Pharmacotherapy of Posterior Segment Disease

Joseph J. Pizzimenti, OD, FAAO
pizzimen@nova.edu

Sam Snead Quotes

"Keep close count of your nickels and dimes, stay away from whiskey, and never concede a putt."

"If a lot of people gripped a knife and fork the way they do a golf club, they’d starve to death."

"Thinking instead of acting is the number-one golf disease."

Financial Disclosure

- I have received honoraria from, participated in advisory boards and speaker panels for:
  - Alcon
  - Carl Zeiss Meditec
  - Reichert
  - VSP
  - Zeavision

- I have no proprietary interest in any product, and my affiliations have no influence on the content of this lecture.

Course Goals

- Rapid-fire clinical rounds
  - Vitreo-retinal cases
- Audience participation
- Emphasis on current and emerging treatments
- New knowledge from clinical studies and trials
  - Impact on clinical practice
Functional Anatomy of Posterior Segment

Clinical Landmark - Equator

Peripheral vs Central Retina

Approx 6 Disc Diameters
Exit Site of Vortex Ampulla

Peripheral vs Central Retina

"Mid-Periphery"

SD-OCT Healthy Macula

The Choriod

- Loose connective tissue
- Melanocytes
- Choriocapillaris
  - Fenestrated endothelium allows diffusion of proteins
  - High blood flow
  - Very little O-2 extracted, so high venous O-2
**Anatomic Anomaly #1**

- Cilioretinal artery
  - 10-30% have it
  - May spare central vision in CRAO
  - If occluded, central vision loss

---

**Metallic FB**

**Cilioretinal Artery in CRAO**

**Cilioretinal Artery Occlusion**
Cilioretinal Artery Occlusion

Venous System Anatomy
- Central Retinal Vein
  - Retinal veins join at disc to form CRV
  - Drains into superior ophthalmic v.

Anatomic Anomaly #2
- “Dual Trunk” anomaly
- 2 central retinal veins
- CV Dx. can lead to a special type of sup or inf hemispheric RVO
Identifying the Signs of Retinal Disease

- Signs of vascular disease
- Signs of degenerative disease
- Signs of other disease
  - Infectious
  - Inflammatory
  - Retina/Optic N.
  - Hereditary
  - Neoplastic
  - Trauma

Mystery Macula

- Subjective
  - 35 y/o WM
  - sudden, unilateral blur OD
  - no pain or trauma
  - “Type A”
- Objective
  - VA
    - OD 20/60
    - OS 20/20
  - Hyperopic shift

- DFE shows large, serous elevation
- Focal detachment of sensory retina
What other tests would you like to perform?

OCT

What is your assessment?
What is your plan?
Idiopathic Central Serous Chorioretinopathy (ICSC)

**Objective**
- Breakdown of outer blood-retina barrier
- FA shows classic “smoke-stack”
  - Pooling beneath RPE detachment
  - Dye ascends vertically, then laterally in SRS

**Differential Diagnosis**
- Tumor
- RPE detachment
- Steroid-induced CSC

---

**Retina Quiz**

- In ICSC, fluid leakage most likely occurs at the level of:
  a. nerve fiber layer
  b. inner retina
  c. outer retina
  d. choroid
Plan

- Observation
  - 60% regain 20/20 w/no intervention
  - monitor q4wks for 6 mon

- Focal Laser
  - if unresolved after 4-6 mon
  - if recurrent
  - Focal, direct treatment
  - Leak must be outside FAZ (500 um)

Outcome

- VA recovered to 20/25 at week 12
- Reduction of fluid, 20/40 VA at week 5

Photodynamic Therapy for CSC

- Serous detachment before PDT.
- Resolution of detachment with residual RPE mottling after PDT.
Treatments for CSC

- Thermal laser

- Photodynamic Therapy
  - Visudyne (Verteporfin)
  - A light-activated drug

Limitations of Laser

Photodynamic (Visudyne) Therapy: A 2-Step Process

Step 1: 10 Min Infusion

Step 2: 83 Sec Activation
A 38-year-old Caucasian male

Subjective
- migraine-like headaches and sudden-onset distortion OS
- symptoms began 5 days after lumbar epidural injection of methylprednisolone acetate 120 mg x 5 days
- to treat chronic lower back pain associated with spondylosis.
- no other diseases/drug therapy.

Objective
- Best-corrected VA was 20/20 OD and 20/60 OS.
- Amsler testing revealed a large, gray area of central visual distortion OS.
- OS VA improved to 20/25 within 4 weeks.
- One month later, the patient received another epidural steroid injection of methylprednisolone acetate 120 mg.
- Five days later, he experienced acute visual blurring in the OS, headache, retinal sequelae similar to those in the first episode.
- His visual acuity recovered within several weeks, and the condition resolved without treatment.

38 y/o WM: DFE
- "dome" of elevated retina involving the inferior aspect of the left macula.

38 y/o WM: FA
- Small spot of focal hyperfluorescence with early, transit, and late-stage features of CSC.
Conclusions

- Importance of a thorough medical history.
- Patients in whom CSC develops after epidural analgesia with steroids should be alerted to the possible relationship between CSC and this treatment.
- Clinicians should advise all patients with CSC to avoid systemic corticosteroids administered by any route, unless they have a compelling medical indication.

81 year old Caucasian female

CC: Decreased vision OU but OS getting much worse

Ocular History: + Dry AMD OU x 15 years, + Cataracts OU

Medical History: + Hypertension x 27 years (controlled with meds)

Allergies: + Sulfa drugs  
Meds: Ocuvite

VA: 20/100 OD  10/400 FB OS

EOMS: smooth/full  
TA: 12 mm Hg OU

Pupils: PERRLA – APO  
BP: 135/90 RAS

GF: Full periphery OU  
Central scotoma OU, confirmed w/Amsler

SLE: Unremarkable  
Vitreous: PVD OU
Fluorescein Angiography

Outcome:
- Diagnosis:
  - Geographic Atrophy (End-stage Dry AMD) OD
  - Choroidal Neovascularization (Wet AMD) OS
- FA ordered
- Avastin injections OS
- Subsequent PDT ("double therapy")
- 20/200 VA (OD) 20/200 (OS) at 1 year
- Low Vision Referral
- D/C Ocuvite; switch to BS MV w/L & Z
Soft Drusen

- Soft, confluent more inclined to lead to _______ AMD *

Stages of AMD

- Early AMD
- Intermediate AMD
- Advanced AMD
  - “wet”
  - “dry”

Retina Quiz

- The clinical feature of Wet AMD that distinguishes it from Dry is:
  a. Geographic atrophy of the RPE
  b. soft, confluent drusen
  c. vision 20/60 or worse
  d. Choroidal neovascular membrane (CNVM) formation

AMD Risk Factors

- Age
- Gender - F > M
- Smoking
- Iris Color - lighter iris
- Obesity
- CV Disease
- AMD Family History
- Poor nutrition
- Low Macular Pigment
- Dietary and Serum Levels - Complex analyses (most, but not all) show a relationship.
- MPOD- Most (but not all) studies have shown reduced MPOD in AMD (by multiple measurement techniques)
AREDS 2: Purpose

- To study effects of high supplemental doses of dietary xanthophylls (lutein and zeaxanthin) and omega-3 long-chain polyunsaturated fatty acids on development of advanced AMD.
- To study the effects of these supplements on cataract and moderate vision loss.
- To study the effects of eliminating beta-carotene from original AREDS formulation on development and progression of AMD.
- To study the effects of reducing zinc in the original AREDS formulation on the development and progression of AMD.
- To contribute data for validation of the photographic AMD scales developed from the Age-Related Eye Disease Study.

AREDS 2 Formulation

- Lutein at 10 mg/day
- Zeaxanthin at 2 mg/day
  - and/or omega-3 fatty acids at a total of 1 g/day
- Zinc at 40 mg/day

Is There a Strategy?

- USDA Food Triangle
- 5+ daily portions of fruits & veggies
  - at least 1 dark green, leafy veg (spinach, kale)
- Low fat, low cholesterol
- Antioxidant for “nutritionally-challenged”
- Address Cardiovascular Disease, exercise
- Avoid smoking, UV
Retina Quiz

Approximately what percentage of dry (non-exudative) AMD eyes progress to wet (exudative) AMD?

- a. 37 %
- b. 50 %
- c. 2 %
- d. 15-20 %

Clinical Features of Exudative (Wet) AMD

Clinical Features of Exudative (Wet) AMD

Available technologies for early detection and monitoring of AMD

- Non-invasive Methods
- Macular Pigment Optical Density – MPOD
- Preferential Hyperacuity Perimetry – PHP
- Optical Coherence Tomography – OCT
Optical Coherence Tomography

Subfoveal CNVM w/ ret thick, serous RD

TD-OCT

Cystic change in Wet AMD

SD-OCT

Wet AMD: Earlier Detection, Better Treatments

Management of Exudative AMD

- UV/blue WL protection
- Home Amsler
- Antioxidants/Nutrition/Diet/
- Smoking/Exercise
- FA - Stat I (ICG - as indicated)
- Retinal Consult and Treatment
  - Laser Photocoagulation
  - Photodynamic Therapy
  - Anti-angiogenic Therapy
  - Surgical or Other Medical Intervention
- Low Vision Consult
Combination Treatments

- Anti-VEGF agents
- Steroids
- PDT

Targeting Vascular Endothelial Growth Factor (VEGF)

- Macugen
- Lucentis
- Avastin

Antiangiogenic Drugs: VEGF Inhibitors

- Pegaptanib sodium-Macugen (Pfizer/Eyetech)
  - FDA Approved
  - Aptamer (decoy): inhibits protein activity
- Ranibizumab-Lucentis (Genentech) $2,000.00
  - FDA Approved
  - Antibody-based
  - Compared favorably to PDT in ANCHOR study
- Bevacizumab-Avastin (Genentech) $40.00
  - Off label
  - Anti-neoplastic
  - Intravitreal injection
  - 1 injection/mon x 3 mon
Treatments for Wet AMD

Intravitreal Injection

James C. Folk, MD
University of Iowa

Wet AMD
VEGF Inhibition for Wet AMD

Pre and Post Avastin Treatment

VA 55 L

VA 78 L

VEGF Blockade Reduces Retinal Edema, Not CNV Lesion Size
Combination Treatments

- Anti-VEGF agents
- Steroids
- PDT

Which therapy(ies) is/are “off-label” for Wet AMD?

a. Argon Laser Photocoagulation
b. Visudyne Photodynamic Therapy
c. Intravitreal Ranibizumab (Lucentis)
d. Intravitreal Bevacizumab (Avastin)
e. Intravitreal Triamcinolone (Kenalog)

Wet AMD Treatments on the Horizon

VEGF Inhibitors

- Squalamine lactate- *Envizon* (Genera): Phase II
  - Isolated from dogfish shark tissue
  - Originally developed for oncology
  - Aminosterol
    - Inhibits plasma membrane ion channels
    - Blocks proliferation of endothelial cells
  - Administered Intravenously
    - Weekly x 4 wks
  - Small sample showed improved or stabilized VA
  - Low systemic toxicity
Squalamine lactate- **Envizon** (Genaera)

Squalamine works **INSIDE** endothelial cells to block multiple intracellular pathways generated by the binding of VEGF and PDGF to receptors.

**VEGF Inhibitor not yet approved**

- **VEGF-Trap** (Regeneron)
  - Intravitreal injection completed Phase II
  - No adverse effects
  - Now entering Phase III
  - Binds tightly to VEGF receptors
  - Rapid decrease in foveal thickening, improved VA

**Case From NSU Macula Clinic**

- 65 yo BM
- Healthy, recent physical
  - (-) DM, HTN
- CC: gradual central blur OS x 1 wk
- VA: OS 20/400

Acknowledgement: Dr. Sherrol Reynolds
What is your assessment?

What is your plan?

What is your assessment?

Idiopathic Juxtafoveal Telangectaisia

What is your plan?
Fluorescein angiograms

Idiopathic Juxtafoveolar Retinal Telangiectasia (IJRT)

- A condition characterized by exudation or diffusion abnormalities from ectatic (dilated and tortuous) blood vessels and incompetent retinal capillaries in the juxtafoveolar region.

S/P Intravitreal Kenalog
VA 20/60-20/80

Describe That Fundus!
Questions and Comments?

74 year old WM: Subjective
- **CC**: Blurred "central" vision (OD) @ distance and near
  - Onset gradual, over 3-4 days
  - Last visit 3 weeks prior showed 20/25 VA OD
- **Ocular History**: 7 weeks s/p uneventful cataract surgery w/ IOL OD
- **Medical History**: + HTN x 12 years,
  + Hypercholesterolemia (both under control w/meds)
- **Family Ocular History**: + AMD (mother)
- **Allergies**: None
- **Topical Meds**: artificial tears

Exam Findings: Objective
- **VA**: c Rx OD 20/70 PHTN OS 20/30 PHTN
- **Pupils**: (-)APD, PERRLA
- **EOMS**: Smooth / Full
- **SLE**: Well-centered IOL OD, 1+ CC OS
- **IOP**: 12 mm Hg OD, 14 mmHg OS
- **CF**: Full OU (periphery) Central blur OD Amsler +
- **Vitreous**: Clear OU

Fundus Evaluation
- DFE shows macular detail obscuration
- "Honeycomb" lesion w/cystic spaces
- Macular elevation
Are there any other tests you would perform?

Optical Coherence Tomography

Additional Testing
- FA demonstrates typical p________ appearance
- No scanning lasers at the time

What is your assessment?
Irvine-Gass Syndrome

Post-operative Cystoid Macular Edema (CME)

Hypothesis of Mechanism

Operative Irritation/Inflammation
Aging
Systemic Vasculopathy
Glaucoma

Prostaglandins in Aqueous & Vitreous

Breakdown of the Blood/Aqueous Barrier & Blood/Retina Barrier

Cystoid Macular Edema

What is your plan?

Actual Treatment and Outcome

- Ketorolac (Acular) 0.5%
  - 1 gt qid x 8 weeks
- Minimal improvement in VA, fundus
- Patient referred back to cataract surgeon
  - sub-Tenon’s steroid injection
- VA eventually improved to 20/30
Irvine-Gass Syndrome (CME)

- Most frequent cause of visual decline after uncomplicated cataract sx.
- Late onset (4 to 6 weeks post-operatively)¹
- Occurs in 12% of low-risk cataract cases*²
- Due to p____________-mediated breach of blood-retinal barrier³


Risk Factors for CME

- Pre-existing ocular inflammation
- Epi-retinal or vitreo-retinal interface
- ________ retinopathy
- Ocular vascular or cardiovascular disease
- Topical prostaglandin use
- History of r________ p__________

Treatment of CME

- Topical NSAID x 3-4 mon
- Topical steroid
- Topical NSAID + topical steroid
- YAG laser
  - lysis of postoperative vitreous strands present in the wound or pupil (limited success)

Sub-Tenon's Kenalog injection
Intra-vitreal Kenalog injection
Intra-vitreal Anti-VEGF drugs
  - Decreases vascular permeability
Surgical therapy
  - Pars plana vitrectomy (PPV)
Reduction of Inflammation

- NSAIDs work synergistically with steroid therapy to minimize inflammation following ocular surgery.
- NSAIDs primarily act on COX1 and COX2.
- Steroids primarily act on phospholipase A2.
- Inhibit the release of arachidonic acid.

Mechanism of Action

[Diagram showing the mechanism of action of NSAIDs and steroids on phospholipids, arachidonic acid, lipoygenases, and prostaglandins.]

Review of Common NSAIDs

- Diclofenac 0.1% and Ketorolac 0.5% shown to be equally effective in:
  - Treating post-operative CME
  - Treating post-operative inflammation

Adverse Events Associated with Conventional NSAID Therapy

- Mild/Moderate corneal side effects:
  - Burning and irritation
  - Superficial punctate keratitis
  - Delayed wound healing
- Severe corneal issues:
  - Thinning
  - Perforation due to melts

References:
New NSAID

- **Xibrom™** (ISTA Pharm.)
  - Claims enhanced ocular penetration
  - Unique bid dosing

---

Appropriate use of NSAIDs in prevention of CME

**Recommended NSAID Dosing**

- **At-Risk Patients**
  - Preoperative: 1 week
  - Postoperative: 4 weeks to several months

- **Not At-Risk Patients**
  - Preoperative: 1-2 Days
  - Postoperative: 4 weeks

---

That was then…

- In 1998, the older conventional NSAIDs did not work on our CME patient.

---

A Novel Class of Non-Steroidal Anti-Inflammatory Therapy
Nepafenac Ophthalmic Suspension 0.1% (NEVANAC™)

**Indication:**
- Treatment of pain and inflammation following cataract surgery

**Dosing:**
- One drop TID one day pre-op, DOS, 14 days post-op

**Formulation:**
- First and only ophthalmic non-steroidal ___-_____
- Preservative: 0.005% BAK
- pH: 7.4 (physiologic)

**Prodrug Structure: Metabolic Conversion**
- Nepafenac is converted to amfenac, a COX inhibitor, by intraocular hydrolases
  - Amfenac exhibits potent anti-inflammatory activity with greatly reduced toxicity

**Optimizes Penetration**
- Upon dosing, nepafenac rapidly penetrates the intraocular tissues

**Target-Specific Efficacy**
- Nepafenac is converted to amfenac for optimal efficacy
  - Cornea
  - Iris/ CB
  - Retina/Choroid

Take Home Points - CME

- Topical NSAIDs pre/post-surgery help maximize surgical outcomes.
- NSAIDs work synergistically with _______ to prevent/control CME.
- Must have appropriate duration of treatment for routine and high risk patients.
- Ideal topical NSAID maximizes intraocular efficacy while minimizing corneal toxicity.

Questions

- Do patients taking topical prostaglandins for glaucoma need to be d/c'd or switched to another med before/after cataract surgery?

Questions and Comments?

70 year old Caucasian male

CC: Blurred "central" vision (OD) x 2 days @ distance and near

Ocular History: +Corneal abrasion OS x 15 years ago
+Anterior Cortical Cataracts / NS 1 OU

Medical History: + Hypertension x 20 years (under control) – with meds
+ Hypercholesterolemia (not under control) – with meds

Family Ocular History: + Primary Open Angle Glaucoma (mother)

Allergies: +Penicillin +Keflex

VA: c Rx OD 20/70 OS 20/30

Pupils: (+) APD Grade 1 OD

FOMS: Smooth / Full

SLE: Unremarkable OU

CF: Full OU (periphery)

Vitreous: Clear OU

BP: 140 / 80 RAS

IOP: 15 mm Hg OU
Are there any other tests you would perform?

Fluorescein Angiography
What is your assessment?

What is your plan?
Outcome:
- Diagnosis: Branch Retinal Artery Occlusion OD
  - Vision remained 20/70 x 1 year
  - Carotid Studies revealed 75% obstruction Right Side
  - Carotid Studies revealed 70% obstruction Left Side
  - Echocardiogram – no abnormalities
  - Patient has not reported any new ocular complaints
  - Patient did have a “TIA” x 8 months post BRAO
  - Now taking “Baby Aspirin”
  - Cholesterol was lowered by PCP

39 year old Hispanic female
CC: Total loss of vision x 1 hour ago OD @ distance and near
Ocular History: + Glasses and Contact lenses x 20 years
+ Diabetic Hypertension x 7 years
Systemic History: + Hypertension x 3 years (Controlled with Meds)
+ Diabetes x 3 months (Controlled with Meds)
+ Hypercholesterolemia x 3 years (Controlled with Meds)
Social History: + Smokes 1 pack of cigarettes a day / Patient takes BCP
Allergies: No known drug allergies / No environmental allergies
VA: CF OD 20/25 OS TA: 26 OD 26 OS
EOMS: Smooth / Full
Vitreous: Clear OU
PUPILS: PERRLA + APD Grade 4 OD BP: 155 / 95 RAS
CF: Restricted OD Full OS SLE: Unremarkable

Describe That Fundus!
What is your assessment?

What is your plan?

Retina Quiz

In CRAO of < 24 hrs duration, best initial management is:
- a. digital ocular massage, STAT retinal consult
- b. IV methylprednisone
- c. po steroid
- d. observe without treatment; prognosis excellent for visual recovery

The Real Deal on BRAO

Usually:
- cholesterol, calcific, fibrin
- FA shows delayed filling of affected artery and hypofluorescence in surrounding area
- Retinal infarct results in permanent VF defect
- 80-90% improve to a VA of 20/40 or better
- No acute intervention
- Observe closely for NVI/NVA
- Systemic co-management with PCP
Clinical Significance of RAOs

- **Thrombus**
  - A hardened lump of blood within a vessel.

- **Emboli**
  - Sudden blockage of an artery by a blood clot (thrombus) or another material.

Both are common causes of stroke.

The Real Deal on CRAO

- **CRAO** can be **embolic** or **thrombotic**
  - Atherosclerotic changes, inflammatory endarteritis
  - BP, carotid auscultation

- **Acute management (< 24 hours)**
  - Ocular Massage: 10 seconds/release → Retinal consult **
  - AC paracentesis (<24 hr)
  - IV Acetazolamide
  - Carbogen (95% O-2, 5% CO-2)
  - Medical evaluation to ID and treat underlying cause
  - Carotid, cardiac studies
  - ESR if > 55 y/o, no visible emboli
  - If suspect GCA, hi-dose steroids

- **Follow-up**
  - Monitor for NVI/NVA → PRP

---

69 year old Caucasian Female

**CC**: Reduced central vision OD x 3 weeks @ distance and near

**Ocular History**: Unremarkable

**Systemic History**: Unremarkable; Last PCP exam 15 years ago

**Social History**: Smokes ½ pack of cigarettes a day
Alcohol 5-10 drinks a day

**Meds**: Multivitamin

**Allergies**: +Penicillin

**VA**: Rx 20/80 OD 20/20 OS

**EOM**: Smooth / Full

**Faucia**: PERRLA - APD

**CE**: Central blur OD Full Periphery OD

**BP**: 158 / 98 RAS

Describe That Fundus!
Fluorescein Angiography
What is your assessment?

Hemispheric Retinal Vein Occlusion

What is your plan?

BRVO

CRVO
Outcome:

- Diagnosis: Inferior Hemi-Central Retinal Vein Occlusion OD
- Treated as a non-ischemic CRVO (Why?)
- Follow-Up in 1 month
- Patient sent to PCP to rule out Diabetes, Hypertension, Cholesterol
- Hypertension diagnosed
- Patient received intravitreal injection of Kenalog at 4 months for CME
- Patient had IOP spike after Kenalog injection – given Alphagan P
- No NVD or NVE occurred
- Vision at 1 year was OD 20/25

Hemi-Central Retinal Vein Occlusion

- Uncommon type of hemispheric RVO
  - Occurs in "Dual Trunk" anomaly
- Same pathophysiology as CRVO.
- May affect either the superior or inferior CRV before they unite into common central retinal vein.
- Usually occurs at or near the optic disc.

The Real Deal on BRVOs

- Caused by a______________of overlying artery
- BRVO Study
  - Observe monthly for first 6 mon
  - DFE, OCT
  - Gonio
  - Chronic findings include ME, collateral BVs
  - Macular grid laser helpful for ME >6 mon
  - After initial 6 mon, observe q 3-4 mon for RNV, NVIA
  - Scatter laser for RNV, VHeme
  - IV Kenalog, Avastin off-label for ME
- Medical workup
  - CV Dx, DM, hyperviscosity, lipids
Arteriosclerosis with calcification of vessel wall

The Real Deal on CRVOs

- T________ in CRV at lamina
- CRVO Study
  - Prophylactic PRP did not prevent NVI/NVA in ischemic CRVO
  - Therefore, wait for development of NVI/NVA before PRP
  - No real benefit of macular grid laser for ME
- Follow-up
  - Observe monthly for first 4-6 mon
  - Angiography when heme, retinal edema reduces
  - Monitor for NVI/NVA \(\rightarrow\) PRP
  - Medical workup
    - CV Dx, DM, hyperviscosity, lipids
  - Non-ischemic CRVO may convert to ischemic (30%)!

Retina Quiz

- In an ischemic CRVO, which is **false**?
  - a. it carries high risk of NVI/NVA
  - b. complications may include ME, ischemic damage
  - c. risk of NVG is 5%
  - d. it carries some risk for NVD, NVE, leading to vitreous heme

Non-ischemic vs. Ischemic CRVO

- **Functional Tests**
  - VA
  - Pupil testing
  - Visual fields
  - Electroretinography

- **Structural Tests**
  - Ophthalmoscopy
    - SL Fundoscopy
    - BIO
  - Fluorescein angiography
Ischemic CRVO

- Note disc edema, several CWS
- Capillary non-perfusion on FA
- VA < 20/200, +APD, retinal/macular edema
- More likely to result in NVI/NVA than non-ischemic
- 45% of cases result in NVG

Blood Flow in the Optic Nerve:

- Blood Flow = Perfusion Pressure / Resistance to flow
- Perfusion Pressure = Mean BP – IOP
- Mean BP = Diastolic BP + 1/3 (systolic BP – diastolic BP)

Retinal Blood Flow = Retinal Arterial Pressure – Retinal Venous Pressure

To improve retinal blood flow in CRVO there are two options:
   Lower the venous pressure or increase the arterial pressure

No scientific basis for lowering IOP in to improve retinal blood flow

Should Ischemic Venous Occlusions be Referred to a Retinologist Before NVI/NVA?
Emerging Treatments for BRVO/CRVO

- Intravitreal Kenalog
  - Intravitreal injection for ME
  - The Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) Study: Two Randomized Trials to Compare the Efficacy and Safety of Intravitreal Injections(s) of Triamcinolone Acetonide with Standard Care to Treat Macular Edema
  - One for CRVO and One for BRVO
  - IVK found useful for ME in CRVO, not BRVO when compared to standard

SCORE – Standard Care vs. Corticosteroid for Retinal Vein Occlusion

To evaluate the clinical benefits of triamcinolone for treating macular edema associated with vein occlusion.

84 clinics and sponsored by the National Eye Institute

One group received the standard clinical care for the condition
  - One group got 4 milligram
  - One group got 1 milligram

Results: SCORE (CRVO) – 27%(1milligram) group and 26%(4milligram) group experienced a substantial visual gain of 3 or more lines. The results up to 2 years. The 4 milligram group had the highest rates of cataract formation, cataract surgery, and elevated pressure. The 1 milligram dose is safer for patients.

SCORE (BRVO) – 29%(laser), 26%(1mg), 27%(4mg) gained 3 or more lines. 3 yr. Laser treatment may have fewer side effects for patients.

Emerging Treatments for BRVO/CRVO

- Dexamethasone Drug Delivery System
  - OZURDEX (intravitreal implant) 0.7mg (Allergan)
  - Intraocular, biodegradable implant for the treatment of persistent ME
  - Clinical trial underway

- Anti-VEGF drugs
  - Lucentis
  - Avastin
DR: CSME Treatment

- **Iluvien** (formerly known as Medidure)
  - Tube 3.5mm x 0.37mm containing fluocinolone
  - Implanted into vitreous w/ 25g (~0.5mm) inserter
  - Sutureless
  - Designed to provide sustained effect up to 24 months
  - **FAME** (fluocinolone acetонide in DME) trial under way

Emerging Treatments for BRVO/CRVO

BRAVO and CRUISE studies – Lucentis clinical trials for RVO

**BRAVO** – Phase III study (12 month study) 0.3 or 0.5 mg of Lucentis
Safety and effectiveness of Lucentis in macular edema secondary to BRVO

**CRUISE** – Phase III study (12 month study) 0.3 or 0.5 mg of Lucentis
Safety and efficacy of Lucentis in macular edema secondary to CRVO

An analysis of the 6 month data from both studies showed a safety profile consistent with previous Lucentis Phase III trials in wet ARMD.

As early as seven days after the first injection, patients who received monthly injections of Lucentis had, on average, a statistically significant improvement in their vision that lasted 6 months.

Final thoughts on CRVO

- When NV occurs in ischemic CRVO, it most often occurs in the anterior segment.
- Neovascular glaucoma is seen in ~ 45% of eyes with ischemic CRVO.
- M____e_____ may occur in either ischemic or non-ischemic CRVO, leading to permanent central scotoma.
- Non-ischemic CRVO may convert to ischemic (30%)!
- 2/3 of non-ischemic CRVO will have 20/40 or better w/o ocular Tx.
54 year old Asian male

Chief Complaint (CC):
Intermittent blurred vision OU @ distance and near x 5 months

Ocular History:
+ mild cortical cataracts OU

Systemic History:
+ DM x 12 years (controlled with meds)
  HbA1c = 9%
  + Hypertension x 10 years (controlled with 2 meds)

Family History:
+ POAG (mother and father)

No known drug or environmental allergies / Pt. smokes 5-7 cigarettes a day

VA:
20/25 OD/OS c Rx Dist. / Near

TA:
16 mm OU

FDM:
Smooth / Full

Vitreous:
Clear OU

Pupils:
PERRLA – APD

BP:
145 / 90 RAS

SLE:
Unremarkable OU

Questions and Comments?
**Fluorescein Angiography**

**Outcome**

**Diagnosis:**
- OD: Proliferative Diabetic Retinopathy
- OS: Severe Non-Proliferative Diabetic Retinopathy

- No macular edema OD/OS
- FA performed
- Photos taken
- PRP given (OD) over 4 sessions
- Letter written to PCP
- F/U Q 3 mon

**Diabetes Mellitus**

- DM is the most frequent cause of new cases of blindness in the USA. (Prevent Blindness America 2003)
- Severe vision loss from DR is often preventable with timely detection and treatment. (ETDRS)
- 2 million people w/DM in CN
- Type 2 on the rise in CN
**Risk Factors for DR**
- Age
- Race
- Smoking
- Obesity (BMI)
- Early Age at Initial Diagnosis of DM
- Long Duration of DM
- CV Dx.
- Poor glycemic control

**Anatomy Review: Retinal Capillaries**
- Capillary Network
  - Pericytes surround each endothelial cell and provide support
  - Tight junctions between endothelial cells
  - Pericytes + tight junctions form inner normal mouse retina in which pericytes marked by ng2 staining (blue) and endothelial cells are marked by PECAM (red).

**DIABETIC RETINOPATHY (pathogenic mechanisms)**
- Capillary hypertension
- Systemic hypertension
- Insulin resistance
- Endothelial dysfunction
- Hyperglycemic pseudohypoxia
- Non-enzymatic glycosylation
- Increased vascular permeability
Pathogenesis of Diabetic Retinopathy

- Pericyte loss → Thickening (occlusion) and weakening → (leaking) vessels

Retina Quiz

What is the distinguishing feature of PDR?

a. MAs
b. CWS
c. IRMA
d. NVD or NVE
**NPDR**

- **MICROANEURYSMS** and blot-and-dot hemorrhages
- **INCREASED VASCULAR PERMEABILITY** (hard exudates)
- **ISCHEMIA** (cotton-wool spots)
  - damage to axoplasmic flow in the nerve fiber layer
  - focal infarct

**NPDR**

- Venous "beading"
- **IRMA** (intraretinal microvascular anomalies)
- Extensive capillary occlusion and ischemia

**PDR**

- CHARACTERIZED BY **NEWLY FORMED VESSELS**!
  - originate from vessels of the optic nerve or from the surface of the retina
  - Newly formed vessels are abnormal, extremely fragile!
Management Guidelines: NPDR

For Mild and Moderate NPDR
- Observe patient q3-12 months
- Visual function testing
- DFE, photography, OCT, gonio
- DM education

For Severe and Very Severe NPDR
- More frequent observation
- Visual function testing
- DFE, photography, OCT, gonio
- Angiography/retina consult
- DM education

4-2-1 Rule

Severe NPDR
- At least one of:
  - intraretinal hemorrhages in four quadrants
  - venous beading in two quadrants
  - intraretinal microvascular abnormalities in 1 quadrant

Standard photographs available at:
eyephotographonlinelibrary.wisc.edu/ResearchAreas/Diabetes/Diabetes/DiabStds.htm

Intraretinal hemorrhages in four quadrants

Venous Beading and Intraretinal Microvascular Anomalies (IRMA)
Management Guidelines: PDR
- R/O NVI/NVA
  - Co-manage if NVG
- Angiography
- Retina consult for treatment of NV
  - Laser photocoagulation
    - Focal
    - Grid
    - Scatter
  - PPV
  - Vitrectomy if massive VH or pre-retinal membrane at macula

Management Guidelines: CSME
- Establish whether CSME exists
  - Stereoscopic fundoscopy
  - Angiography
  - OCT may be helpful
- Can have DME that is non-clinically significant, CME
- ETDRS demonstrated that laser Tx. significantly reduced risk of vision loss in CSME.

DIABETIC MACULAR EDEMA

CSME Defined
- CSME, as defined by the ETDRS, exists with any of the following findings:
  - Retinal thickening within 500 mm of the center of the fovea
  - Hard exudates within 500 mm of the center of the fovea with adjacent retinal thickening
  - At least 1 disc area of retinal thickening, any part of which is within 1 disc diameter of the center of the fovea
Diagnosing CSME: Choose One

DCCT showed that intensive glycemic control was effective in delaying the onset, as well as slowing the progression, of diabetic retinopathy in patients with type 1 diabetes.

DRVS findings showed that an early vitrectomy was beneficial in restoring and preserving vision in patients with proliferative DR (PDR) with or without associated vitreous hemorrhage.

PRP was beneficial only in cases that had developed proliferative changes or in which it was imminent. It also showed that focal or grid photocoagulation was beneficial in reducing visual loss due to macular edema.

ETDRS-Early Treatment for Diabetic Retinopathy Study, 1984-1986
DRVS-Diabetic Retinopathy Vitrectomy Study, 1981-1984
DCCT-Diabetes Control and Complications Trial, 1983-1989

Important DM Studies
In phase III clinical trials, intravitreal injections of ovine hyaluronidase (Vitrase) have been shown to be safe and to have modest efficacy for the clearance of severe vitreous hemorrhage.

More recently, bevacizumab (Avastin) has been used to treat vitreous hemorrhage.

- In phase III clinical trials, intravitreal injections of ovine hyaluronidase (Vitrase) have been shown to be safe and to have modest efficacy for the clearance of severe vitreous hemorrhage.
- More recently, bevacizumab (Avastin) has been used to treat vitreous hemorrhage.

DR: Emerging Treatments

- Minimum-intensity Photocoagulation
  - Laser w/o scar
  - Low levels of argon laser energy for PDR
- Pegaptanib and Ranibizumab (Anti-VEGF)
- Octreotide
  - Somatostatin analog and insulin-like growth factor 1 antagonist
- Intravitreal Corticosteroids for DME

PKC Inhibition for NPDR, CSME

- Protein kinase C (PKC) enzymes, upon activation, may cause hyperglycemia-related microvascular damage
- Ruboxistaurin Mesylate
  - Po med
  - Initial results from the PKC-DRS show improved vision and reduced risk of CSME in patients treated with 32 mg.
Diabetes is a Risk Factor for:

- Stroke
- Heart Disease
- CRVO
- BRVO
- Sleep Apnea

Questions and Comments?
Conclusions
- We have an important role in the diagnosis and (co-)management of posterior segment vascular, degenerative, and other diseases.
- Don’t miss the telltale symptoms and signs.
- Used evidence-based guidelines.
- Medical retinal care is expanding!

Thank You!
- For the opportunity to meet and discuss these cases with you.

Joe Pizzimenti
– pizzimen@nova.edu