1) Goals/Objectives

Using cases as a framework, review current science behind that evaluation and management of ocular vascular occlusive events, including

- Branch retinal artery occlusion
- Central retinal artery occlusion
- Branch retinal vein occlusion
- Central retinal vein occlusion

2) Case 01 - Branch and Central Retinal Artery Occlusions

27 year old Caucasian male, with no systemic conditions, no medications, no allergies, and 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 OS vision decrease 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 defect OS
- Inferior defects OS
- SLEx – normal
- IOPs - normal
- DFEx and threshold visual fields – see enclosed

Typical profile of patient with vascular occlusions?

- Age
- Sex
- Associated Systemic Disease
- History of Tobacco Use

Etiology of vascular occlusions

- Embolus
  - Cholesterol
  - Calcium
  - Platelet-fibrin
- Thrombosis
- Giant cell arteritis (GCA)
- Other collagen-vascular disease
  - Systemic lupus erythematosus
  - Polyarteritis nodosa
c. Other
e) Polycythemia
f) Multiple myeloma
g) Cryoglobulinemia
h) Waldenström macroglobulinemia
i) Anti-phospholipid syndrome
j) Factor V Leiden
k) Activated protein C resistance
l) Hyperhomocysteinemia
m) Protein C & S deficiency
n) Anti-thrombin II mutation
o) Prothrombin mutation G20210A
p) Trauma
q) Rare
   a. Migraine
   b. Behçet disease
c. Syphilis
d. Sickle cell disease

Additional Testing
a) Patient older than 55
   i. Rule out GCA
      i. ESR
      ii. CRP
      iii. Platelets
   ii. Evaluate blood pressure
   iii. Evaluate blood sugar
      i. Fasting blood sugar (FBS)
      ii. Glycosylated hemoglobin (HA1C)
   iv. Complete blood count with differential (CBC with DIFF)
v. Prothrombin time/activated partial thromboplastin time (PT/PTT)
vi. Evaluate carotid artery - duplex doppler ultra-sonography
vii. Cardiac evaluation
      i. Electrocardiography (ECG)
      ii. Echocardiography
      iii. Holter monitoring
viii. To confirm diagnosis
      i. IVFA
ii. Electro-retinography (mf-ERG)
b) Patient younger than 50
   i. Lipid profile
   ii. Anti-nuclear antibody (ANA)
   iii. Rheumatoid factor (RF)
   iv. Fluorescent treponemal antibody absorbed (FTA-ABS)
   v. Serum protein electrophoresis
   vi. Hemoglobin electrophoresis
   vii. Further evaluation for hyper-coagulable state

Patient Test Results
a) Likely anti-phospholipid syndrome (APS) with high beta-2 glycoprotein I antibodies, IgM
b) Retest recommended in 12 weeks to confirm
c) Recommended anti-coagulant treatment
d) Consider impact of prior chest/neck trauma
   a. Echocardiogram recommended
   b. Carotid doppler recommended
e) Patient saw multiple ECPs and PCPs; lost to follow up.

Management Options
1) None
2) No evidence
   a) Ocular massage
   b) Fundus contact lens
3) Digital
4) IOP reduction
   a) Anterior chamber parencentesis
   b) Acetazolamide 500 mg IV or 500 mg PO
   c) Topical beta-blocker BID
5) Hyper-ventilation
6) Follow up
   a) Refer to family doctor/internist
   b) See again in 1-4 weeks. Rule out…
      i) Neovascularization of the iris (± NVI)
      ii) Neovascularization of the angle (± NVA)
      iii) Neovascularization of the disc (± NVD)
      iv) Neovascularization of the retina (± NVE)
7) If neovascularization
a) Pan-retinal photocoagulation (PRP)
b) Anti-vascular endothelial growth factor (anti-VEGF)

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

3) Case 02 – CRAO and BRVO Case
   A. 65 year old Caucasian male reports for an urgent exam with loss of vision OD x 4 days
   B. LEE: last month but patient refused DFE, “doc said BP 200/160”
   C. Systemic health – no systemic health conditions reported, last physical examination unknown, smokes ~1 pack/day
   D. Systemic medications – none reported
   E. BCVAs - OD 20/400 with eccentric fixation, OS 20/15^2
   F. APD OD
   G. Blood Pressure: 230/120
   H. Confrontation VF: very constricted field OD, FTEF OS
   I. SLEEx - corneal arcus OD, OS
   J. DFEx - See picture OD, Patient refused DFE OS
   K. Dx: Branch and Central Retinal Vein Occlusions

4) Case 03 - BRVO
   A. 65 year old Caucasian male presents for annual eye examination
   B. Systemic conditions - diabetes since 2004, HTN, hyperlipidemia
   C. Systemic medications – Metformin (DM), Lisinopril (HTN), Norvasc (HTN), Doxazosin (HTN), HCTZ (HTN), Lipitor (Cholesterol)
   D. BCVAs - OD 20/40^-1 OS 20/30^-1
   E. No Amsler defects OD, OS
   F. SLEEx
      i) Nuclear sclerosis grade 2+ OD, OS
   G. DFEx
      i) Multiple dot and flame hemorrhages located inferior to macula OD
H. Assessment
   i) 362.36 Branch Retinal Vein Occlusion OD
   ii) 366.16 Cataract, Nuclear Sclerosis OU
I. Plan
   i) Perform OCT and FA to assess leakage
   ii) FA showed mild leakage OD
   iii) Patient scheduled for intra-vitreal injections (IVI) of Avastin (bevacizumab)
J. 1 week post Avastin IVI
   i) "Feel like vision has improved"
   ii) BCVA OD 20/25 (improved from 20/40+)
   iii) Patient received 2 additional Avastin IVI over next 2 months
   iv) BCVA - stable at 20/25

Branch Vein Occlusion Study (BVOS)
I. Is argon laser photocoagulation useful in improving visual acuity in eyes with branch vein occlusion and macular edema reducing vision to 20/40 or worse?
J. Recruited 139 participants
   i. Center-involved macular edema 2° to BRVO
   ii. BCVA of 20/40 or worse
   iii. Divided participants into two equal groups
   iv. Grid photocoagulation
   v. Control
K. BVOS Results
   i. Grid photocoagulation
      i) 65% of eyes gained 2+ lines of visual acuity
      ii) 60% attained visual acuities of 20/40 or better
   ii. Control
      i) 37% of eyes gained 2+ lines of visual acuity
      ii) 34% attained visual acuities of 20/40
L. Established grid photocoagulation as standard therapy for macular edema 2° to BRVO
M. Grid photocoagulation recommended for BRVO when
   i. BCVA 20/40 or worse for 3-18 months and
   ii. FA shows macular edema without foveal heme
N. Other results
   i. Laser significantly reduces likelihood of vitreous hemorrhage
   ii. Perform PRP after the development of neovascularization rather than prophylactically

Central Vein Occlusion Study (CVOS)
O. Recruited 155 participants
Retinal Vascular Occlusions For the Primary Care Clinician
Todd D. Peabody, OD and Jeffrey D. Perotti, OD

i. Center-involved macular edema secondary to CRVO
ii. BCVA 20/50 or worse

P. Results
i. Macular grid laser photocoagulation helped angiographic macular edema
ii. Little effect on BCVA
iii. Established observation as standard therapy for macular edema 2° to CRVO

Other CVOS Results
i. Safe to wait to perform PRP until neovascularization forms
ii. 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 – BRVO (Standard of Care versus Corticosteroid for Retinal Vein Occlusion Study)
A. Examined the effectiveness and safety of grid photocoagulation (standard of care from BVOS) versus intra-vitreal injection of triamcinolone for macular edema 2° to BRVO
B. Recruited 411 participants
   a. Center-involved macular edema secondary to BRVO
   b. ETDRS BCVA approximately 20/40 to 20/400
C. Divided participants into 3 equal groups
   a. Observation or grid photocoagulation per BVOS criteria
   b. 1 mg triamcinolone intra-vitreal injection
   c. 4 mg triamcinolone intra-vitreal injection
D. SCORE – BRVO Results
   a. % of patients who gained ETDRS BCVA of ≥ 15 letters at 12 months
      i. 29% - observation/grid photocoagulation
      ii. 26% - 1 mg triamcinolone IVI
      iii. 27% - 4 mg triamcinolone IVI
E. SCORE – BRVO Other Results through month 12
   a. IOP lowering treatment initiated
      i. 2% - observation/standard treatment
      ii. 7% - 1 mg triamcinolone
      iii. 25% - 4 mg triamcinolone
   b. Cataract onset or progression
      i. 13% - observation/standard treatment
      ii. 25% - 1 mg triamcinolone
      iii. 35% - 4 mg triamcinolone
F. SCORE – BRVO Conclusion
   a. For BRVO with vision loss 2° to center-involved macular edema
   b. Grid photocoagulation remains the standard of care and
c. Grid photocoagulation remains the benchmark against which other treatments are measured

SCORE – CRVO (Standard of Care versus Corticosteroid for Retinal Vein Occlusion Study)

A. Examined the effectiveness and safety of observation (standard of care from CVOS) versus intra-vitreal injection of triamcinolone for macular edema 2° to CRVO

B. Recruited 271 participants
   a. Center-involved macular edema secondary to CRVO
   b. ETDRS BCVA approximately 20/40 to 20/400

C. Divided participants into 3 equal groups
   a. Observation - per CVOS
   b. 1 mg triamcinolone intra-vitreal injection
   c. 4 mg triamcinolone intra-vitreal injection

D. SCORE – CRVO Results

E. % of patients who gained ETDRS BCVA of ≥ 15 letters at 12 months
   a. 7% - observation
   b. 27% - 1 mg triamcinolone IVI
   c. 26% - 4 mg triamcinolone IVI

F. SCORE – CRVO Other Results through Month 12
   a. IOP lowering treatment initiated
      i. 8% - observation
      ii. 20% - 1 mg triamcinolone
      iii. 35% - 4 mg triamcinolone
   b. Cataract onset or progression
      i. 18% - observation
      ii. 26% - 1 mg triamcinolone
      iii. 33% - 4 mg triamcinolone

G. SCORE – CRVO Conclusion
   a. For CRVO with vision loss 2° to macular edema consider 1 mg triamcinolone intra-vitreal injections as an alternative to observation (old standard)

BRAVO (Ranibizumab for the treatment of macular edema following Branch Retinal Vein Occlusion Study)

A. Can Lucentis (ranibizumab), an anti-VEGF agent, increase visual outcome in patients with macular edema secondary to BRVO?

B. Phase 3 clinical trial

C. Recruited 397 participants
   a. Edema in foveal center
   b. ETDRS BCVA from 20/40 to 20/400

D. Divided participants into 3 equal groups
a. Six monthly 0.3 mg Lucentis intra-vitreal injections (IVI)
b. Six monthly 0.5 mg Lucentis intra-vitreal injections (IVI)
c. Six monthly sham intra-vitreal injections (IVI)
E. Rescue laser an option after 3 months
F. BRAVO Results - % of patients who gained ETDRS BCVA of ≥ 15 letters at six months
   a. 55% - monthly 0.3 mg Lucentis IVI
   b. 61% - monthly 0.5 mg Lucentis IVI
   c. 29% - monthly sham IVI
G. BRAVO – Other Results
   a. At 7 days, mean improvement of 7.5 letters in both Lucentis groups
   b. Safety with multiple injections overall good
   c. 1 case of retinal detachment/tear
   d. 1 case of endophthalmitis
H. After initial 6 month results, 6 additional months of monthly observation
I. Lucentis injection triggered if any of the following
   a. BCVA ≤ 20/40
   b. OCT central subfield thickness (CFT) ≥ 250 µm
J. Protocol
   a. 0.3 mg Lucentis IVI group receives 0.3 mg Lucentis
   b. 0.5 mg Lucentis IVI group receives 0.5 mg Lucentis
   c. Sham IVI group receives 0.5 mg Lucentis
K. BRAVO – Conclusion
   a. No direct comparison with BVOS standard of care
   b. At 6 months, mean gain from baseline in BCVA letter scores
      i. 17 in 0.3 mg Lucentis group
      ii. 18 in 0.5 mg Lucentis group
      iii. 7 in sham group
   c. At 12 months, mean gain from baseline in BCVA letter scores
      i. 17 in 0.3 mg Lucentis group
      ii. 19 in 0.5 mg Lucentis group
      iii. 13 in sham/0.5 mg Lucentis group

Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety (CRUISE)
A. Can Lucentis (ranibizumab), an anti-VEGF agent, increase visual outcomes in patients with macular edema secondary to CRVO?
B. Phase 3 clinical trial
   a. Recruited 392 participants
b. Age ≥ 18

c. Foveal center-involved macular edema due to CRVO

d. BCVA from 20/40 to 20/320

C. Divided subjects into three equal groups

a. Six monthly intra-ocular injections of 0.3 mg Lucentis (ranibizumab)

b. Six monthly intra-ocular injections of 0.5 mg Lucentis

c. Six monthly sham injections

D. CRUISE Results - % of patients who gained BCVA of ≥ 15 letters at six months

a. 46% - 0.3 mg monthly Lucentis injection

b. 48% - 0.5 mg monthly Lucentis injection

c. 17% - sham injection

E. Good safety profile

F. CRUISE – Other Results

a. After initial 6 month results, 6 additional months of monthly observation

b. Lucentis injection triggered if any of the following:

i. BCVA ≤ 20/40

ii. OCT central subfield thickness (CFT) ≥ 250 µm

Protocol

i. 0.3 mg Lucentis IVI group receives 0.3 mg Lucentis

ii. 0.5 mg Lucentis IVI group receives 0.5 mg Lucentis

iii. Sham IVI group receives 0.5 mg Lucentis

G. CRUISE - Conclusion

H. At 6 months, sham injection results are similar to CVOS observation arm

I. At 6 months, mean gain from baseline in BCVA letter scores

a. 13 in 0.3 mg Lucentis group

b. 15 in 0.5 mg Lucentis group

c. 1 in sham group

J. At 12 months, mean gain from baseline in BCVA letter scores

a. 14 in 0.3 mg Lucentis group

b. 14 in 0.5 mg Lucentis group

c. 7 in sham/0.5 mg Lucentis group

K. Consider anti-VEGF for treatment of center-involved macular edema 2° to CRVO

HORIZON Study

A. After 12 months of BRAVO and CRUISE, patients followed approximately 14 additional months

B. Examined at baseline and every three months after

C. Lucentis injection triggered if any of the following

a. BCVA ≤ 20/40
b. OCT central subfield thickness (CFT) ≥ 250 µm

D. Protocol
   a. 0.3 mg Lucentis IVI group receives 0.5 mg Lucentis
   b. 0.5 mg Lucentis IVI group receives 0.5 mg Lucentis
   c. Sham IVI group receives 0.5 mg Lucentis

E. HORIZON – BRAVO Group
F. At Horizon baseline, mean gain from baseline in BCVA letter scores
   a. 17 in 0.3 mg/0.5 mg Lucentis group
   b. 19 in 0.5 mg/0.5 mg Lucentis group
   c. 13 in sham/0.5 mg Lucentis group

G. 12 months later, mean gain from baseline in BCVA letter scores
   a. 15 in 0.3 mg/0.5 mg Lucentis group
   b. 18 in 0.5 mg/0.5 mg Lucentis group
   c. 16 in sham/0.5 mg Lucentis group

H. HORIZON – CRUISE Group
I. At Horizon baseline, mean gain from baseline in BCVA letter scores
   a. 15 in 0.3 mg/0.5 mg Lucentis group
   b. 16 in 0.5 mg/0.5 mg Lucentis group
   c. 9 in sham/0.5 mg Lucentis group

J. 12 months later, mean gain from baseline in BCVA letter scores
   a. 8 in 0.3 mg/0.5 mg Lucentis group
   b. 12 in 0.5 mg/0.5 mg Lucentis group
   c. 8 in sham/0.5 mg Lucentis group

K. Long-term Outcomes with Ranibizumab
   Determine the % of Lucentis-treated patients with RVO who had resolution of edema for at least 6 months after last injection
   a. 20 patients with BRVO
   b. 20 patients with CRVO

L. Treated with Lucentis monthly x 3 months and as needed for recurrent/persistent edema

M. If persisted after month 40, patients received scattered and grid photocoagulation

N. Outcome measures:
   a. Change in BCVA and change in area of retinal nonperfusion

O. BRVO Results
   a. 45% had resolution from injections
   b. Mean time 20.2 months
   c. 20% resolved after laser
   d. 20% did not resolve
P. CRVO Results
   a. 25% had resolution from injections
   b. Mean time 14.0 months
   c. 0% resolved after laser
   d. 40% did not resolve
   e. 35% exited prior to resolution

Q. Those who resolved:
   a. Were younger (52.8 vs. 71.6 years old)
   b. Had shorter duration of disease (4.4 vs. 14.4 months)
   c. Had better BCVA

R. Long-term Outcomes with Ranibizumab similar Study – RETAIN
   a. 34 patients with BRVO
   b. 32 patients with CRVO

S. Outcome measures
   a. Mean improvement in BCVA
   b. % of patients with edema resolution

T. Long-term Outcomes with Ranibizumab

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

V. CRVO Results
   a. Mean follow-up of 49.7 months
   b. 44% edema resolution for 6 months after last injection
   c. Last injection was given within 2 years of treatment initiation in 71%
   d. Mean improvement in BCVA 25.2 letters vs. 4.3 letters in unresolved patients
      i. In resolved group, 64.3% had final BCVA of 20/40 or better
      ii. In unresolved group, 27.8% had final BCVA of 20/40 or better

W. Conclusions from both studies

X. Lucentis alone
   a. About 45-50% of patients with BRVO resolved
   b. About 25-44% of patients with CRVO resolved
   c. Laser photocoagulation may be necessary for persistent or recurrent edema
   d. Longer course and more frequent injections more likely to be necessary for CRVO
Copernicus

Looked to assess the efficacy and safety of VEGF Trap-Eye (aflibercept injection) in eyes with macular edema 2° to CRVO

A. Aflibercept
   a. Binds with - and inactivates - VEGF
   b. Thought to have greater binding affinity with VEGF than both bevacizumab and ranibizumab

B. Recruited 189 participants
   a. Macular edema secondary to CRVO
   b. Retinal thickness greater than 250 µm

C. Participants divided into two groups in a 3:2 ratio
   a. VEGF Trap-Eye 2.0 mg IVI every month for 6 months
   b. Sham injection every month for 6 months (equivalent to CVOS observation)

D. After initial 6 months, patients seen monthly for 6 months and received
   a. VEGF Trap-Eye 2.0 mg IVI if retreatment indicated
   b. Sham injection if no retreatment indicated

E. Copernicus Results

F. % of patients who gained BCVA of ≥ 15 letters at 6 months
   a. 56% of VEGF Trap-Eye
   b. 12% of sham group

G. Mean gain in visual acuity at 6 months
   a. 17 letters in VEGF Trap-Eye
   b. -4 letters in sham group

H. Secondary outcome - decrease in central retinal thickness at 6 months
   a. 457 µm in VEGF Trap-Eye
   b. 145 µm in sham group

I. Copernicus Conclusions
   a. VEGF Trap-Eye (aflibercept injection) results comparable to 0.3 mg and 0.5 mg IVI of Lucentis (ranibizumab)
   b. 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

1) Prospective, multicenter trial in Europe, India, and Brazil

2) For CRVO management compared
   a. Radial optic neurotomy (RON) vs.
   b. Intra-vitreal triamcinolone (IVT) vs.
   c. Observation
3) N = 90
4) What is Radial Optic Neurotomy?

5) ROVO Results
   a. RON – 47% showed increase in VA
   b. IVT – 20% showed increase in VA
   c. Placebo – 10% showed increase in VA

5) What does it all mean?
   A. We continue to look for different ways to treat our patients
   B. BRVO
      i. Grid photocoagulation remains the standard of care for center-involved macular edema 2° to BRVO
      ii. Lucentis can be considered but may be needed frequently over long period of time to control the edema
   C. CRVO
      i. Consider triamcinolone, VEGF Trap-Eye, anti-VEGF, and RON for center-involved macular edema 2° to CRVO
   D. “Head to head” studies needed to determine which of these therapies is superior
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