mg sublingual dose of Δ-9-THC reduced the IOP temporarily and was well tolerated by most patients. Sublingual administration of 20 mg CBD did not reduce IOP, whereas 40 mg CBD produced a transient increase IOP rise.

Key Words: delta-9-tetrahydrocannabinol, cannabidiol, glaucoma, IOP

(*J Glaucoma* 2006;15:349–353)

Glaucoma is one of the leading causes of blindness in the world. A range of medical and surgical options for glaucoma is currently available but treatment efficacy is variable and side effects can occur. Thus, the search for new therapeutic alternatives continues.

Cannabis and its derivatives are known to have therapeutic potential in a range of medical conditions.[1] Hepler and Frank[2] reported in 1971 the intraocular pressure (IOP)-lowering effect of smoking marijuana in a small number of subjects. Since these early observations numerous studies have been conducted confirming that different cannabinoids, including delta-9-tetrahydrocannabinol (Δ-9-THC), cannabidiol (CBD), cannabigerol, endogenous cannabinoids, and some synthetic cannabinoids, can reduce the IOP when administered systemically and topically.[3–12]

In glaucoma, the final pathway leading to visual loss is the selective death of retinal ganglion cells through apoptosis.[13] Substances that prevent apoptosis and inhibit retinal ganglion cell death could have a therapeutic benefit in glaucoma. Recent studies have documented the neuroprotective properties of cannabinoids independent of their effect on IOP.[14–20]

The best possible route for the administration of cannabinoids is also under investigation. Although smoking marijuana is an extremely efficient way of delivering cannabinoids, this form of administration cannot be justified in a medicinal context on ethical, medico-legal or safety grounds.[21] In addition to the acute side effects, the dose is difficult to control, long-term cannabis smoking is associated with emphysema-like lung changes and a possible increased frequency of lung cancer. Oral administration of cannabinoids has been evaluated.[3] However, the very low water solubility of key cannabis constituents aggravates still further the normal variability of absorption from the gastro-intestinal tract, resulting in poor predictability of both the timing and the intensity of peak effects. This is an important consideration given the wide variation in individual sensitivity to both the therapeutic and unwanted effects of cannabis derivatives and thus making this route undesirable. An additional drawback to the oral route is the conversion of the ingested form to larger quantities of THCs primary metabolite, the reputedly psychoactive 11-OH-Δ-9-THC.[22] For glaucoma patients topical administration of cannabinoids would be ideal, but presents pharmaceutical challenges that have yet to be overcome.[23,24]

Received for publication February 27, 2006; accepted May 30, 2006.
From the *Department of Ophthalmology, Aberdeen Royal Infirmary; §School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, UK; †Cannabinoid Research Institute, Magdalen Centre, Oxford Science Park, Oxford OX4 4GA; and ‡GW Pharmaceuticals plc, Ely, Cambs CB7 4ZA.
Supported by GW Pharmaceuticals, manufacturers of the sublingual cannabinoid used in this study, and the Grampian Glaucoma Fund.
Reprints: Augusto Azuara-Blanco, MD, PhD, The Eye Clinic, Aberdeen Royal Infirmary, Aberdeen AB25 2ZN, UK (e-mail: azablanco@aol.com).

Conclusions: A single 5 mg sublingual dose of Δ-9-THC reduced the IOP temporarily and was well tolerated by most patients. Sublingual administration of 20 mg CBD did not reduce IOP, whereas 40 mg CBD produced a transient increase IOP rise.

> Invest Ophthalmol Vis Sci. 2018 Dec 3;59(15):5904-5911. doi: 10.1167/iovs.18-24838.

Δ9-Tetrahydrocannabinol and Cannabidiol Differentially Regulate Intraocular Pressure

Sally Miller [1], Laura Daily [1], Emma Leishman [1], Heather Bradshaw [1], Alex Straiker [1]

Affiliations + expand

PMID: 30550613 PMCID: PMC6295937 DOI: 10.1167/iovs.18-24838

Free PMC article

Abstract

Purpose: It has been known for nearly 50 years that cannabis and the psychoactive constituent Δ9-tetrahydrocannabinol (THC) reduce intraocular pressure (IOP). Elevated IOP remains the chief hallmark and therapeutic target for glaucoma, a major cause of blindness. THC likely acts via one of the known cannabinoid-related receptors (CB1, CB2, GPR18, GPR119, GPR55) but this has never been determined explicitly. Cannabidiol (CBD) is a second major constituent of cannabis that has been found to be without effect on IOP in most studies.

Methods: Effects of topically applied THC and CBD were tested in living mice by using tonometry and measurements of mRNA levels. In addition the lipidomic consequences of CBD treatment were tested by using lipid analysis.

Results: We now report that a single topical application of THC lowered IOP substantially (~28%) for 8 hours in male mice. This effect is due to combined activation of CB1 and GPR18 receptors each of which has been shown to lower ocular pressure when activated. We also found that the effect was sex-dependent, being stronger in male mice, and that mRNA levels of CB1 and GPR18 were higher in males. Far from inactive, CBD was found to have two opposing effects on ocular pressure, one of which involved antagonism of tonic signaling. CBD prevents THC from lowering ocular pressure.

Conclusions: We conclude that THC lowers IOP by activating two receptors-CB1 and GPR18-but in a sex-dependent manner. CBD, contrary to expectation, has two opposing effects on IOP and can interfere with the effects of THC.

THC versus CBD

CannaBinoiDs (CBD)

- Discuss cannabidiol (CBD) use as well as THC marijuana with your patients
  - CBD elevates IOP
  - Patients are often self medicating choosing CBD because it has no psychoactive effects, and it can be the cause of the high IOP
  - CBD is now sold over the counter "everywhere"
- Plurality of studies do show that cannabinoids (especially extracts with THC) can temporarily reduce IOP
- There is no solid evidence at the present time supporting beneficial disease modifying effects of these agents or clinical trials that demonstrate risk/benefit relationships
- There is also no solid evidence indicating cannabinoids are harmful with regard to the glaucomatous disease process
- Animal studies showing that CBD might increase IOP require carefully designed human studies to truly determine if CBD is problematic in humans
- It's clear that we need more research focused on how to optimize glaucoma treatment decision-making

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)

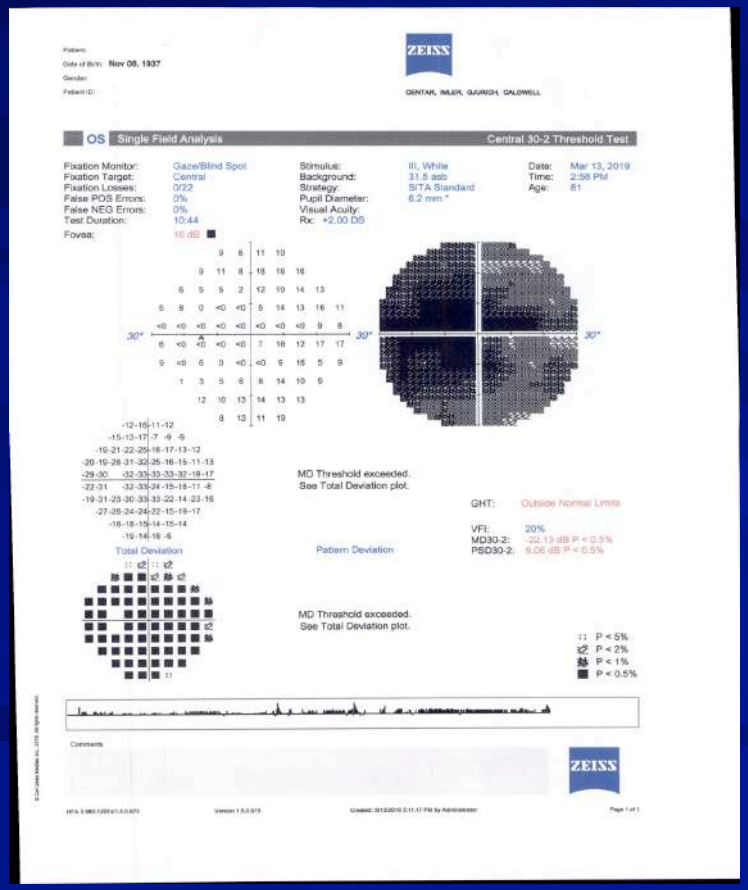
Ethambutol

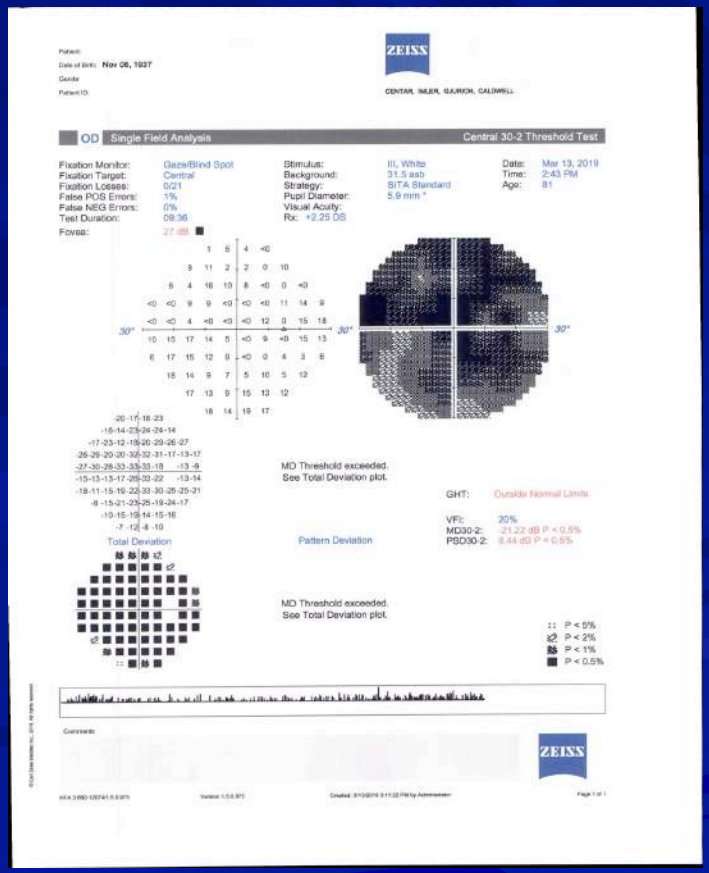
- Toxic optic neuropathy
- 2 cases in the past 12 months (2019)

81 year old woman

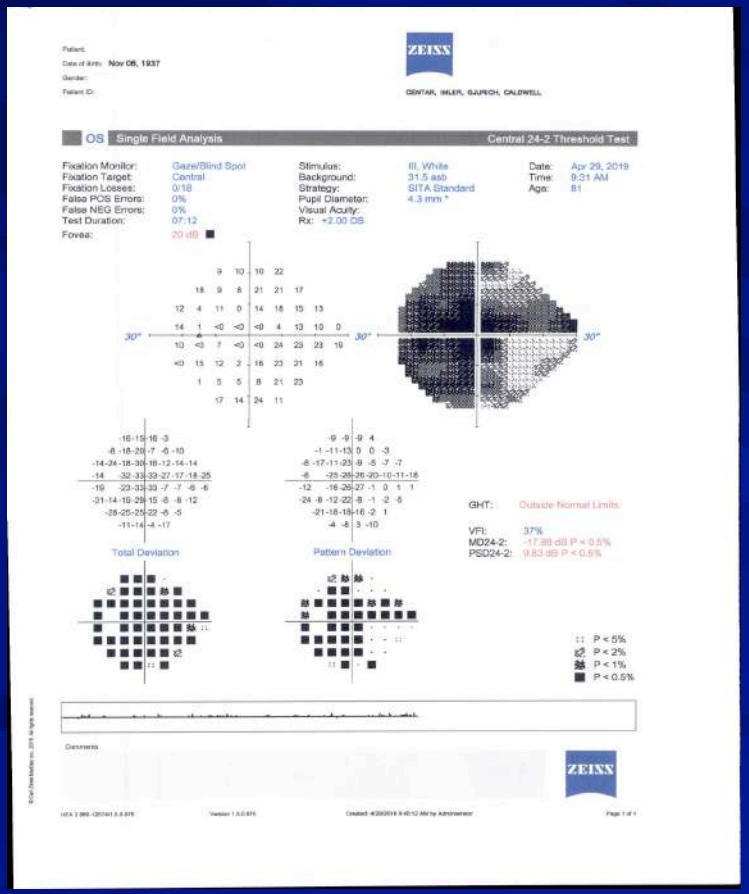
- Calls the office reporting decreased vision (3-13-19)
  - Was warned vision could decrease due her medications
  - Glaucoma patient
- Mycobacterium avium infection
- Ethambutol, rifampin, and azithromycin
  - Ethambutol started October 2017
- Glaucoma patient
  - Was on latanoprost and Rhopressa
 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

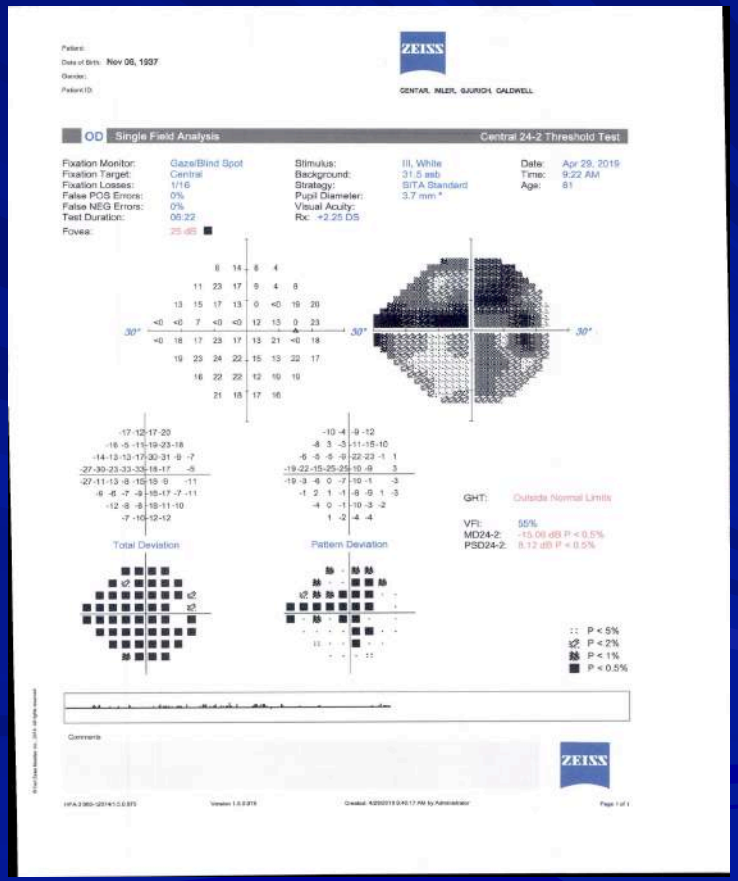
3/13/19 20/30, 20/100, 20/25



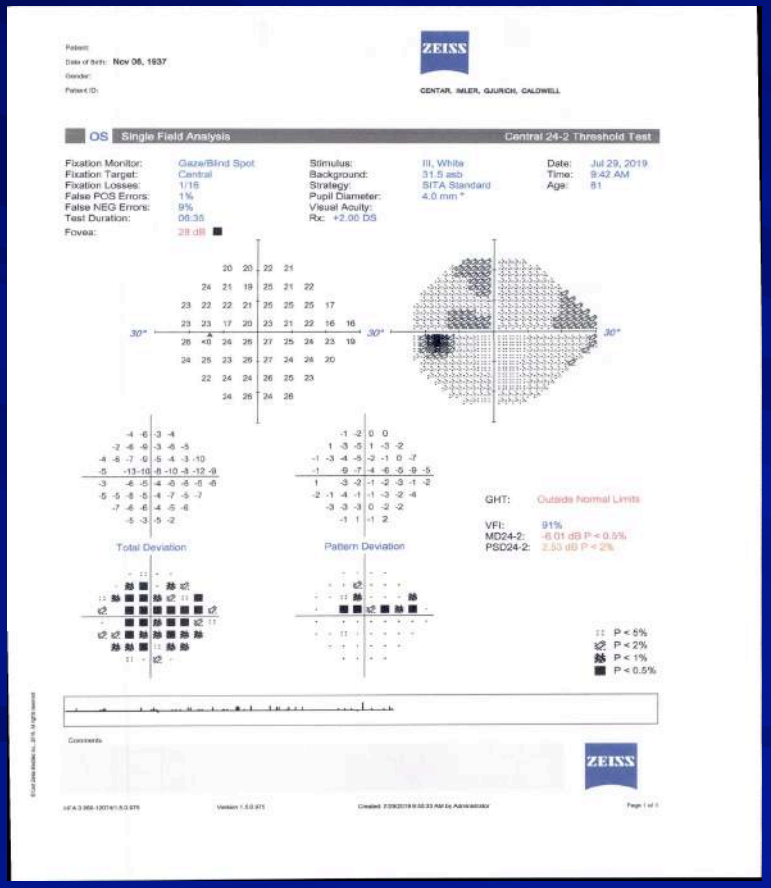


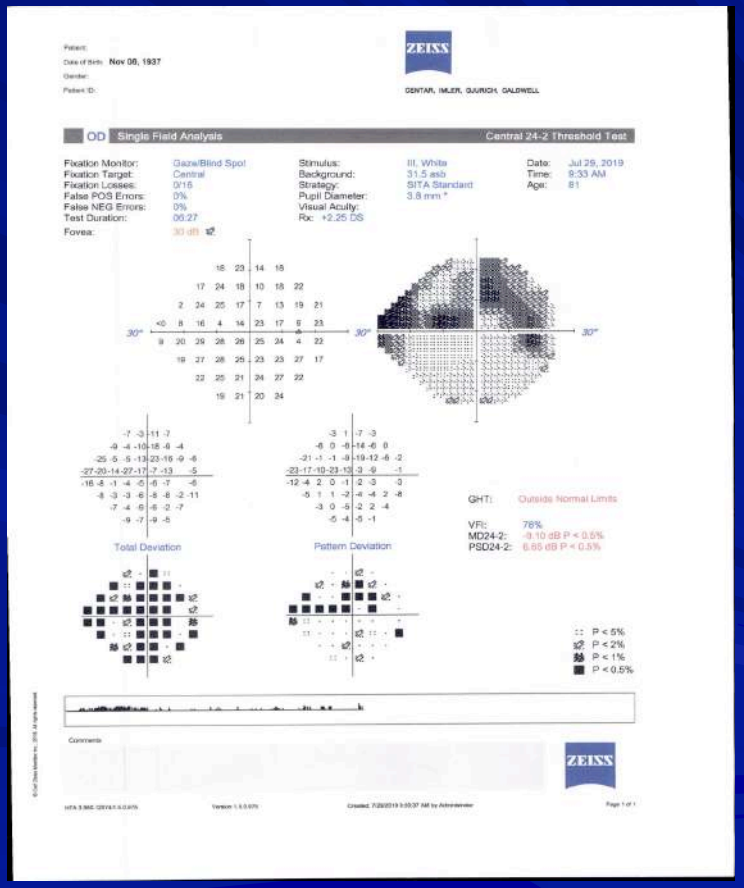
4/29/19 20/25, 20/50, 20/20



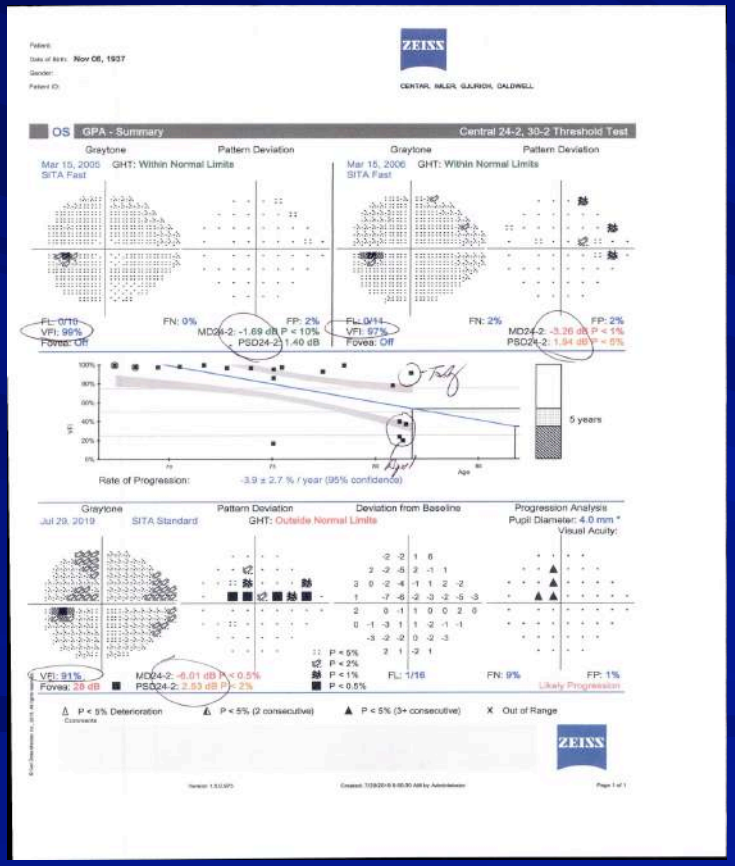


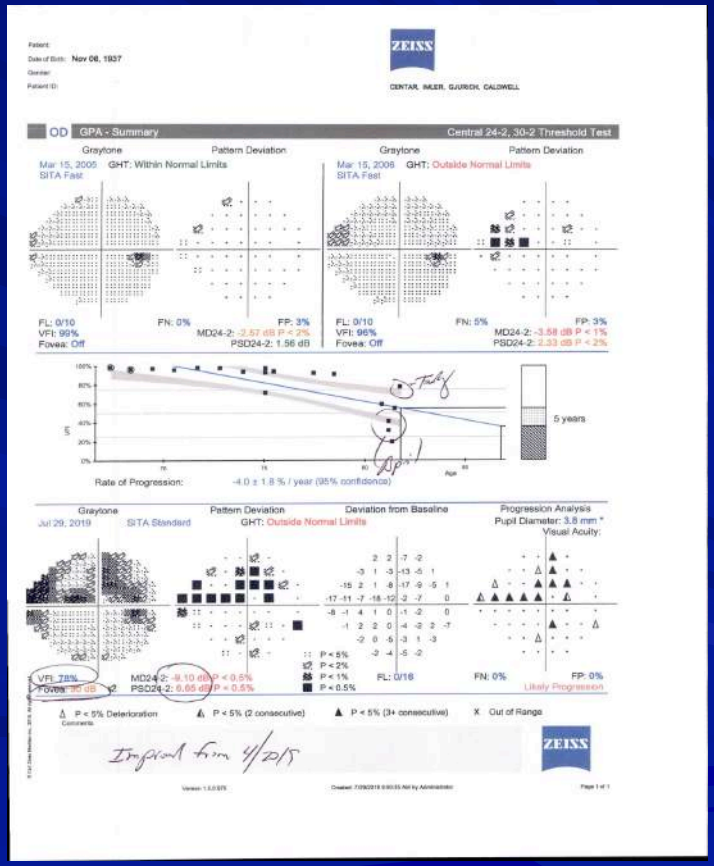
7/29/19 20/20, 20/25, 20/20





Progression





Osteoporosis Medications

- Bisphosphonates:
  - Fosamax™ (Alendronate)
  - Actonel™ (Risedronate)
    - Episcleritis
    - Uveitis
    - Iritis

- Typically, the benefit of using these agents outweigh the risks for ocular side effects
- Encourage patients to get regular ophthalmic exams and to report any acute changes!

COX-2 Specific Inhibitors

- Celebrex™ (celecoxib)
  - Cataracts
  - Glaucoma
  - Conjunctival hemorrhage
  - Vitreous floaters

- Hey Celebrex™, where did your brothers **Vioxx**™ and **Bextra**™ go?!?! Oh how we miss them…

Anticonvulsants

- Sabril™ (vigabatrin)
  - Uncommon agent used in infantile spasms and in refractory partial complex seizures
  - FDA mandated BLACK BOX WARNING:
    - Optic atrophy
    - Optic neuritis
    - Peripheral constriction of visual field
    - Decrease in visual acuity

Sabril™ (vigabatrin)

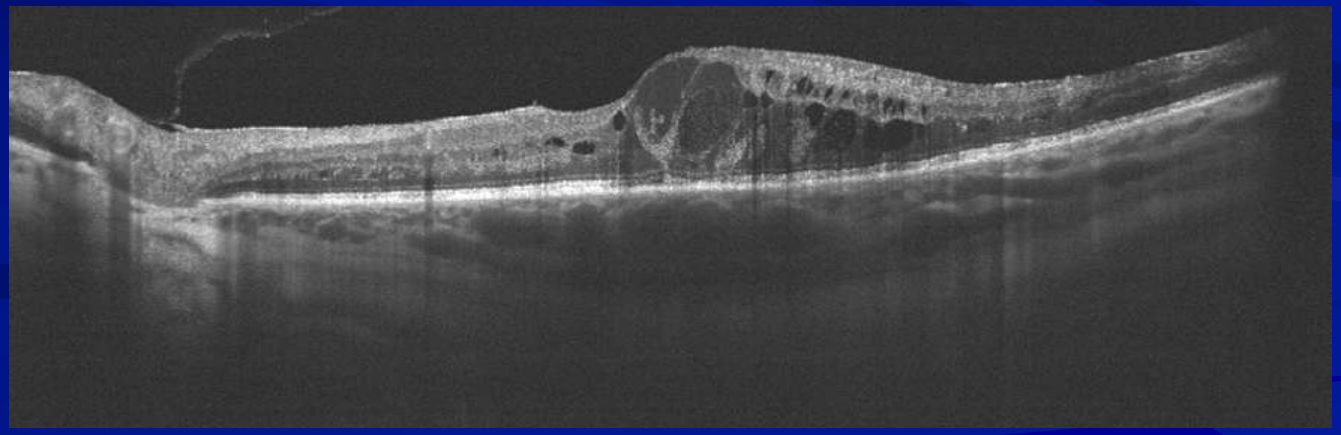
- Toxic Optic Neuropathy
- Selective, irreversible, inhibitor of GABA transaminase for refractory complex partial seizures and infantile spasms
- Clearly been shown to cause a dose-dependent, permanent peripheral field constriction.
- The earliest reports of toxicity were after 11 months of exposure
  - The vision loss is usually asymptomatic and spares the macula
  - Sub-clinical depression of macular function and color vision deficits have been reported
- Mechanism has not yet been fully demonstrated
  - Most likely involves toxicity to both retinal photoreceptors and ganglion cells
- Possibly induces a taurine deficiency that leads to toxicity
  - Taurine supplementation may prevent toxicity

Autoimmune Agents

- Treatment of Multiple Sclerosis
  - ★ Gilenya™ (fingolimod)
    - FDA-approved oral agent for the treatment of relapsing forms of multiple sclerosis (MS) in September 2010
    - Macular edema
      - FAME - Fingolimod-Associated Macular Edema

52-year-old woman

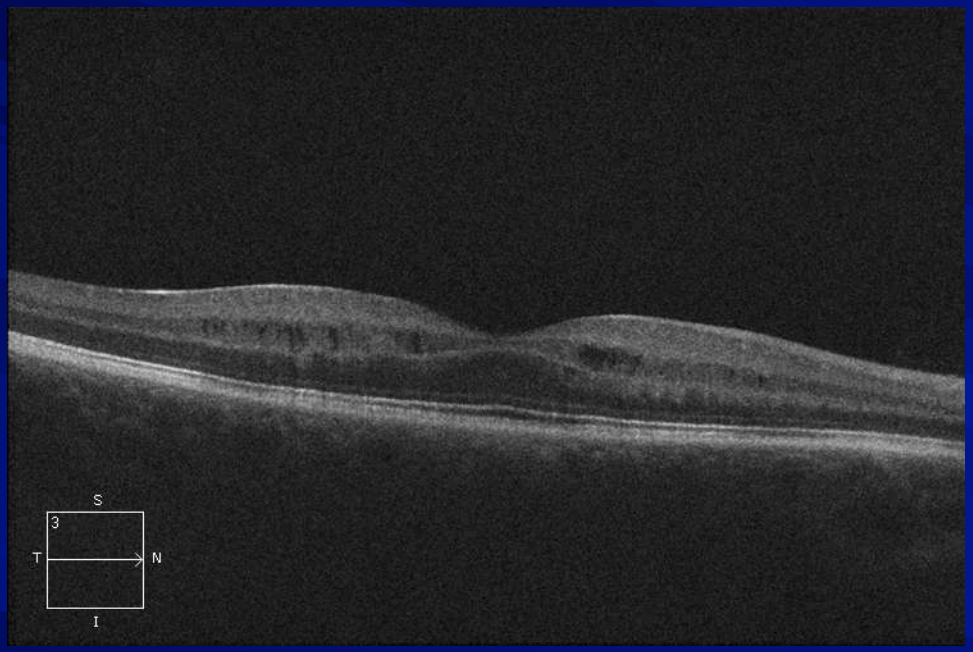
- History of MS was switched from Tysabri™(natalizumab) to Gilenya™ (fingolimod)
- Blurred vision in her left eye, BVA 20/40
  - Noticed blurred vision 7-8 weeks after starting Gilenya™

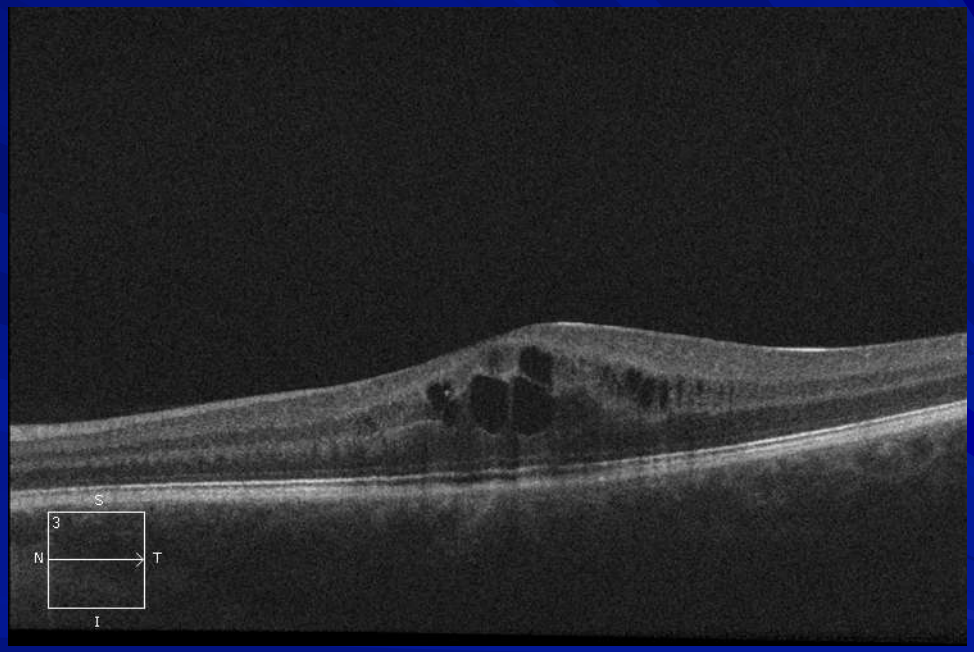


Gilenya™ (fingolimod) & FAME

- Prior to starting medication
  - Follow up in 3-6 months after medication started
- Be aware of FAME
- If FAME occurs
  - Stopping Gilenya typically will reverse edema
    - May need topical NSAID and/or steroid

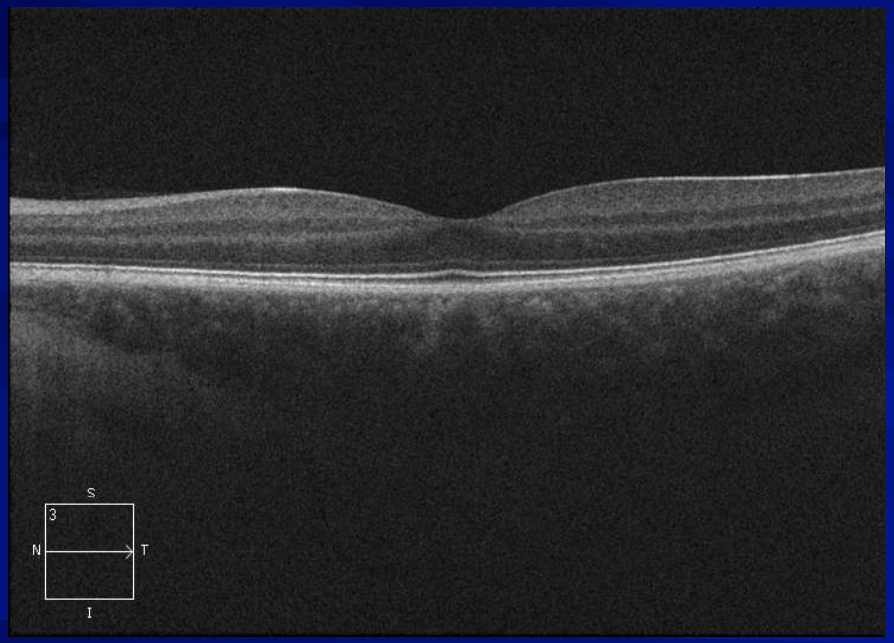
Another Gilenya™ (fingolimod) and FAME

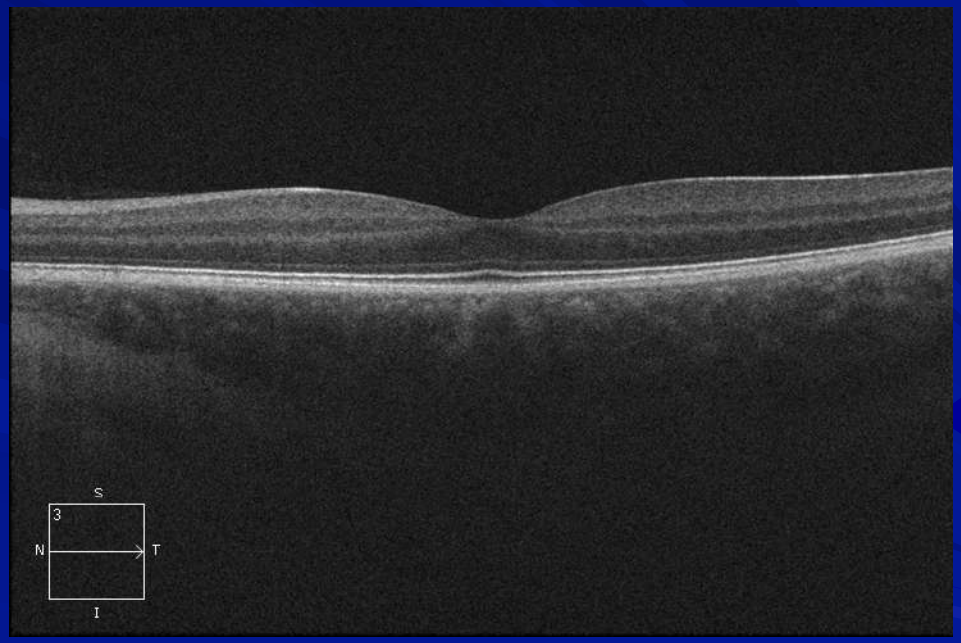




Courtesy of Joe Shovlin, OD, FAAO

After D/C Gilenya™ (fingolimod)

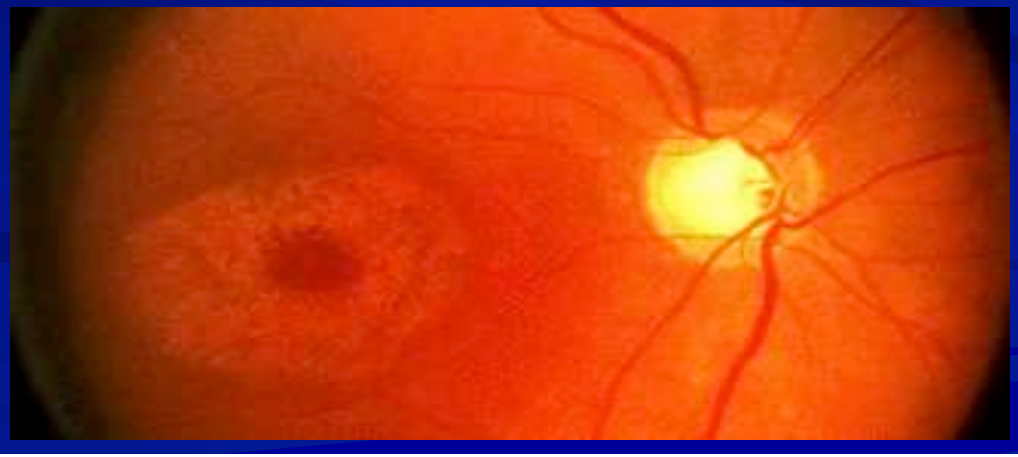




Courtesy of Joe Shovlin, OD, FAAO

Autoimmune Agents

- Treatment of rheumatologic conditions
  - ★ Rheumatoid arthritis, systemic lupus erythmatosis
- 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™)

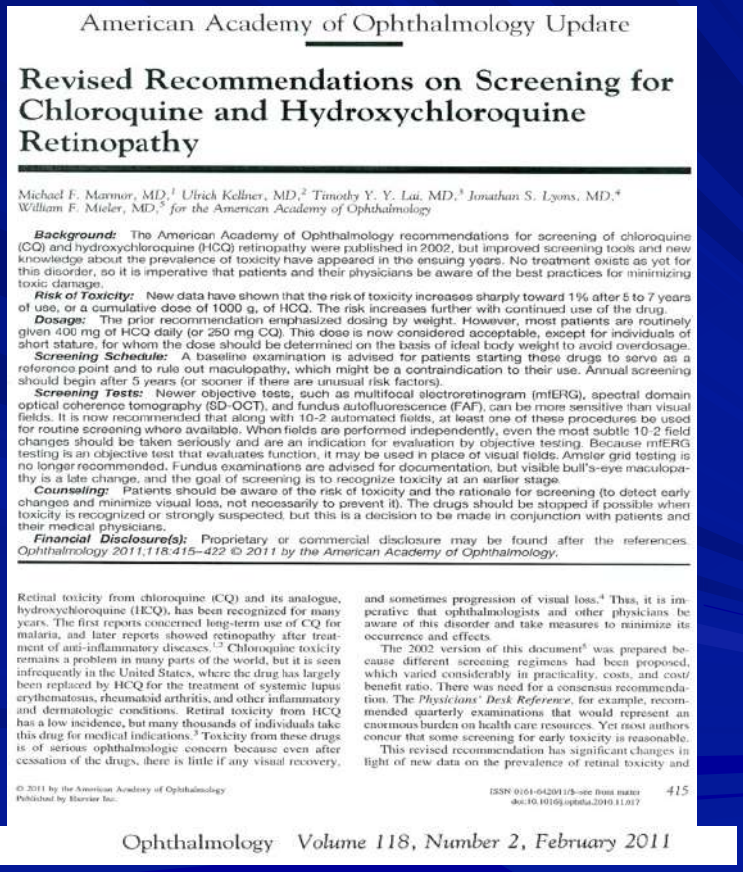
Plaquenil™

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] This, 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 document[5] 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

ISSN 0161-6420/11/$–see front matter
doi:10.1016/j.ophtha.2010.11.017

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

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. Melles, 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.*

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 2011[1] 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.

http://dx.doi.org/10.1016/j.ophtha.2016.01.058
ISSN 0161-6420/16

Revised
Again

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 $\leq$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 $\leq$2.3 mg/kg real weight.

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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*

PLAQUENIL ZONE

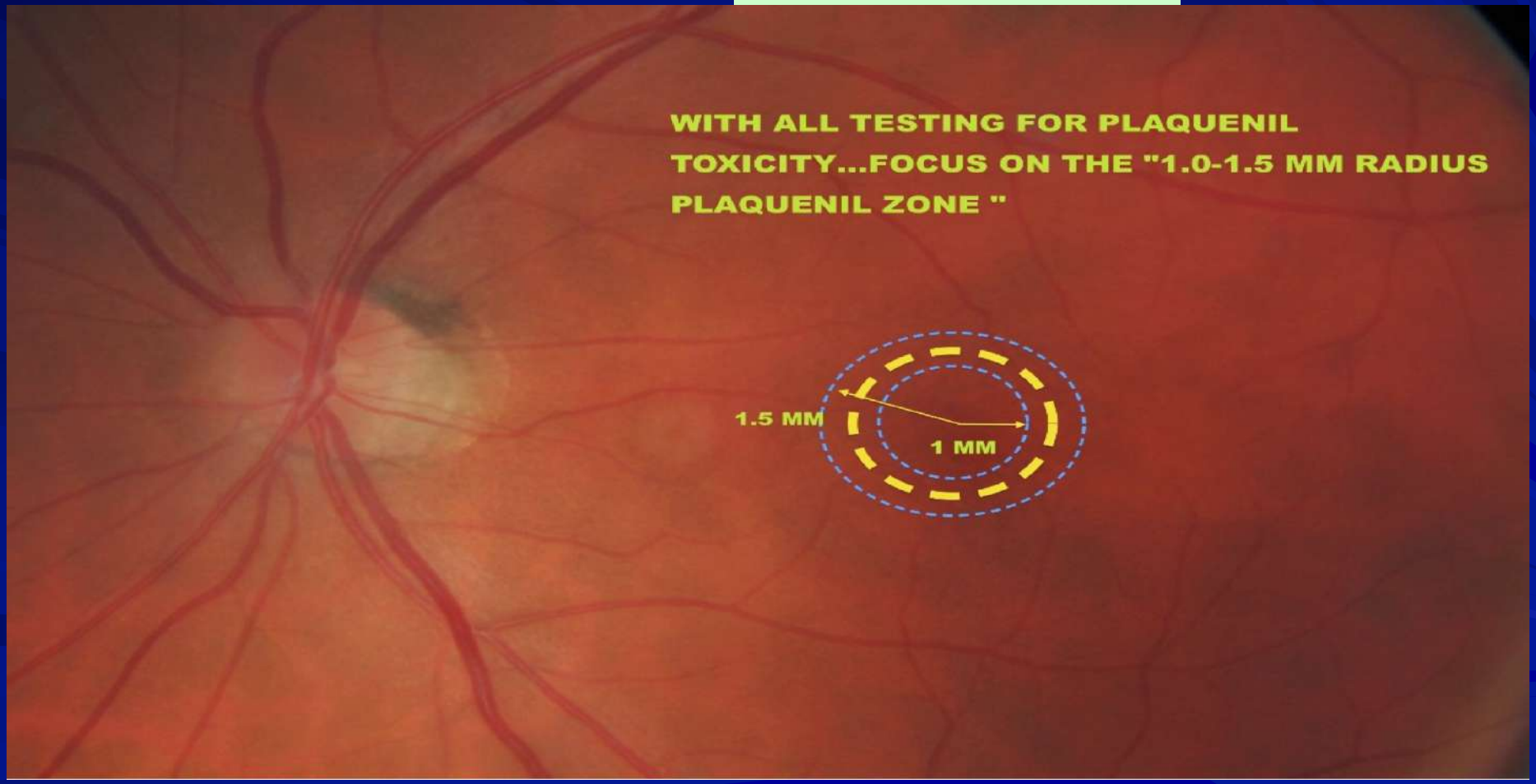
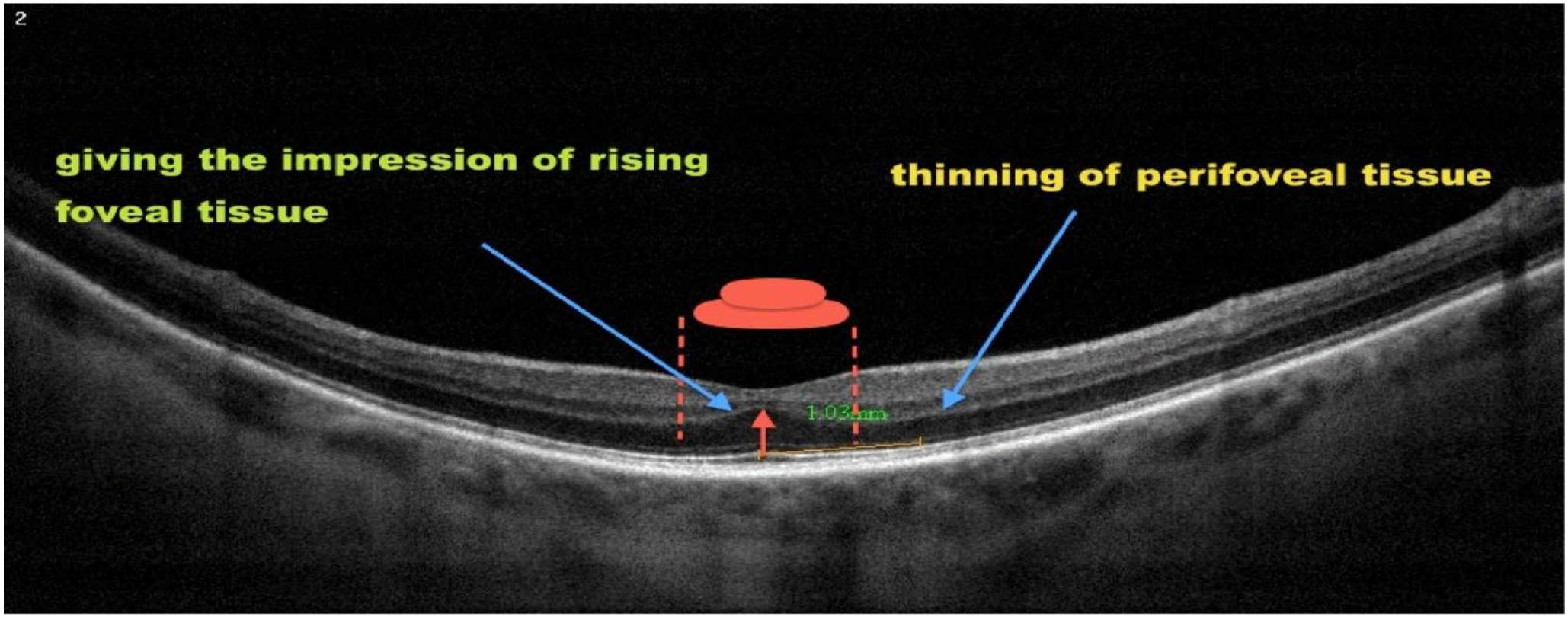
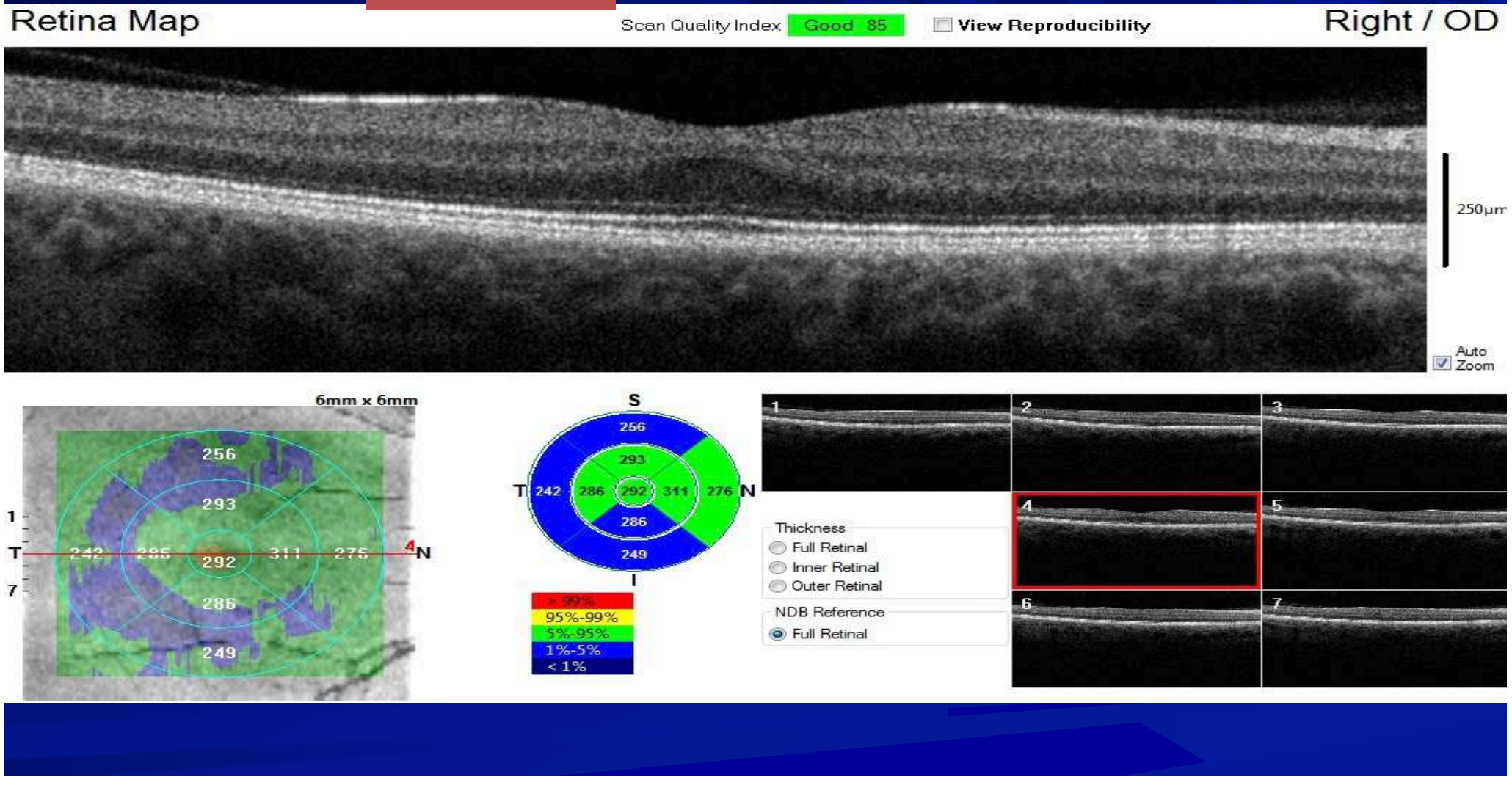


Figure 1 The flying saucer sign representing compromise of the perifoveal retinal tissue with maintenance of the foveal retinal tissue. From Chen E, Brown DM, Benz MS, et al. Spectral domain optical coherence tomography as an effective screening test for hydroxychloroquine retinopathy (the "flying saucer"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



AUGUST 2014


Retina Map
Scan Quality Index
Good 85
View Reproducibility
Right / OD
250µm
Auto Zoom
6mm x 6mm
256
293
1
T
242
286
292
311
276
4
N
7
286
249
S
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293
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242
286
292
311
276
N
286
249
I
> 99%
95%-99%
5%-95%
1%-5%
< 1%
Thickness
Full Retinal
Inner Retinal
Outer Retinal
NDB Reference
Full Retinal
1
2
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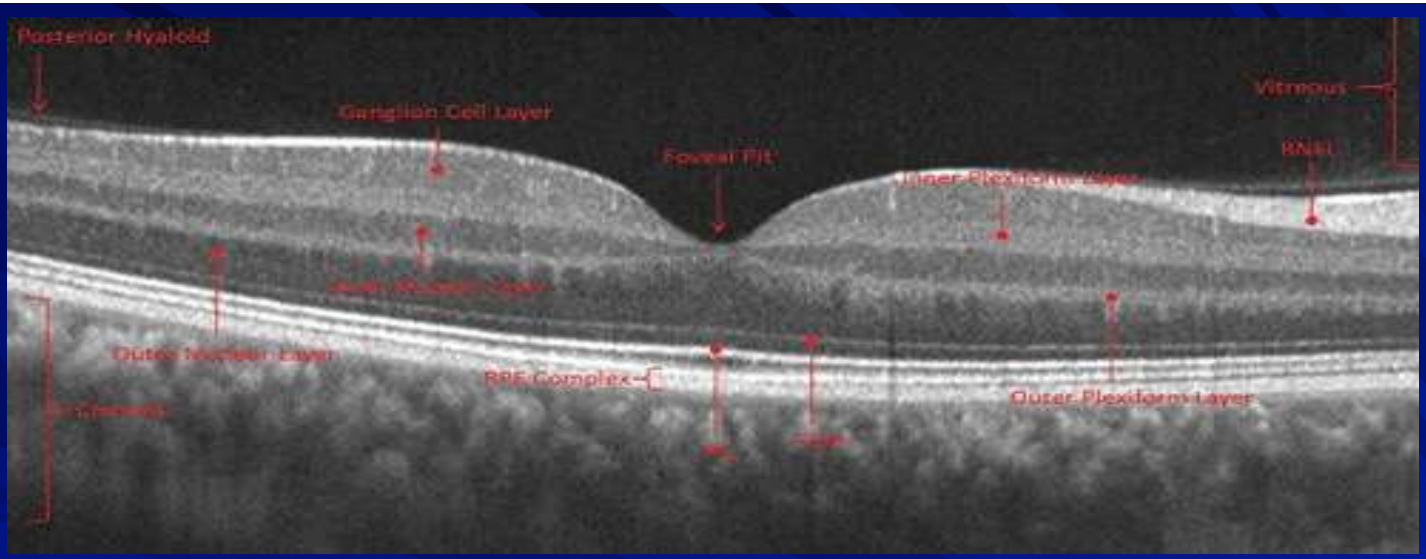
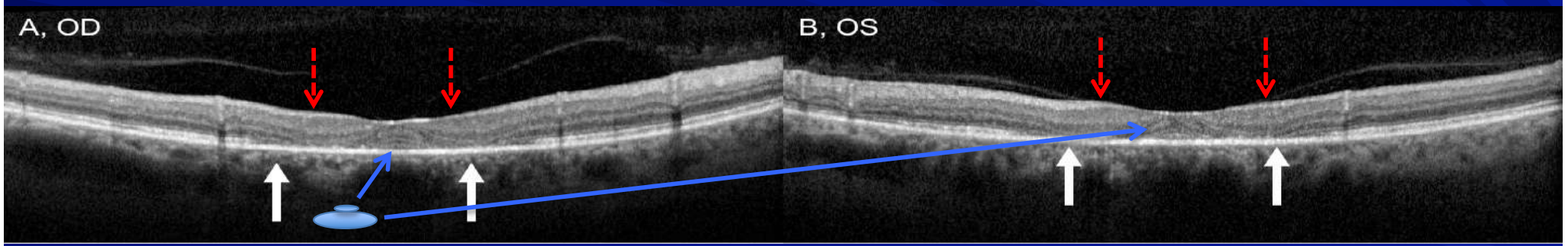
5
6
7



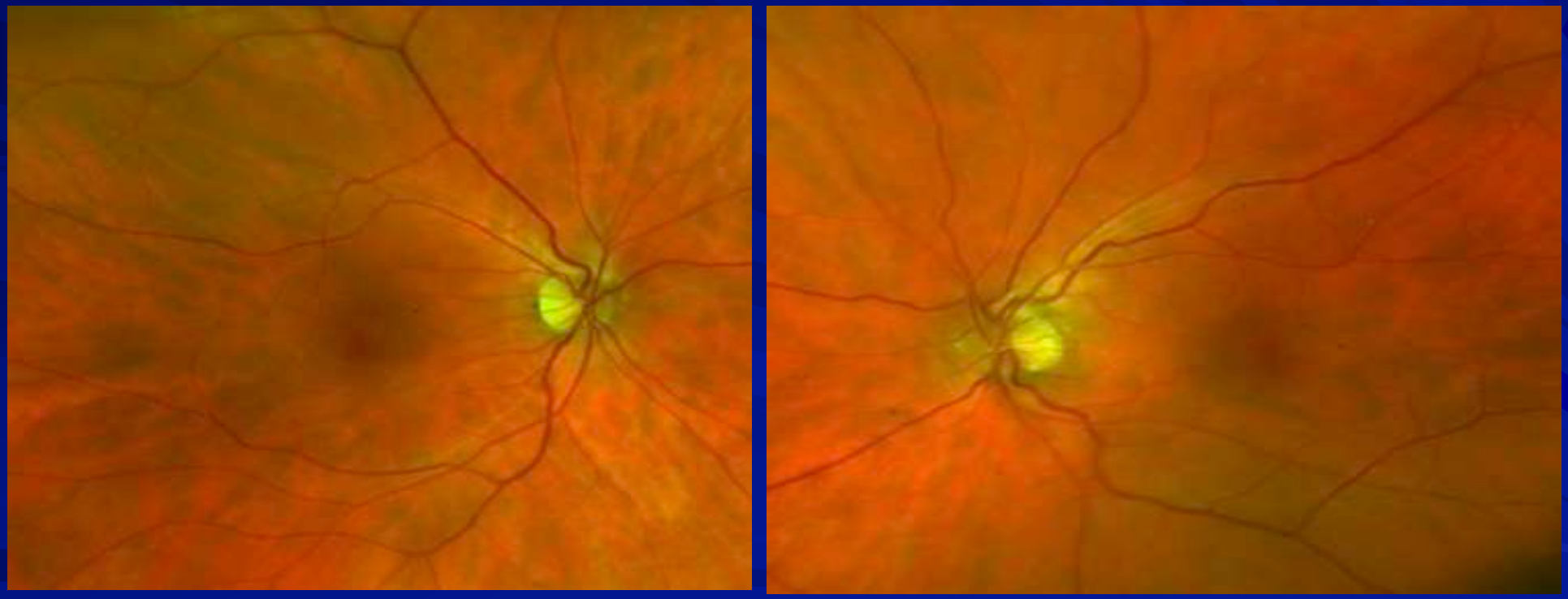


BILATERAL COMPROMISE OF THE PIL (WHITE ARROWS) AFTER COLLAPSE OF PERIFOVEAL RETINA (RED DASHED ARROWS) WITH FLYING SAUCER ATTACK (BLUE ARROWS)

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



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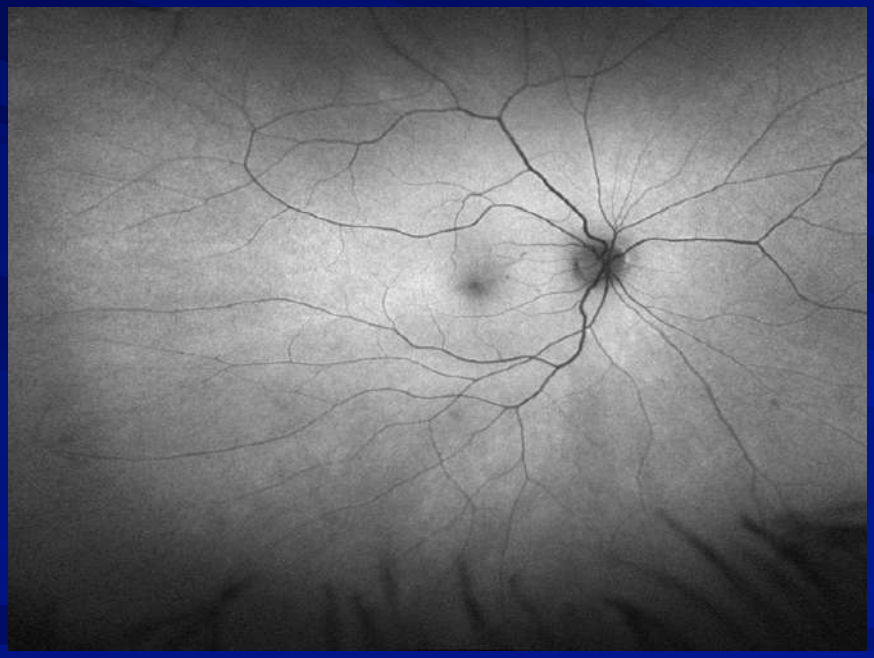
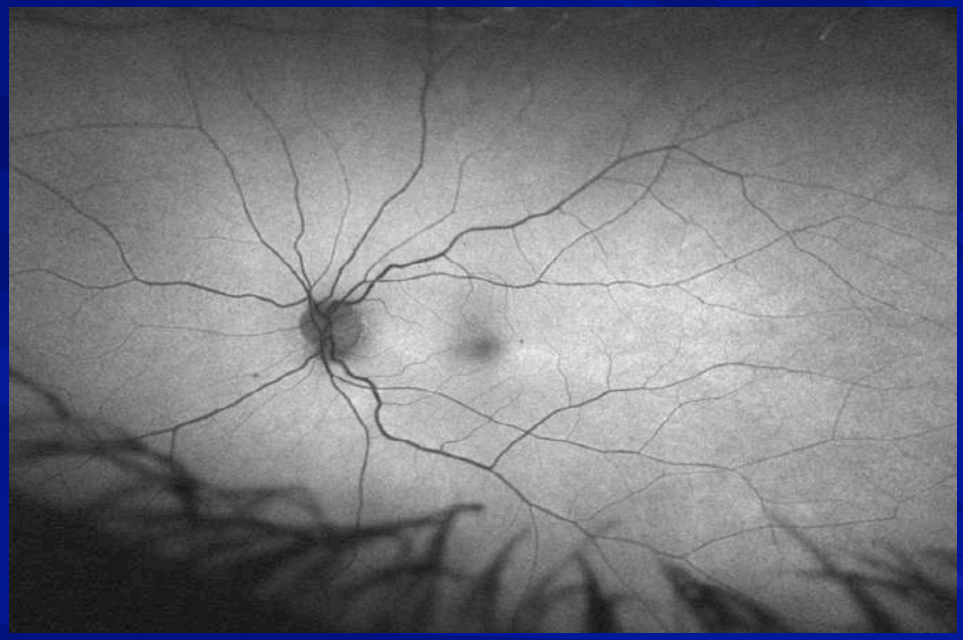




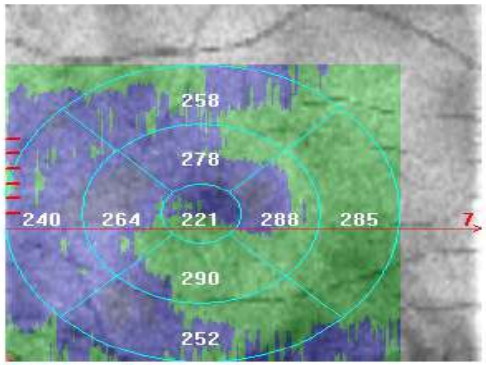
Retina Map Change Analysis

Right / OD

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

Scan Quality Index Good 66

6.00 x 6.00 Scan Size (mm)



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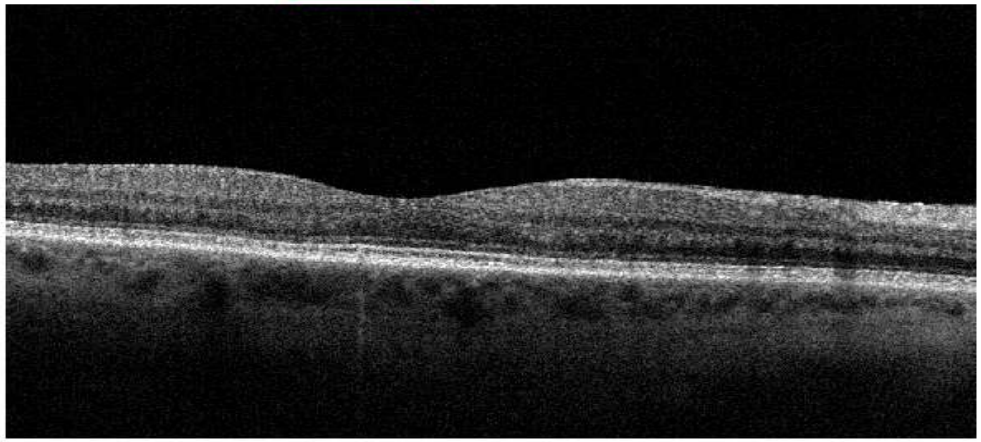
95%-99%
5%-95%
1%-5%
< 1%

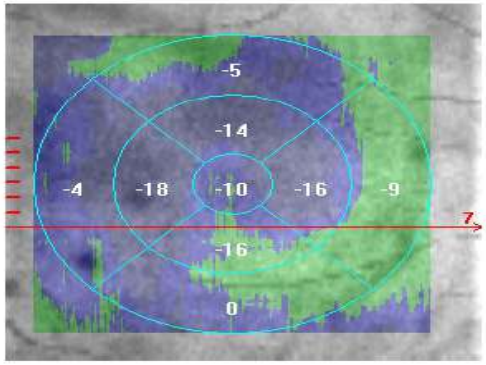
☑ Auto Zoom
☐ Show Original

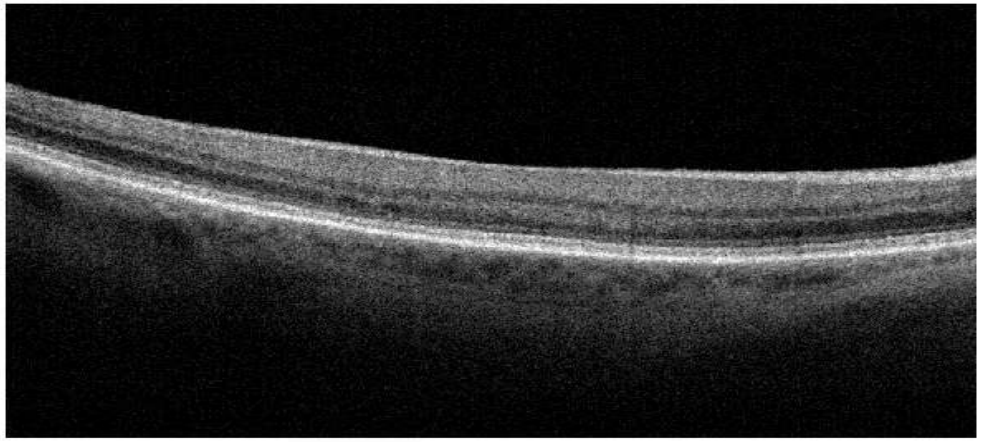


250µm

Thickness
○ Full Retinal ○ Inner Retinal ○ Outer Retinal

NDB Reference
◉ Full Retinal





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

Scan Quality Index Good 61

Print

OU Report

optovue

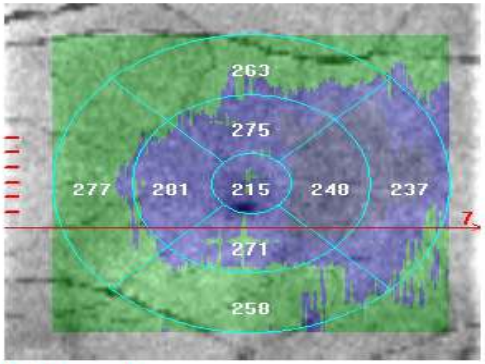
Retina Map Change Analysis

Left / OS

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

Scan Quality Index Good 77

6.00 x 6.00 Scan Size (mm)



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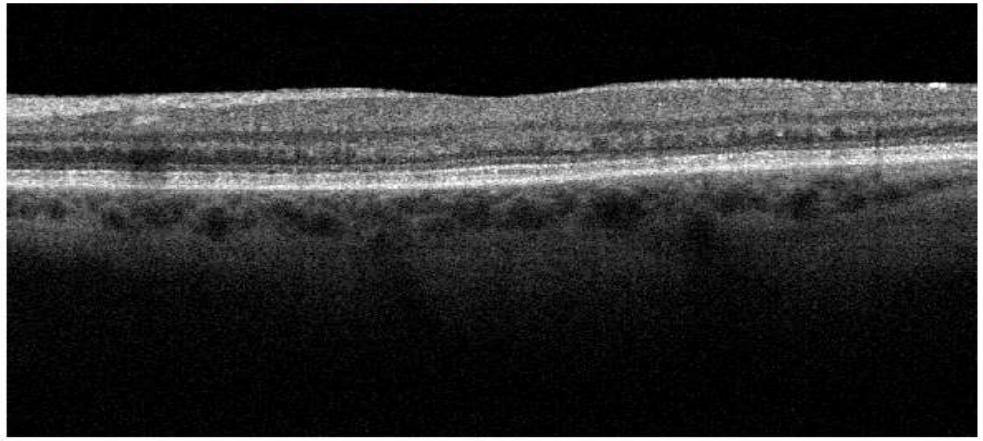
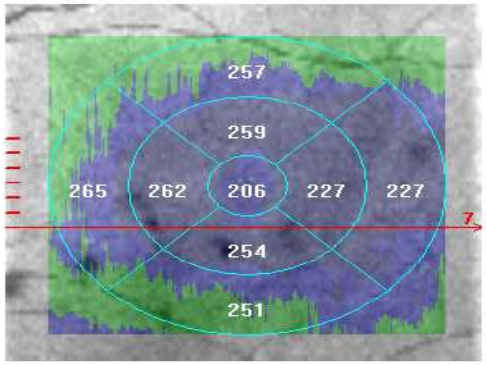
☑ Show Original

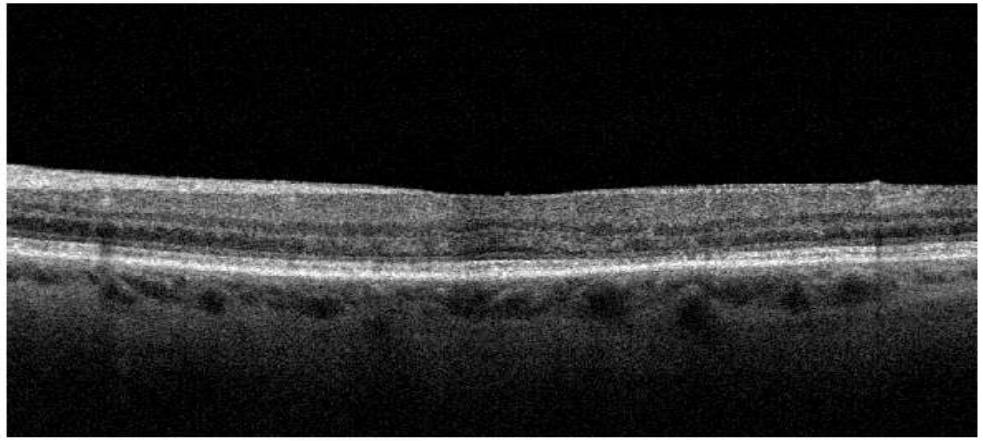


250µm

Thickness
○ Full Retinal ○ Inner Retinal ○ Outer Retinal

NDB Reference
◉ Full Retinal





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

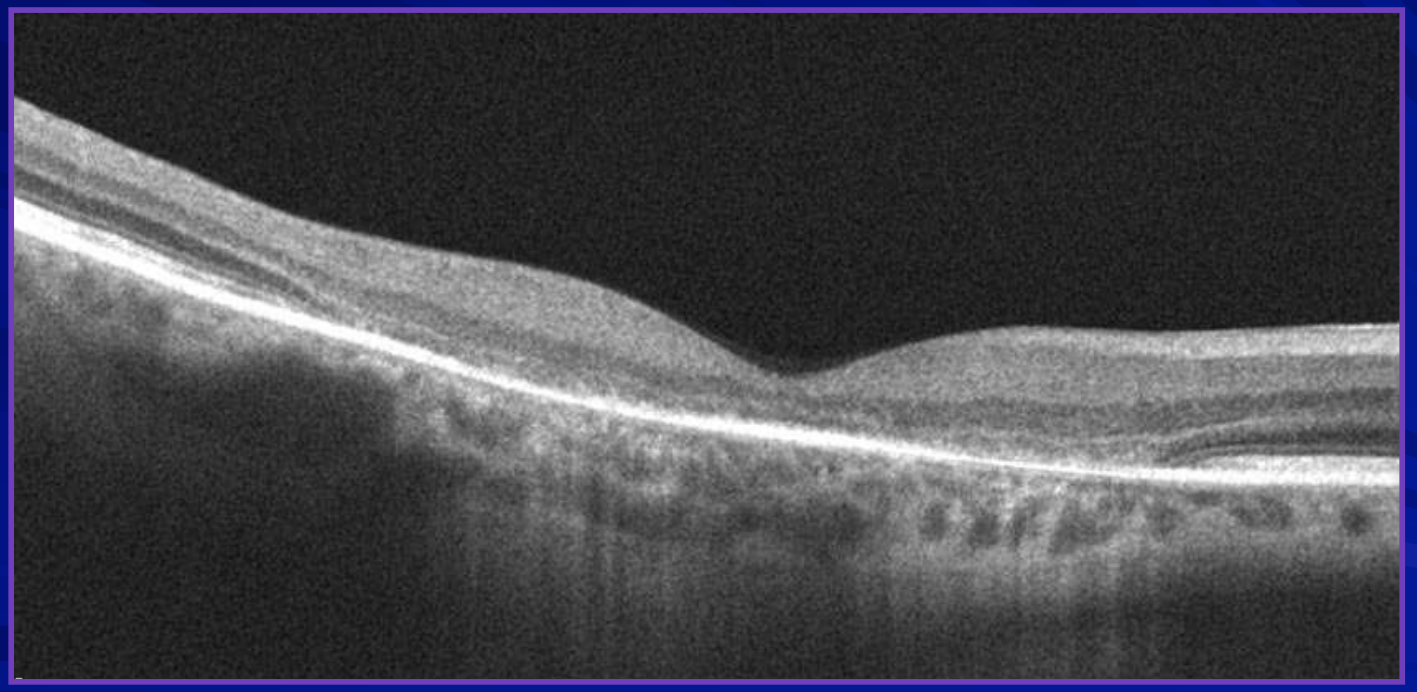
Scan Quality Index Good 65

Print

OU Report

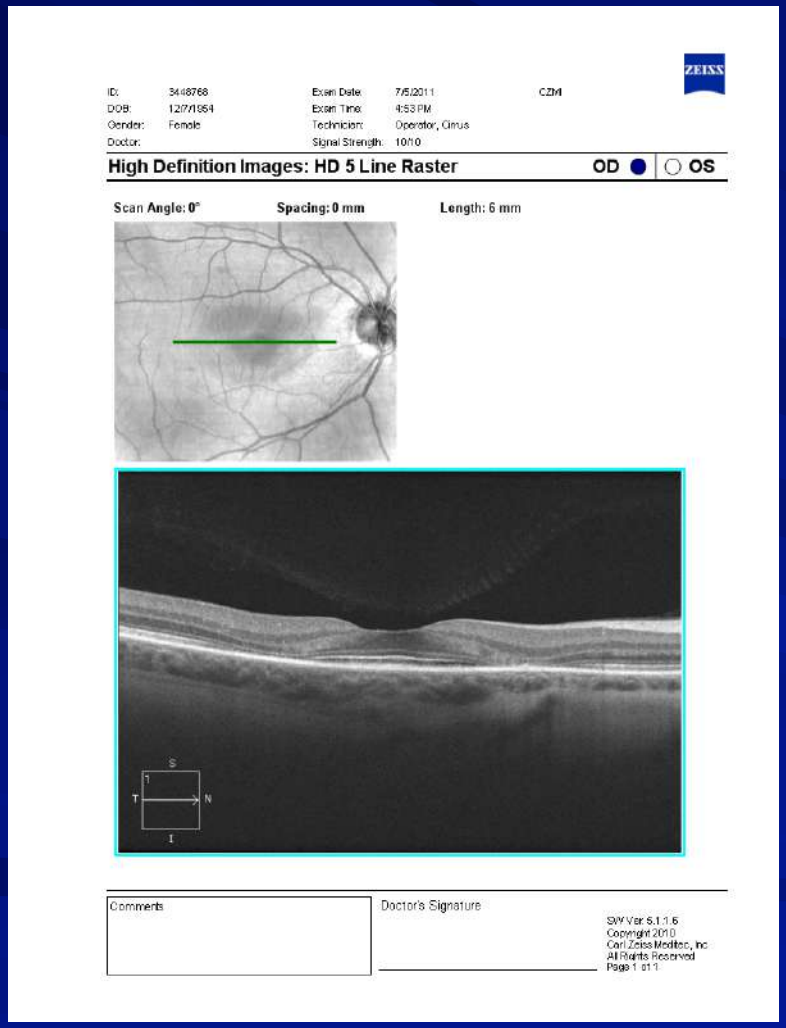
optovue

Plaquenil Toxicity

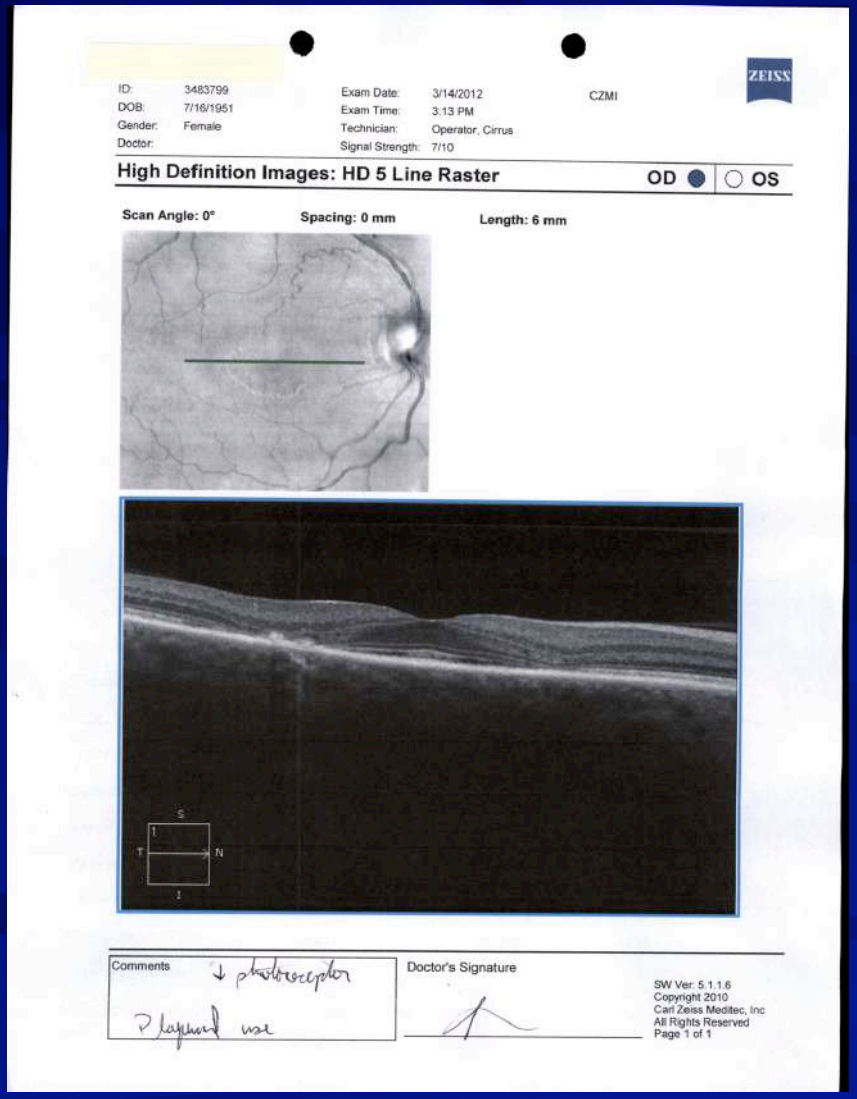


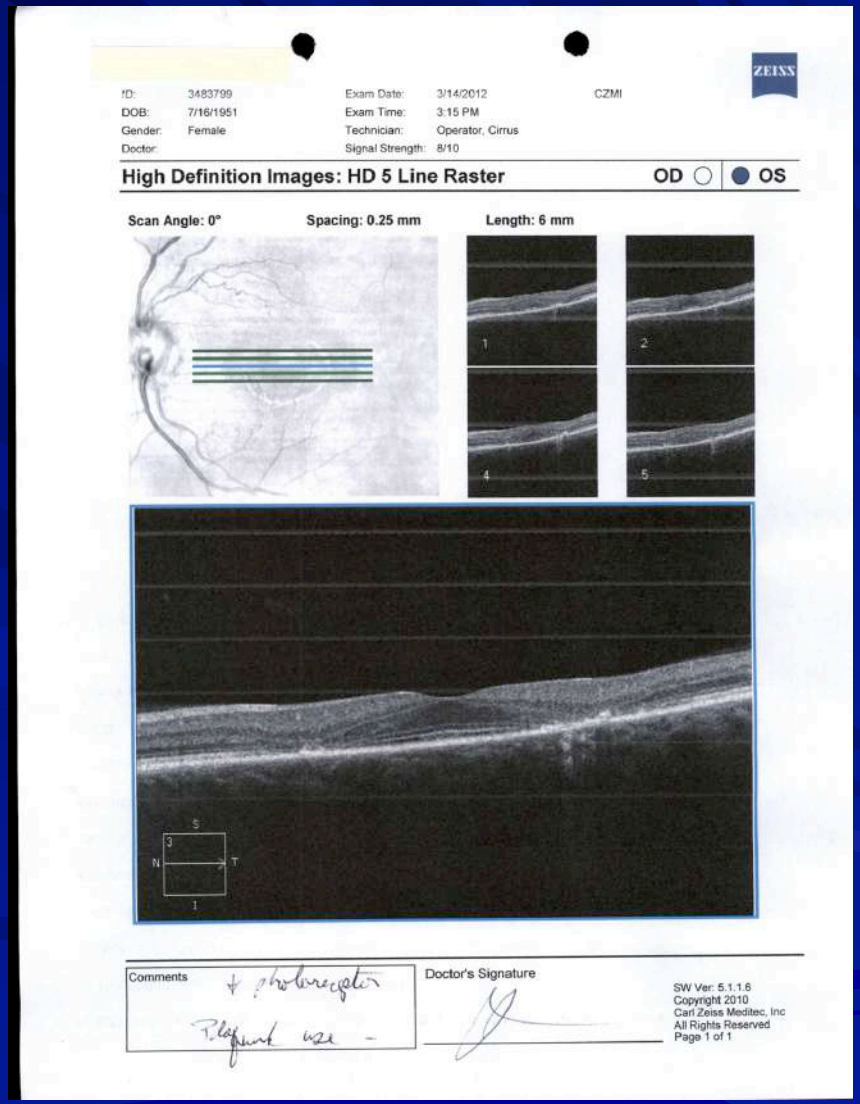
Courtesy of Joe Shovlin, OD, FAAO

Plaquenil Toxicity



Courtesy of Joe Shovlin, OD, FAAO





Courtesy of Joe Shovlin, OD, FAAO

SINGLE FIELD ANALYSIS

EYE: LEFT

NAME: [redacted] ID: 348379-9 DOB: 07-16-1951

10-2 THRESHOLD TEST

FIXATION MONITOR: GAZE/BLINDSPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 1/15
FALSE POS ERRORS: 0 %
FALSE NEG ERRORS: 5 %
TEST DURATION: 05:56

FOVEA: OFF

STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-FAST

PUPIL DIAMETER: 3.8 MM
VISUAL ACUITY:
RX: +4.75 DS DC X

DATE: 04-12-2012
TIME: 1149 PM
AGE: 60

TOTAL DEVIATION

PATTERN DEVIATION

MD -7.62 DB P (1%
PSD 8.88 DB P (1%

:: (5%
∅ (2%
% (1%

NORTHEASTERN EYE INSTITUTE
200 MIFFLIN AVENUE
SCRANTON, PA 18503
570-342-3145
570-344-1389 FAX

SINGLE FIELD ANALYSIS

EYE: RIGHT

NAME: [redacted] ID: 348379-9 DOB: 07-16-1951

CENTRAL 10-2 THRESHOLD TEST

FIXATION MONITOR: GAZE/BLINDSPOT
FIXATION TARGET: CENTRAL
FIXATION LOSSES: 1/14
FALSE POS ERRORS: 1 %
FALSE NEG ERRORS: 0 %
TEST DURATION: 04:55

FOVEA: OFF

STIMULUS: III, WHITE
BACKGROUND: 31.5 ASB
STRATEGY: SITA-FAST

PUPIL DIAMETER: 3.3 MM
VISUAL ACUITY:
RX: +5.00 DS DC X

DATE: 04-12-2012
TIME: 1142 PM
AGE: 60

TOTAL DEVIATION

PATTERN DEVIATION

MD -6.58 DB P (1%
PSD 8.78 DB P (1%

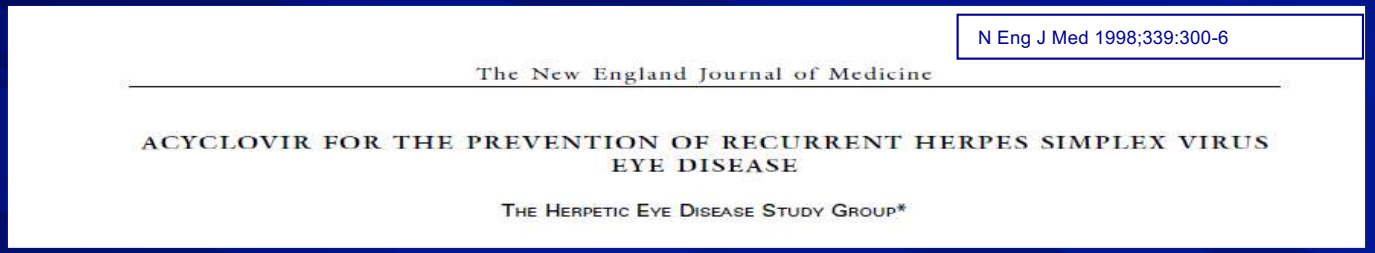
:: (5%
∅ (2%
% (1%

NORTHEASTERN EYE INSTITUTE
200 MIFFLIN AVENUE
SCRANTON, PA 18503
570-342-3145
570-344-1389 FAX

Antivirals

Beside the dosing frequencies…

- What is different about the oral antivirals?



N Eng J Med 1998;339:300-6

The New England Journal of Medicine

ACYCLOVIR FOR THE PREVENTION OF RECURRENT HERPES SIMPLEX VIRUS EYE DISEASE

THE HERPETIC EYE DISEASE STUDY GROUP*

- 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

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

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.

Zovirax® contains lactose

Presence or absence of lactose in generic acyclovir varies

Valtrex® and all generics are free of lactose

Generics available in the US contain lactose

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

Acyclovir vs. Valacyclovir vs. Famciclovir

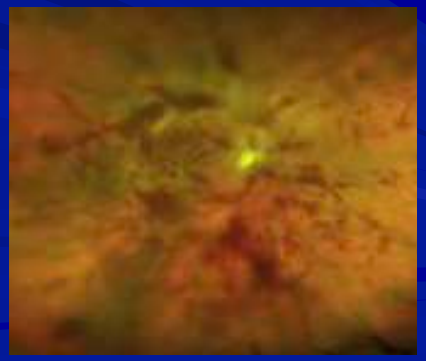
What is the difference?

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

Beovu (brolucizumab)

- Indication: injection is used for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD)
  - Offers a 3-month dosing schedule in the first year of treatment
- Warning issued by the American Society of Retinal Specialists about a series of intraocular inflammation events—some of which led to severe vision loss
- On April 8, 2020, Novartis announced its completion of the review, which included an assessment by an external, independent Safety Review Committee
- Complications: n=1098
  - Intraocular inflammation (IOI) - 4.6% (n=50)
  - IOI + retinal vasculitis – 3.3% (n=36)
  - IOI + retinal vasculitis –retinal (artery) vascular occlusion – 2.1% (n=23)
  - Vision loss of 15 letters or more - <1%



Optometric Education Consultants

Thank You!

Complications of Pharmaceuticals Every Optometrist Should Know!

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Sunday, June 27, 2021