## Review of Central and Branch Retinal Vein Occlusions: etiology, risks, work-up, and new treatment paradigms (TPA)

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### Introduction

Central retinal vein occlusions (CRVO) affect 0.1% of the population and are a dramatic cause of sudden, painless visual morbidity in our aging society.[1] It is critical to differentiate the subgroups of CRVO, its etiology, management and prognosis. Although CRVO has been recognized since 1855,[2] it is the advent of anti-VEGF therapy in the last decade that has caused a drastic shift in the treatment paradigm of macular edema secondary to vein occlusions.

### Pathophysiology

Central Retinal Vein Occlusions occur as a thrombus forms at the level of the lamina cribrosa secondary to impingement of the central retinal vein by an adjacent atherosclerotic central retinal artery. The hemodynamic changes and turbulence which cause endothelial damage lead to the creation of a thrombus. CRVOs can be broadly categorized into 2 subgroups: a non-ischemic group with better visual potential and an ischemic group with a higher rate of complications.

**Non-ischemic Central Retinal Vein Occlusion** leads to loss of vision better than 20/200 with evidence of diffuse retinal hemorrhages in the four quadrants of the retina, mild capillary nonperfusion and mild angiographic cystoid retinal edema. Few cotton-wool spots may be seen, especially in hypertensive patients. Approximately 10-20% of patients over 65 will progress from a non-ischemic to an ischemic CRVO.[3]

**Ischemic Central Retinal Vein Occlusion** leads to significant vision loss, usually worse than 20/200 along an afferent pupillary defect, diffuse retinal hemorrhages along with more cotton-wool spots, disc edema and angiographic evidence of significant retinal circulation delay and capillary dropout. An ischemic CRVO can usually be shown with an inability to collapse the central retinal vein with digital pressure secondary to a high central retinal vein pressure.[4]

Interestingly neovascularization secondary to a branch retinal vein occlusion occurs more frequently than neovascularization secondary to CRVO. [5] Ischemic CRVO has a 45% chance of leading to neovascular glaucoma.[5]
It is critical to perform an undilated gonioscopic exam as neovascularization of the angle can be present in 12% of cases without any evidence of iris neovascularization.[6]

It is also important to follow patients with non-ischemic CRVO as 34% of initially perfused patients convert to an ischemic CRVO after 3 years.[7] Patients should also be informed of the possibility of a CRVO in the other eye as occurs in 10-15% of cases and the importance of a complete work-up with control of underlying systemic diseases.[8]

### Risks

CRVO occurs equally between men and women and is typically a unilateral disease although 7% of patients who may develop another CRVO in the contralateral eye within 5 years.[3,8] Predisposing factors important in the evaluation of patients with CRVO include a history of glaucoma, hypertension, diabetes

mellitus, homocysteinemia, polycythemia, sickle-cell trait, carotid artery insufficiency and oral contraceptive use among others.[4]

**Evaluation and Work-up**

Evaluation should include an Optical Coherence Tomography scan to determine the degree of macular edema and a fluorescein angiogram to assess the amount of ischemia.

A work-up should be done in consultation with an internist to include a comprehensive medical history and evaluation with attention to the common causes of vasculopathy and hypercoagulopathy.

Further testing should be pursued based on clinical suspicion, especially in patients less than 60 years of age.

**Risks factors associated with retinal vein occlusions:**

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|---|---|
| a) Systemic vascular diseases: hypetension, diabetes mellitus, carotid insufficiency<br>b) Hypercoagulability states: polycythemia, Factor V Leiden, homocysteinemia, abnormality in the fibrinolytic system, protein C/S or antithrombin III deficiencies | c) Neoplastic process leading to hypercoagulable state: lymphoma, leukemia, multiple myeloma<br>d) Drugs: oral contraceptives, cocaine, amphetamine<br>e) Infectious: syphilis, HIV, herpes zoster<br>f) Inflammatory or autoimmune: sarcoidosis, systemic lupus erythematosus<br>g) Traumatic: closed-head trauma<br>h) Ocular diseases: glaucoma, congenital optic disc anomalies,optic disc drusen, thyroid associated orbitopathy, orbital pseudotumor[4] |

**Studies and Treatments**

The CRUISE clinical trial showed that subjects who underwent monthly treatment with intravitreal injections of 0.5 mg ranibizumab gained 14.9 letters compared to 0.8 letter in the untreated group after 6 months.[9] COPERNICUS and GALILEO clinical trials demonstrated the benefits of intravitreal aflibercept (Eylea, Regeneron, Tarrytown, NY) in the treatment of macular edema secondary to CRVO with 55% and 60% gaining 3 lines.[10,11] Although anti-VEGF therapy has become the mainstay of treatment in macular edema, refractory cases still occur as inflammation plays a critical role in its pathophysiology. High levels of VEGF and inflammatory cytokines, including interleukin 6 (IL-6) and IL-8 among others have been found in the aqueous and vitreous of patients with retinal vein occlusions. Inflammatory cytokines play a key role in increasing vascular permeability leading to macular edema.[12]

Prior to the advent of anti-VEGF therapy, steroids played a major role in the treatment of macular edema secondary to CRVO. They continue to be an important treatment in refractory cases of macular edema. However their side profile which include progression of cataract formation and increase in intraocular pressure need to be taken into account. The Standard care vs Corticosteroid for Retinal vein Occlusion (SCORE) study showed improvement in visual loss with both 1 mg and 4 mg intravitreal treatments of triamcilonone with the lower dose having less side effects.[13]

Ozurdex, a sustained-release intravitreal dexamethasone implant was approved by the Food and Drug Administration (FDA) in 2009. A multicenter study that included patients with macular edema secondary to both branch and central retinal vein occlusion showed that patients that received the dexamethasone intravitreal implant had a significant gain in vision.[14] A subgroup analysis of patients with CRVO receiving the 0.7 mg group had an increased rate of ≥15 letters gains when compared to sham (28% versus 7% at 30 days, 29% versus 9% at 60 days). Ocular hypertension developed in 4% of patients that responded to topical therapy in the majority of cases.

The Central Retinal Vein Occlusion Study (CRVOS) showed that in order to prevent neovascular glaucoma, panretinal photocoagulation should be administered if anterior chamber angle neovascularization or two or more clock hours of iris neovascularization develop.[15]

**Branch Retinal Vein Occlusions**

A more common cause of visual morbidity are branch retinal vein occlusions (BRVO) which were found to have a 15-year cumulative incidence of 1.8% and occur equally in men and women mainly above the age of 60.[16] Patients may present with a painless loss of visual field or vision if it affects the macula and may be asymptomatic in cases of peripheral BRVO.

### Pathophysiology
The retinal vein and artery are surrounded by a common adventitial sheath. It is postulated that the compression of the vein by the artery may cause turbulence in the blood flow that in turn damages the endothelial wall resulting in a thrombus and an occlusion. Increase in intralumen venous pressure in turn can cause rupture of its wall leading to intraretinal hemorrhage.Visual morbidity is more commonly secondary to macular edema or ischemia and in some cases from vitreous hemorrhage in the setting of neovascularization.

### Clinical Presentation and Work-up
BRVO can occur in any location of the retina. However, most areseen in the superotemporal quadrant where arteriovenous crossings are the highest.[17] It is characterized by a pattern of intraretinal hemorrhage or cotton-wool spots that encompass part of the area drained by the occluded vein.

In addition to evidence of macular edema on dilated funduscopic examination, an optical coherence tomography (OCT) scan can be taken to evaluate the degree of intraretinal and possible subretinal fluid. Fluorescein angiography allows detection of the degree of ischemia which is critical for visual prognosis and to determine how closely the patient needs to be followed. Patients with an ischemic BRVO (>5 disc diameters of nonperfusion) are more likely to develop neovascularization or a vitreous hemorrhage based on the findings of the Branch Retinal Vein Occlusion Study.[18] Fluorescein angiography typically shows delayed filling of the vein in the area of occlusion with possible areas of capillary dropout or leakage. More chronic cases may have microaneurysms, telangiectatic collateral vessels or evidence of neovascularization.

A work-up is not indicated in patients above the age of 60 with a prior history of hypertension or atherosclerotic diseases unless they have evidence of bilateral BRVO.[19] Patients younger than 60 with a BRVO should be evaluated alongside an internist for hypertension, diabetes or hypercoagulable states that can be infectious, inflammatory or coagulopathies in etiology.

### Studies and Treatments
Laser was the initial treatment modality for macular edema secondary to BRVO. Based on the Branch Retinal Vein Occlusion Study (BRVOS), laser was applied to the areas leakage on FA up to the edge of the foveal avascular zone.[20] Patients gained on average one Snellen line compared to untreated patients. This older studywas accomplished prior to the advent of anti-VEGF therapy, and provided the basis of laser treatment with the recommendation to wait 3 to 6 months, and consider laser photocoagulation treatment if vision is worse or equal to 20/40 in the presence of macular edema.

The advent of anti-VEGF therapy revolutionized the field of retina and provided clinicians with today's first-line therapy for macular edema secondary to BRVO. The BRAnch Retinal Vein Occlusion (BRAVO) study determined that 0.5 mg of monthly intravitreal ranibizumab (Lucentis, Genentech, South San Francisco, CA) provided the best visual outcome with 61.1% gaining ≥ 15 letters compared to 28.8% in the sham group after 6 months.[21]

The SCORE and GENEVA studies already mentioned for CRVO included patients with BRVO as well and showed that steroids were an effective treatment in retinal vein occlusions. However their side effect profile with possible increase in intraocular pressure and progression in cataract need to be taken into account. Steroids are currently mainly used in cases of refractory macular edema to anti-VEGF.[22,13]

### Case studies

### Case 1

## History

A 92-year-old man with a history of hypertension, diabetes mellitus, hypercholesterolemia and dry age-related macular degeneration presented with complaints of painless significant decrease in vision in his left eye and seeing a black spot in the center of his vision for 3 days.

## Examination

Best-corrected visual acuity was 20/30 in the right eye and 20/200 in the left. No relative afferent pupillary defect was noted.Biomicroscopic examination of the anterior segment was unremarkable except for evidence of pseudophakia in both eyes. Intraocular pressure was 12 mmHg in the right eye and 14 mmHg in the left.
Dilated funduscopic examination was significant for a few microaneurysms and arteriovenous nicking in the right eye and extensive intraretinal hemorrhages in all 4 quadrants with significant dilation and tortuosity of veins in the left eye. (image 1: Multicolor fundus photograph)

## Diagnostic Data

Spectralis Optical Coherence Tomography showed significant intraretinal fluid at the fovea with few drusen. (image 2: pre-treatment OCT)
Fluorescein angiography showed a delay in arteriovenous transit time and staining of venous walls along significant blockage of fluorescence from the intraretinal hemorrhages. No significant area of capillary non-perfusion was noted. (image 3: fluorescein angiogram)

## Treatment

Given the significant cystoid macular edema and loss of vision, monthly intravitreal anti-Vascular Endothelial Growth Factor (anti-VEGF) therapy was initiated with bevacizumab.

## Outcome

Foveal intraretinal fluid resolved after 3 intravitreal injections of bevacizumab with vision in the left eye improving to 20/25-3. The factors favoring this outcome were the perfusion status of the retina, as there was no significant area of capillary nonperfusion on the fluorescein angiogram. Based on the CRVOS, 21% of patients with intermediate visual acuity (which was defined as 20/50 to 20/200) improved to better than 20/50. (image 4: post-treatment OCT)

## Case 2
### History

A 58-year-old woman with a history of hypertension, diabetes, hypercholesterolemia and coronary artery disease presented with a complaint of decreased vision and a blind spot in her right eye for the last 2 months.

### Examination

Visual acuity was 20/40-3 with no improvement upon pinhole in the right eye and 20/20 in the left. No relative afferent pupillary defect was noted. Biomicroscopic examination of the anterior segment was unremarkable. Intraocular pressure was 13 mmHg in the right eye and 16 mmHg in the left.
Dilated funduscopic examination was significant for intraretinal hemorrhage of superior retina encompassing area of superior hemiretinal vein draining, with macula edema in the right eye, and arteriovenous nicking in both eyes with few microaneurysms. (image 5: Multicolor fundus photograph)

### Diagnostic Data

Spectralis Optical Coherence Tomography showed significant intraretinal fluid at the fovea. (image 6: Pre-treatment OCT)
Fluorescein angiography showed a mild delay in superior venous filling along some blockage of fluorescence from the intraretinal hemorrhages. Cystoid leakage was noted at the fovea. No significant area of capillary non-perfusion was noted.  Scattered microaneurysms were noted. (image 7: fluorescein angiogram)

### Treatment

Given the significant cystoid macular edema and decrease in vision, monthly intravitreal anti-Vascular Endothelial Growth Factor (anti-VEGF) therapy was initiated with ranibizumab.

**Outcome**

Foveal intraretinal fluid resolved after 2 intravitreal injections of ranibizumab with vision improving to 20/20. The factors favoring this outcome were the perfusion status of the retina as there was no significant area of capillary nonperfusion on the fluorescein angiogram. (image 8: post-treatment OCT)

**Case 3**
**History**

A 78-year-old woman with a history of hypertension, hypercholesterolemia and atrial fibrillation presented with decreased vision in her right eye secondary to a BRVO that occurred 18 months ago. She reported a history of failing anti-VEGF therapy by an outside retina specialist who switched her to _intravitreal steroid treatment for her right eye_. She received her first dexamethasone intravitreal implant (Ozurdex, Allergan, Irvine, CA) 3.5 months prior to presentation. She also reported a distant history of grid laser for a BRVO of the left eye with stable vision.

**Examination**

Visual acuity was 20/100-1 with no improvement upon pinhole in the right eye and 20/40 in the left. No relative afferent pupillary defect was noted. Biomicroscopic examination of the anterior segment was unremarkable. Intraocular pressure was 12 mmHg in the right eye and 11 mmHg in the left.
Dilated funduscopic examination was significant for evidence of an old BRVO in the superior macula with significant edema and cotton-wool spots along an ischemic vein in the right eye, and a grid pattern of laser scars in the macula of her left eye. (image 9: Multicolor fundus photograph of the right eye) (image 10: Multicolor fundus photograph of the left eye)

**Diagnostic Data**

Spectralis Optical Coherence Tomography showed significant intraretinal fluid at the fovea. (image 11: pre-treatment OCT)

**Treatment**

Given the significant cystoid macular edema and decreased vision in the setting of intravitreal anti-VEGF therapy failure, intravitreal dexamethasone treatment was continued for the right eye.

**Outcome**

Foveal intraretinal fluid resolved completely 1 month after intravitreal dexamethasone treatment and vision improved to 20/20 in the right eye. This case shows that intravitreal steroids can be an effective alternative in patients who have macular edema that is refractory to intravitreal anti-VEGF therapy. (image 12: post-treatment OCT)

**Discussion:**

Retinal vein occlusions are a significant cause of visual morbidity as presented by these 3 case studies. Vision is primarily affected by macular edema and retinal ischemia. The treatment of macular edema secondary to retinal vascular diseases has undergone a significant revolution with new treatment algorithms combining anti-VEGF and steroids.

The advent of anti-VEGF therapy in the last decade has replaced the need for laser in most cases of macular edema as it provides an alternative that yields better visual outcomes and no retinal scarring or loss of ellipsoid zone. Refractory cases can still be treated with steroids as they affect other inflammatory pathways.

Subthreshold micropulse laser photocoagulation therapy can also provide another treatment option in the armamentarium of the retina specialist as it spares photoreceptors compared to conventional threshold laser for macular edema.[23] However laser photocoagulation to areas of retinal ischemia continues to play a critical role in cases of neovascularization affecting the retina and anterior segment.

It is an exciting era in the treatment of retinal vein occlusions with a future that may allow combination therapy to be given in extended-release devices.

**Retina Vein Occlusions References**

1. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc. 2000;98:133–41

2. Liebreich R. Ophthalmoskopische Notizen: Ueber die Farbe des Augengrundes. Albrecht Von Graefes Arch Ophthalmol. 1855;1:333–43.

3. Hayreh SS, Zimmerman MB, Podhajsky P. Incidence of various types of retinal vein occlusion and their recurrence and demographic characterisitics. Am J Ophthalmol 1994; 117:429-41

4. Hahn P, Mruthyunjaya P, Fekrat S. Central Retinal Vein Occlusion. In: Ryan SJ, Schachat AP, Sadda SR, editors. Retina. London: Elsevier Saunders; 2013. p. 1039-49

5. Hayreh SS, Rojas P, Podhajsky P, Montague P, Woolson RF. Ocular neovascularization with retinal vascular occlusion-III. Incidence of ocular neovascularization with retinal vein occlusion. Ophthalmology. 1983;90:488-506

6. Browning DJ, Scott AQ, Peterson CB, et al. The risk of missing angle neovascularization by omitting screening gonioscopy in acute central retinal vein occlusion. Ophthalmology 1998; 105:776-784

7. The Central Vein Occlusion Study Group. Natural history and clinical management of central retinal vein occlusion. Arch Ophthalmol. 1997;115:486-491

8. Pollack A, Dottan S, Oliver M. The fellow eye in retinal vein occlusive disease. Ophthalmology. 1989 Jun;96(6):842-5.

9. Brown DM, Campochiaro PA, Singh RP, et al; CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010;117(6):1124-1133

10. Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. Ophthalmology. 2012;119(5):1024-1032

11. Korobelnik JF, Holz FG, Roider J, et. al. Intravitreal aflibercept injection for macular edema resulting from central retinal vein occlusion: one-year results of the phase 3 Galileo study. Ophthalmology. 2014;121(1):202-208

12. Feng, J., Zhao, T., Zhang, Y., Ma, Y., & Jiang, Y. (2013). Differences in aqueous concentrations of cytokines in macular edema secondary to branch and central retinal vein occlusion. PloS one, 8(7), e68149.

13. Ip MS, Scott IU, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. Arch Ophthalmol.2009;127(9):1101-1114

14. Haller JA, Bandello F, Belfort R Jr., et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology. 2010;117(6):1134-1146

15. The Central Vein Occlusion Study Group A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. Ophthalmology. 1995;102:1434–1444

16. Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. Arch Ophthalmol. 2008;126:513–518

17. Feist RM, Ticho BH, Shapiro MJ, Farber M. Branch retinal vein occlusion and quadratic variation in arteriovenous crossings. Am J Ophthalmol. 1992 Jun 15;113(6):664–668

18. The Branch Vein Occlusion Study Group Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion. Arch Ophthalmol. 1986;104:34–41

19. Yuan A, Kaiser P. Branch Vein Occlusion. In: Ryan SJ, Schachat AP, Sadda SR, editors. Retina. London: Elsevier Saunders; 2013. p. 1029-38

20. The Branch Vein Occlusion Study Group Argon laser photocoagulation for macula edema in branch vein occlusion. Am J Ophthalmol. 1984;98:271–282

21. Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study.Ophthalmology. 2010;117(6):1102-1112

22. Scott IU, Ip MS, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. Arch Ophthalmol.2009;127(9):1115-1128

23. Parodi MB, Spasse S, Iacono P, et al. Subthreshold grid laser treatment of macular edema secondary to branch retinal vein occlusion with micropulse infrared (810 nanometer) diode laser. Ophthalmology. 2006 Dec;113(12):2237-42

1) The first-line therapy for macular edema secondary to vein occlusions is?
   a) intravitreal dexamethasone
   b) intravitreal anti-VEGF
   c) intravitreal triamcilonone
   d) grid pattern photocoagulation

2) The following are all possible causes of a CRVO except:
   a) hypertension
   b) lymphoma
   c) asthma
   d) polycythemia vera

3) What is the lifetime risk of getting another CRVO in the fellow eye?
   a) 0-5%
   b) 10-15%
   c) 20-30%
   d) 35-45%

4) What is the most common ocular risk factor for a CRVO?
   a) history of macular degeneration
   b) history of glaucoma
   c) history of retinal detachment
   d) history of uveitis

5) Photocoagulation should be recommended for ischemic CRVO immediately after iris, angle or retinal neovascularization develops. True or False?

6) Neovascularization occurs more often in BRVO than CRVO. True or False?

7) A BRVO in a healthy patient younger than 60 requires a systemic work-up. True or False?

8) BRVO occurs more commonly in which quadrant of the retina?
   a) superonasal
   b) superotemporal
   c) inferotemporal
   d) inferonasal

9) Intravitreal steroid therapy should not be used in cases of macular edema refractory to intravitreal anti-VEGF. True or False?

10) Compression of a branch retinal vein by an artery causes turbulence of the blood flow which in turn damages the endothelial wall and results in a thrombus and occlusion. True or False?