Evolving trends in retinal vascular disease
Instructor: Jessica Steen OD, FAAO

Category: Treatment and Management of Ocular Disease: Posterior Segment

This course will provide an analysis of common retinal vascular diseases including diabetic retinopathy, macular degeneration, and retinal vein occlusion. It will emphasize current and emerging therapies, imaging strategies and trends in treatment and management.

Objectives:
1. Understand the underlying pathophysiology of retinal vascular disease
2. Evaluate key clinical and ancillary testing features of retinal vascular disease
3. Enhance patient care by understanding current and emerging treatments of retinal vascular disease

I. Evolving trends in retinal vascular disease

II. Financial disclosures
   A. None

III. Outline
   A. Pathophysiology review
   B. The era of anti-VEGF
   C. Imaging strategies and treatment trends and developments in
      1. Diabetic retinopathy
      2. Exudative macular degeneration
      3. Retinal vein occlusion

IV. Retinal vascular anatomy and physiology

V. Capillary networks
   A. Superficial capillary plexus
   B. Deep capillary plexus
   C. Radial papillary plexus
      1. Do not anastomose as often as other capillary networks
   D. Capillary structure

VI. Vascular response to insult
   A. After initial vascular insult, only two responses are possible:
      1. 1) Exudation
         a) Edema
         b) Hard exudate
      2. 2) Ischemia
         a) Microaneurysms
         b) Cotton wool spots
         c) Retinal collateral vessel formation
         d) Neovascularization
3. Both responses may occur together

VII. Retinal hemorrhages
A. Flame-shaped hemorrhage
   1. Classically associated with hypertension, although occur in other conditions
   2. Localized hypoxia
      a) Oxygenated arterial blood
B. Dot hemorrhage
   1. Pre-venular capillaries
   2. Typically represent ruptured microaneurysms
   3. Do not leak on fluorescein angiography

VIII. Subretinal hemorrhage
A. Choroidal neovascular membrane

IX. Vascular endothelial growth factor
A. Signaling protein for vasculogenesis and angiogenesis
   1. Secreted by RPE cells, pericytes, astrocytes and endothelial cells
B. Produced in response to ischemia or hypoxia
   1. Leads to neovascularization
   2. Elevated levels found in vitreous samples with PDR

X. Currently available anti-VEGF agents
A. Act to decrease vascular activity
   1. Ranibizumab (Lucentis)
   2. Bevacizumab (Avastin)
   3. Aflibecept (Eyelea)
      a) VEGF trap-inhibits VEGF receptor expression

XI. Diabetic Retinopathy
A. End organ response to systemic disease
   1. Nephropathy, neuropathy, amputation
   2. Precursors to diabetic retinopathy
      a) Insulin resistance and inflammation
   3. End result is tissue damage to metabolically active sites
      a) Retina, kidney, nerves
B. Type 2 diabetes: high incidence of DR at the time of presentation
   1. Annual examination recommended in the absence of diabetic retinopathy
   2. Insulin-dependent type 2 patients are considered to be of higher risk for the development of diabetic retinopathy
C. Type 1: No matter how poorly controlled, typically no retinopathy for 5-7 years
D. Gestational DM
   1. Do not seem to have increased risk of DR, no eye examination during pregnancy

XII. Retinal imaging
A. Color fundus photography
   1. Great for documentation
B. Fundus autofluorescence
   1. Few indications that alter management
C. FA
   1. Evolved to be a test primary of the the retinal periphery
D. ICG
1. Limited availability and utility

E. OCT
1. Currently, the most important ancillary test in retinal disease

F. OCTA
1. Principle based that the only thing that moves in the retina over a period of time are red blood cells
   a) Takes the difference between multiple B scans at the same location to produce a decorrelation signal
2. En face flow information and cross sectional structural information
   a) Not a replacement for FA/OCT
   b) Important in the diagnosis of neovascularization and macular ischemia
3. Clinical uses
   a) Choroidal neovascularization
   b) Diagnosis of retinal vascular disease-mactel type 2, RVO
   c) Diabetic retinopathy
      (1) Identifying microaneurysms
      (2) Macular ischemia
      (3) Confirming the presence of NV
   d) AMD
      (1) Non-exudative lesions in eyes with intermediate AMD

G. Disadvantages of OCTA
1. Static blood flow information
   a) No leakage, pooling or staining
2. Small field of view
   a) 3x3mm, 6x6mm, 8x8mm
   b) Generally reduced resolution with increased field size

XIII. Diabetic Retinopathy
A. Vision loss occurs secondary to:
1. Diabetic macular edema
2. Macular ischemia
3. Proliferative diabetic retinopathy
B. Diabetic Macular Edema
1. Strong association with MAs and hard exudates
2. “Clinically significant diabetic macular edema” as defined by ETDRS
3. Trend has been towards OCT-based definition
   a) Center or non-center involving DME
C. Microaneurysms
1. Early clinical feature of non-proliferative diabetic retinopathy
   a) 12-100 µm
      (1) Those less than approximately 30 µm not typically clinically visible
2. Local weakening and bulging of capillary wall following pericyte loss
D. Intraretinal hemorrhages
1. Rupture of microaneursym, capillary or venule
   a) Dot
   b) Blot
   c) Flame
d) White centered hemorrhage (Roth spot)
   (1) Auto-occlusion if source was a microaneursym
   (2) May represent accumulation of platelets or fibrin

E. Hard exudate
   1. Serum lipoproteins which have leaked from permeable capillaries
      a) Resorbed as a result of mobilization of macrophages
         (1) Permanent plaques may form if resorption fails

F. Diabetic macular ischemia

G. Cotton wool spot
   1. Ischemic event
      a) Disruption of axoplasmic flow in ganglion cell axons and swelling of nerve fibers
         (1) After resolution, cause atrophy of inner retinal nerve fibers and ganglion cells

H. IRMA
   1. Segmental dilation of tortuous capillary channels between arterioles and venules
      a) Indicator of ischemia
      b) May represent intra-retinal neovascularization
         (1) Difficult to differentiate from NV
         (2) Utility of fluorescein angiography

XIV. Monitoring in DM
   A. Fundus photography is useful for documentation, but rarely for diagnosis or treatment evaluation
   B. Fluorescein angiography
      1. Trend is moving away from it on a routine basis
      2. Important prior to focal laser treatment
   C. Trend is to treat based on OCT

XV. Pharmacology in DM
   A. Intravitreal steroids
      1. Ozurdex
         a) Must have an intact posterior capsule
      2. Iluvien
   B. Anti-VEGF
      1. More than 75% of patients with moderately severe of severe NPDR improved over 3 years and almost non progressed to PDR with anti-VEGF treatment (monthly)

XVI. PVD is protective for diabetic retinopathy
   A. Akiba et al. 1990
   B. So is vitrectomy
   C. Why?
      1. Oxygen is easily transported from well-perfused areas to ischemic retinal zones to reduce ischemia and VEGF expression
   D. Development of agents used to induce PVD
      1. ALG-1001 (Luminate)
         a) Anti-angiogenic agent
            (1) Primary effect: blocks receptors on vascular endothelial cells
               (a) Inhibits new vessel growth (neovascularization)
               (b) Secondary effect is vitreolysis
      2. Ocriplasmin (Jetrea)
a) Photopsia, decrease in visual acuity, outer retinal change on OCT

XVII. Brief literature review (because it matters!)

A. DCRR.net
1. Protocol S
   a) 2 year results: Lucentis is non-inferior to PRP in PDR for maintenance of visual acuity in PDR with fewer complications
      (1) PRP vs. Anti-VEGF
         a) PRP is considered the gold standard of DR-related neovascularization
            i) Supported by ETDRS
            ii) PRP associated with increased risk of macular edema initially after treatment

2. Protocol V: “Very good vision”
   a) Center involved DME with good vision (20/25 or better)

3. Protocol I
   a) Lucentis with or without laser for DME in vitrectomized eyes
      (1) Improvement in visual acuity and reduction of central macular thickness over 5 years of follow up

4. Protocol T
   a) Head to head (to head) anti-VEGF comparison
   b) Aflibercept vs. bevacizumab vs. ranibizumab
      (1) All three agents are effective in treatment of DME
      (2) Bevacizumab has greater central thickness-but similar VA after one year
   c) For worse levels of VA (20/50 or worse): Aflibercept showed greatest VA improvement

XVIII. Exudative AMD

A. Types of neovascularization
1. I: subRPE
   a) Less permeable, less actively proliferating
   b) Minimal late leakage on FA
   c) “Occult”

2. II: Has penetrated the BM/RPE complex
   a) Active leakage associated with dye pooling
   b) “Classic”

3. Intraretinal complex
   a) Vascularized activity within the retina with choroidal anastomoses

B. Brief history:
1. ANCHOR & MARINA
   a) Ranibizumab is useful

2. PRONTO
   a) PRN protocol
      (1) OCT and clinical examination are performed once per month
        (a) Is dilation necessary at every visit?
      (2) Inject only if there is a recurrence of fluid or hemorrhage

3. Treat and extend
   a) Once macular fluid is cleared (monthly anti-VEGF injections), extend the interval between treatments by (typically) 2 week increments-as long as macula is dry
(1) Extend the amount of time between visits
(2) Patients are treated on each visit
b) If there is an increase in fluid, shorten the interval
c) OCT guided therapy
(1) Limited role of FA

XIX. Reticular pseudodrusen
A. Abnormal material deposited internal to the RPE on OCT
   1. Visible on FAF, OCT
B. Often found with other hallmarks of AMD
C. May be an indicator to increased progression to late stage AMD-including geographic atrophy

XX. Peripheral exudative hemorrhagic chorioretinopathy
A. Aneurysms-like lesions seen at the margins of vascular networks
   1. Role of ICG
B. Variant of type 1 (occult or sub-RPE) neovascularization

XXI. New targets in AMD therapy
A. Mitochondria
   1. Photoreceptors have high metabolic demand
      a) Dysfunction of lipid and glucose metabolism in photoreceptors may lead to increased VEGF
   2. Mitochondria seem to be affected very early in disease course in drusen formation
B. Complement factors
   1. C5 and C3 inhibition
      a) C5 activation can increase VEGF expression by the RPE
         (1) Currently being investigated in dry AMD and geographic atrophy

XXII. New treatments in AMD therapy
A. Topical squalamine for CNV due to AMD
   1. Squalamine lactate ophthalmic solution
      a) Reduces signaling of VEGF, PDGF (platelet derived growth factor) and basic FGF (fibroblast growth factor)
   2. Will patients use a topical medication BID?
B. Ziv-aflibercept
   1. Variation in osmolarity
C. DARPin
   1. “Designed ankyrin repeat protein”
      a) Small proteins which have high affinity for VEGF-A
D. Combination anti-VEGF/anti-PDGF
   1. Inhibition of PDGF beta results in stripping pericytes from developing new vessels
      a) Capella
      b) Fovista
E. Angiopoietin 2 (Ang-2)
   1. Vascular growth factor
   2. Increased levels of Ang-2 in neovascular AMD and retinal vascular disease
      a) Ang-2 may act with VEGF to cause neovascularization and increase vascular permeability
F. Brolucizumab
1. Anti-VEGF-A
2. Non-inferior to aflibercept in visual acuity improvement
3. May allow extension (12 weeks) of treatment cycle vs. 8 weeks for aflibercept

XXIII. Retinal vein occlusion
A. Branch retinal vein occlusion
B. CRVO
   1. Obstruction of the central retinal vein at the level of the lamina cribrosa
C. HRVO
   1. Anatomic variant of CRVO
   2. Superior or inferior retinal vein blocked at the level of the lamina cribrosa

XXIV. Pathophysiology of RVO
A. Arteriosclerosis
   1. Results in compromise of smaller arteries
   2. Loss of elasticity within the vessel wall
      a) Common adventitia-results in venular compression and turbulent blood flow
         (1) Results in thrombus formation and occlusion
B. Strong association with hypertension
C. Treatment
   1. Anti-VEGF
   2. Intravitreal steroid
      a) Suprachoroidal triamcinolone acetonide with intravitreal aflibercept
      b) Tanzanite trial
         (1) Suprachoroidal space
         (2) Microneedle
         (3) Advantages over intravitreal administration
   3. Observation

XXV. Summary
A. Angiogenesis and exudation are significant causes of vision loss in retinal vascular disease
B. Treatment targets and modalities as well as imaging strategies in retinal vascular disease are rapidly changing
C. Anti-VEGF agents are the current mainstay of treatment in retinal vascular disease
D. Further developments aim to:
   1. Reduce the number of intravitreal injections
   2. Increase time interval between treatments
   3. Develop alternative routes of administration of medications
   4. Reduce cost of treatment
   5. Improve patient quality of life