Goals/Objectives

Using cases as a framework, review current evaluation and management of ocular vascular occlusive events, including:
1. Branch retinal artery occlusion
2. Central retinal artery occlusion
3. Branch retinal vein occlusion
4. Central retinal vein occlusion

Disclosures

- None

Risk Factors

- Age?
- Sex?
- Race?
- Associated systemic disease?
- Tobacco use?

Retinal Artery Occlusions

- Branch and Central

Risk Factors

- RAO and RVO

Updated: September 24, 2014
Case #01

Patient Information
- 27 year old Caucasian male
- No systemic conditions reported
- No medications reported
- No allergies reported
- No hx of tobacco use reported
- Hx of MVA with severe chest and neck bruising 6 months prior

Examination
- Presents with complaint of sudden inferior vision decrease OS X 3 days
- No other complaints
- Visual acuities without correction
  - 20/20 OD
  - 20/20- OS
- EOMs, CT, pupils all normal
- Screening visual field
  - NL OD
  - Inferior defects OS

SLEx – normal
IOPs - normal
DFEx
  - See photos
Visual Field - OD

Visual Field - OS

Etiology
- Embolus
  - Cholesterol
  - Calcium
  - Platelet-fibrin
- Thrombosis
- Giant cell arteritis (GCA)
- Other collagen-vascular disease
  - Systemic lupus erythematosus
  - Polyarteritis nodosa
  - Other

Etiology
- Polycythemia
- Multiple myeloma
- Cryoglobulinemia
- Waldenström macroglobulinemia
- Anti-phospholipid syndrome
- Factor V Leiden
- Activated protein C resistance
- Hyperhomocysteinemia
- Protein C & S deficiency
- Anti-thrombin II mutation
- Prothrombin mutation G20210A

Etiology
- Trauma
- Rare
  - Migraine
  - Behçet disease
  - Syphilis
  - Sickle cell disease

Additional Testing
- Patient older than 55 - rule out GCA
  - ESR
  - CRP
  - Platelets
- Evaluate blood pressure
- Evaluate blood sugar
  - Fasting blood sugar (FBS)
  - Glycosylated hemoglobin (HbA1C)
- Complete blood count with differential (CBC with DIFF)
  - Prothrombin time/activated partial thromboplastin time (PT/PTT)
Additional Testing

- Evaluate carotid artery
  - Duplex doppler ultrasound
- Cardiac evaluation
  - Electrocardiography (ECG)
  - Echocardiography
  - Holter monitoring
- To confirm diagnosis
  - IVFA
  - Electro-retinography (mf-ERG)

Patient Management

- Blood testing
  - Likely anti-phospholipid syndrome (APS) with elevated beta-2 glycoprotein I antibodies, IgM
  - Retest recommended in 12 weeks to confirm
  - Recommended anti-coagulant treatment
- Prior chest/neck trauma
  - Echocardiogram recommended
  - Carotid doppler recommended
  - Patient saw multiple ECPs and PCPs; lost to follow up.

Management

- None
- No evidence
  - Ocular massage
  - Fundus contact lens
  - Digital
  - IOP reduction
  - Anterior chamber paracentesis
  - Acetazolamide 500 mg IV or 500 mg PO
  - Topical beta-blocker BID
  - Hyper-ventilation

Follow up

- Refer to family doctor/internist
- See again in 1-4 weeks. Rule out...
  - Neovascularization of the iris (± NVI)
  - Neovascularization of the angle (± NVA)
  - Neovascularization of the disc (± NVD)
  - If neovascularization
    - Pan-retinal photocoagulation (PRP)
    - Anti-vascular endothelial growth factor (anti-VEGF)

Management

- Recombinant tissue plasminogen activator (t-PA)
  - Protein involved in the breakdown of blood clots
  - Catalyzes the conversion of plasminogen to plasmin, the major enzyme responsible for clot breakdown
  - Use within a few hours of retinal artery occlusion may provide benefit
  - At 3 months, VA had improved in 35 (66%) of 53 patients
    - 47% - VA improved more than 2 lines
    - 19% - VA improved 1 to 2 lines
    - 23% - no improvement in VA
    - 11% - VA decreased

Recombinant tissue plasminogen activator (t-PA)
Case #02

Patient Information
- 65 year old Caucasian male
- Urgent exam
- Loss of vision OD x 4 days
- LEE: last month but patient refused DFE, “doc said BP 200/160”
- Systemic conditions
  - None
  - Last Physical Exam?
  - Smokes ~1 pack/day
- Systemic medications
  - None

Examination
- BCVAs
  - OD 20/400 with eccentric fixation
  - OS 20/15-2
- APD OD
- Blood Pressure: 230/120
- Confrontation VF
  - Very constricted field OD, FTEF OS
- SLEx
  - Corneal arcus OD, OS
- DFEx
  - See picture OD, Patient refused DFE OS

Retinal Vein Occlusions
Branch and Central
Retinal Vein Occlusions

<table>
<thead>
<tr>
<th>Branch Retinal Vein Occlusions (BRVO)</th>
<th>Central Retinal Vein Occlusions (CRVO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result of blockage of blood flow in a branch of the central retinal vein</td>
<td>Compression of central retinal vein</td>
</tr>
<tr>
<td>BRVOs that affect VA almost always are associated with macular edema</td>
<td>An association with primary open angle glaucoma</td>
</tr>
<tr>
<td>Age: 60 - 70s</td>
<td>90% in patients &gt; 50 years old</td>
</tr>
<tr>
<td>No sexual predilection</td>
<td>Men &gt; Women</td>
</tr>
<tr>
<td>3X more common than CRVOs</td>
<td>Can be ischemic or non-ischemic</td>
</tr>
</tbody>
</table>

Case #03

Patient Information

- 65 year old Caucasian male
- Annual eye exam
- Systemic conditions
  - Diabetes since 2004, HTN, hyperlipidemia
- Systemic medications
  - Metformin (DM)
  - Lisinopril (DM)
  - Norvasc (HTN)
  - Doxazosin (HTN)
  - HCTZ (HTN)
  - Lipitor (Cholesterol)

Examination

- BCVAs
  - OD 20/40
  - OS 20/30
- No Amsler defects OD, OS
- SLEx
  - Nuclear sclerosis grade 2+ OD, OS
- DFEs
  - Multiple dot and flame hemorrhages located inferior to macula OD

Fundus Photo OD

- Assessment
  - 362.36 Branch Retinal Vein Occlusion OD
  - 366.16 Cataract, Nuclear Sclerosis OU
- Plan
  - Perform OCT and FA to assess leakage
  - FA showed mild leakage OD
Management

- Patient scheduled for intra-vitreal injections (IVI) of Avastin (bevacizumab)
- 1 week post Avastin IVI
  - “Feel like vision has improved”
  - BCVA OD 20/25 (improved from 20/40)
- Patient received 2 additional Avastin IVI over next 2 months
- BCVA - stable at 20/25

Studies

Branch Retinal Vein Occlusion

Branch Vein Occlusion Study (BVOS)

- Is argon laser photoocoagulation useful in improving visual acuity in eyes with branch vein occlusion and macular edema reducing vision to 20/40 or worse?
- Recruited 139 participants
  - Center-involved macular edema 2° to BRVO
  - BCVA of 20/40 or worse
- Divided participants into two equal groups
  - Grid photoocoagulation
  - Control

BVOS Results

- Grid photoocoagulation
  - 65% of eyes gained 2+ lines of visual acuity
  - 60% attained visual acuities of 20/40 or better
- Control
  - 37% of eyes gained 2+ lines of visual acuity
  - 34% attained visual acuities of 20/40
- Established grid photoocoagulation as standard therapy for macular edema 2° to BRVO

Other results

- Laser significantly reduces likelihood of vitreous hemorrhage
- Perform PRP after the development of neovascularization rather than prophylactically

SCORE - BRVO

- SCORE - Standard of Care versus Corticosteroid for Retinal Vein Occlusion Study
- Examined the effectiveness and safety of grid photoocoagulation (standard of care from BVOS) versus intra-vitreal injection of triamcinolone for macular edema 2° to BRVO
SCORE - BRVO

- Recruited 411 participants
  - Center-involved macular edema secondary to BRVO
  - ETDRS BCVA approximately 20/40 to 20/400
- Divided participants into 3 equal groups
  - Observation or grid photocoagulation per BVOS criteria
  - 1 mg triamcinolone intra-vitreal injection
  - 4 mg triamcinolone intra-vitreal injection

SCORE – BRVO Results

- % of patients who gained ETDRS BCVA of ≥ 15 letters at 12 months
  - 29% - observation/grid photocoagulation
  - 26% - 1 mg triamcinolone IVI
  - 27% - 4 mg triamcinolone IVI

SCORE – BRVO Other Results

- Through month 12
  - IOP lowering treatment initiated
    - 2% - observation/standard treatment
    - 7% - 1 mg triamcinolone
    - 25% - 4 mg triamcinolone
  - Cataract onset or progression
    - 13% - observation/standard treatment
    - 25% - 1 mg triamcinolone
    - 35% - 4 mg triamcinolone

SCORE – BRVO Conclusion

- For BRVO with vision loss 2° to center-involved macular edema
  - Grid photocoagulation remains the standard of care and the benchmark against which other treatments are measured

BRAVO

- BRAVO - Ranibizumab for the treatment of macular edema following Branch Retinal Vein Occlusion Study
  - Can Lucentis (ranibizumab), an anti-VEGF agent, increase visual outcome in patients with macular edema secondary to BRVO?
  - Phase 3 clinical trial

BRAVO

- Recruited 397 participants
  - Edema in foveal center
  - ETDRS BCVA from 20/40 to 20/400
- Divided participants into 3 equal groups
  - Six monthly 0.3 mg Lucentis intra-vitreal injections (IVI)
  - Six monthly 0.5 mg Lucentis intra-vitreal injections (IVI)
  - Six monthly sham intra-vitreal injections (IVI)
- Rescue laser an option after 3 months
BRAVO Results
- % of patients who gained ETDRS BCVA of ≥ 15 letters at six months
  - 55% - monthly 0.3 mg Lucentis IVI
  - 61% - monthly 0.5 mg Lucentis IVI
  - 29% - monthly sham IVI

BRAVO – Other Results
- At 7 days, mean improvement of 7.5 letters in both Lucentis groups
- Safety with multiple injections
  - Overall good
  - 1 case of retinal detachment/tear
  - 1 case of endophthalmitis

After initial 6 month results, 6 additional months of monthly observation
- Lucentis injection triggered if any of the following
  - BCVA ≤ 20/40
  - OCT central subfield thickness (CFT) ≥ 250 µm
- Protocol
  - 0.3 mg Lucentis IVI group receives 0.3 mg Lucentis
  - 0.5 mg Lucentis IVI group receives 0.5 mg Lucentis
  - Sham IVI group receives 0.5 mg Lucentis

BRAVO – Conclusion
- No direct comparison with BVOS standard of care
- At 6 months, mean gain from baseline in BCVA letter scores
  - 17 in 0.3 mg Lucentis group
  - 18 in 0.5 mg Lucentis group
  - 7 in sham group
- At 12 months, mean gain from baseline in BCVA letter scores
  - 17 in 0.3 mg Lucentis group
  - 19 in 0.5 mg Lucentis group
  - 13 in sham/0.5 mg Lucentis group

After BRAVO and CRUISE - HORIZON
- After 12 months of BRAVO and CRUISE, patients followed approximately 14 additional months
- Examined at baseline and every three months after
- Lucentis injection triggered if any of the following
  - BCVA ≤ 20/40
  - OCT central subfield thickness (CFT) ≥ 250 µm
- Protocol
  - 0.3 mg Lucentis IVI group receives 0.5 mg Lucentis
  - 0.5 mg Lucentis IVI group receives 0.5 mg Lucentis
  - Sham IVI group receives 0.5 mg Lucentis

HORIZON – BRAVO Group
- At Horizon baseline, mean gain from baseline in BCVA letter scores
  - 17 in 0.3 mg/0.5 mg Lucentis group
  - 19 in 0.5 mg/0.5 mg Lucentis group
  - 13 in sham/0.5 mg Lucentis group
- 12 months later, mean gain from baseline in BCVA letter scores
  - 15 in 0.3 mg/0.5 mg Lucentis group
  - 18 in 0.5 mg/0.5 mg Lucentis group
  - 16 in sham/0.5 mg Lucentis group
HORIZON – BRAVO Group

- Median time to 1st 15-letter or more gain from baseline
  - Sham = 12.0 months
  - Lucentis 0.3mg = 4.8 months
  - Lucentis 0.5mg = 4.0 months
- Cumulative proportion of patients who gained 15 or more letters from baseline by month 12
  - Sham = 50%
  - Lucentis 0.3mg = 68%
  - Lucentis 0.5mg = 71%
- After 6 months of Lucentis PRN treatment following initial sham-treatment
  - 10.8% of patients ever gained 15 letters or more

Ranibizumab Long-Term Outcomes - BRVO

- Determine % of Lucentis-treated patients with BRVO who had resolution of edema for at least 6 months after last injection
  - >=20
- Treated with Lucentis monthly x 3 months and as needed for recurrent/persistent edema
- If edema persisted after month 40, patients received scattered and grid photocoagulation
- Outcome measures:
  - Change in BCVA and change in area of retinal non-perfusion

Ranibizumab Long-Term Outcomes - RETAIN BRVO

- 34 patients with BRVO
- Outcome measures
  - Mean improvement in BCVA
  - % of patients with edema resolution

Ranibizumab Long-Term Outcomes - RETAIN BRVO

- Mean follow-up of 49.0 months
- 50% had edema resolution for 6 months after last injection
- Last injection was given within 2 years of tx initiation in 76%
- Mean improvement in BCVA 25.9 letters vs. 17.1 letters in unresolved patients
- Both groups, 80% had final BCVA of 20/40 or better

Conclusions from both studies

- Lucentis alone
  - About 45-50% of patients with BRVO resolved
- Laser photocoagulation may be necessary for persistent or recurrent edema
Central Vein Occlusion Study (CVOS)

- Recruited 155 participants
  - Center-involved macular edema secondary to CRVO
  - BCVA 20/50 or worse
- Results
  - Macular grid laser photocoagulation improved angiographic macular edema
  - Little effect on BCVA
  - Established observation as standard therapy for macular edema 2° to CRVO

Other CVOS Results

- Safe to wait to perform PRP until neovascularization forms
- If extensive intra-retinal hemorrhages, treat as if they are ischemic or non-perfused as it is not possible to determine the perfusion status

SCORE – CRVO

- SCORE - Standard of Care versus Corticosteroid for Retinal Vein Occlusion Study
  - Examined the effectiveness and safety of observation (standard of care from CVOS) versus intra-vitreal injection of triamcinolone for macular edema 2° to CRVO
- Recruited 271 participants
  - Center-involved macular edema secondary to CRVO
  - ETDRS BCVA approximately 20/40 to 20/400
- Divided participants into 3 equal groups
  - Observation - per CVOS
  - 1 mg triamcinolone intra-vitreal injection
  - 4 mg triamcinolone intra-vitreal injection

SCORE – CRVO Results

- % of patients who gained ETDRS BCVA of ≥15 letters at 12 months
  - 7% - observation
  - 27% - 1 mg triamcinolone IVI
  - 26% - 4 mg triamcinolone IVI
SCORE – CRVO Other Results

- Through month 12
  - IOP lowering treatment initiated
    - 8% - observation
    - 20% - 1 mg triamcinolone
    - 33% - 4 mg triamcinolone
  - Cataract onset or progression
    - 18% - observation
    - 26% - 1 mg triamcinolone
    - 33% - 4 mg triamcinolone

SCORE – CRVO Conclusion

- For CRVO with vision loss 2° to macular edema
  - Consider 1 mg triamcinolone intra-vitreal injections as an alternative to observation (old standard)

CRUISE

- Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety (CRUISE)
  - Can Lucentis (ranibizumab), an anti-VEGF agent, increase visual outcomes in patients with macular edema secondary to CRVO?
  - Phase 3 clinical trial

- Recruited 392 participants
  - Age ≥ 18
  - Foveal center-involved macular edema due to CRVO
  - BCVA from 20/40 to 20/320

CRUISE Results

- % of patients who gained BCVA of ≥ 15 letters at six months
  - 46% - 0.3 mg monthly Lucentis injection
  - 48% - 0.5 mg monthly Lucentis injection
  - 17% - sham injection
- Good safety profile

CRUISE – Other Results

- After initial 6 month results, 6 additional months of monthly observation
- Lucentis injection triggered if any of the following:
  - BCVA ≤ 20/40
  - OCT central subfield thickness (CFT) ≥ 250 µm
- Protocol
  - 0.3 mg Lucentis IVI group receives 0.3 mg Lucentis
  - 0.5 mg Lucentis IVI group receives 0.5 mg Lucentis
  - Sham IVI group receives 0.5 mg Lucentis
CRUISE - Conclusion

- At 6 months, sham injection results are similar to CVOS observation arm.
- At 6 months, mean gain from baseline in BCVA letter scores:
  1. 13 in 0.3 mg Lucentis group
  2. 15 in 0.5 mg Lucentis group
  3. 1 in sham group
- At 12 months, mean gain from baseline in BCVA letter scores:
  1. 14 in 0.3 mg Lucentis group
  2. 14 in 0.5 mg Lucentis group
  3. 7 in sham/0.5 mg Lucentis group
- Consider anti-VEGF for treatment of center-involved macular edema 2° to CRVO.

After BRAVO and CRUISE - HORIZON

- After 12 months of BRAVO and CRUISE, patients followed approximately 14 additional months.
- Examined at baseline and every three months after.
- Lucentis injection triggered if any of the following:
  1. BCVA ≤ 20/40
  2. OCT central subfield thickness (CFT) ≥ 250 µm
- Protocol:
  1. 0.3 mg Lucentis IVI group receives 0.5 mg Lucentis
  2. 0.5 mg Lucentis IVI group receives 0.5 mg Lucentis
  3. Sham IVI group receives 0.5 mg Lucentis

HORIZON – CRUISE Group

- At Horizon baseline, mean gain from baseline in BCVA letter scores:
  1. 15 in 0.3 mg/0.5 mg Lucentis group
  2. 16 in 0.5 mg Lucentis group
  3. 9 in sham/0.5 mg Lucentis group
- 12 months later, mean gain from baseline in BCVA letter scores:
  1. 8 in 0.3 mg/0.5 mg Lucentis group
  2. 12 in 0.5 mg Lucentis group
  3. 8 in sham/0.5 mg Lucentis group

HORIZON – CRUISE Group

- Median time to 1st 15-letter or more gain from baseline:
  1. Sham = 12.2 months
  2. Lucentis 0.3mg = 5.9 months
  3. Lucentis 0.5mg = 5.2 months
- Cumulative proportion of patients who gained 15 or more letters from baseline by month 12:
  1. Sham = 42%
  2. Lucentis 0.3mg = 61%
  3. Lucentis 0.5mg = 66%
- After 6 months of Lucentis PRN treatment following initial sham-treatment:
  1. 26.2% of patients ever gained 15 letters or more

HORIZON – CRUISE Group

- More than 50% of patients treated with monthly ranibizumab achieved clinically significant vision gains during the initial 6 months of treatment, which largely were maintained using PRN treatment to 12 months.
- In comparison, less than 50% of patients initially randomized to sham (and later receiving ranibizumab 0.5 mg PRN treatment) ever achieved clinically significant vision gains.
- Take Home: TREAT EARLY!

Ranibizumab Long-Term Outcomes CRVO

- Determine % of Lucentis-treated patients with CRVO who had resolution of edema for at least 6 months after last injection:
  1. n=20
- Treated with Lucentis monthly x 3 months and as needed for recurrent/persistent edema.
- If edema persisted after month 40, patients received scattered and grid photocoagulation.
- Outcome measures:
  1. Change in BCVA and change in area of retinal non-perfusion.
### Ranibizumab Long-Term Outcomes - BRVO
- 25% had resolution from injections
  - Mean time 14.0 months
- 0% resolved after laser
- 40% did not resolve
- 35% exited prior to resolution
- Those who resolved:
  - Were younger (32.8 vs. 71.6 years old)
  - Had shorter duration of disease (4.4 vs. 14.4 months)
  - Had better BCVA

### Ranibizumab Long-Term Outcomes - RETAIN CRVO
- 32 patients with CRVO
- Outcome measures
  - Mean improvement in BCVA
  - % of patients with edema resolution

### COPERNICUS
- Looked to assess the efficacy and safety of VEGF Trap-Eye (aflibercept injection) in eyes with macular edema 2° to CRVO
- Aflibercept
  - Binds with - and inactivates - VEGF
  - Thought to have greater binding affinity to VEGF than both bevacizumab and ranibizumab

### COPERNICUS
- Recruited 189 participants
  - Macular edema secondary to CRVO
  - Retinal thickness greater than 250 µm
  - Participants divided into two groups in a 3:2 ratio
  - VEGF Trap-Eye 2.0 mg IVI every month for 6 months
  - Sham injection every month for 6 months (equivalent to CVOS observation)
  - After initial 6 months, patients seen monthly for 6 months and received
    - VEGF Trap-Eye 2.0 mg IVI if retreatment indicated
    - Sham injection if no retreatment indicated

### COPERNICUS
- Mean follow-up of 49.7 months
- 44% edema resolution for 6 months after last injection
- Last injection was given within 2 years of tx initiation in 71%
- Mean improvement in BCVA 25.2 letters vs. 4.3 letters in unresolved patients
- In resolved group, 64.3% had final BCVA of 20/40 or better
- In unresolved group, 27.8% had final BCVA of 20/40 or better

### COPERNICUS
- Conclusions from both studies
  - Lucentis alone
    - About 25-44% of patients with CRVO resolved
  - Laser photocoagulation may be necessary for persistent or recurrent edema
  - Longer course and more frequent injections more likely to be necessary for CRVO patients
COPERNICUS Results

- % of patients who gained BCVA of ≥ 15 letters at 6 months
  - 56% of VEGF Trap-Eye
  - 12% of sham group
- Mean gain in visual acuity at 6 months
  - 17 letters in VEGF Trap-Eye
  - 4 letters in sham group
- Secondary outcome - decrease in central retinal thickness at 6 months
  - 457 µm in VEGF Trap-Eye
  - 145 µm in sham group

COPERNICUS Conclusion

- VEGF Trap-Eye (aflibercept injection) results comparable to 0.3 mg and 0.5 mg IVI of Lucentis (ranibizumab)
- VEGF Trap-Eye (aflibercept injection) is another potential medication to improve visual acuity in eyes with macular edema 2° to CRVO

ROVO

- Radial Optic Neurotomy for Central Vein Occlusion
  - Prospective, multicenter trial in Europe, India, and Brazil
- For CRVO management compared
  - Radial optic neurotomy (RON) vs.
  - Intra-vitreal triamcinolone (IVT) vs.
  - Observation
- N = 90

ROVO

- What is Radial Optic Neurotomy?

What does it all mean?

- We continue to look for safe and effective ways to treat our RAO/RVO patients
  - BRVO
    - Grid photocoagulation remains the standard of care for center-involved macular edema 2° to BRVO
    - Lucentis can be considered but may be needed frequently over long period of time to control the edema
  - CRVO
    - Consider triamcinolone, Avastin/Lucentis, VEGF Trap-Eye, and RON for center-involved macular edema 2° to CRVO
    - “Head to head” studies needed to determine which of these therapies is superior
The End