

WHEN TO USE STEROIDS FOR RETINAL VEIN OCCLUSION

Early, late, or never?

BY MARCELO ZAS, MD, PhD



Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy (DR).¹⁻⁵ It can result in vision impairment or blindness if left untreated. Estimates are that 16 million people worldwide are affected by RVO in one or both eyes, and the incidence of RVO is approximately 520 new cases per 1 million annually.¹⁻⁵

The risk of RVO markedly increases with age, with the disease typically occurring in patients older than 50 years.¹⁻⁵

This article reviews current treatment strategies for RVO with steroids, the mechanisms of action of these drugs, and the rationale for their use in the two major entities of RVO presentation: branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO).

BRVO

BRVO (Figures 1 through 3) is more frequent in men than women, with a ratio of 1.2:1.6. In the United States, the 5-year incidence of BRVO is 0.6%; at 15 years, the incidence is 1.8%.⁴ In fact, its incidence is generally higher

than that of CRVO.⁴ It can present in one of two locations: superotemporal (66%) or inferotemporal (30%).⁶ In 7% of cases, the fellow eye can become involved within 4 years.^{7,8}

The natural history of BRVO can be benign; in approximately 55% of cases, final visual acuity is 20/40 or better without treatment. However, depending on three factors—location and extent of the occlusion, integrity of arterial perfusion, and collateral circulation—complications such as macular edema (ME) and neovascularization can appear in 60% and 25% of cases, respectively.



AT A GLANCE

- If left untreated, RVO can result in vision impairment or blindness.
- In the early stage of RVO there are changes in blood flow and to the dynamics of circulation, which generate the release of inflammatory mediators.
- There is no single therapy for all subtypes of RVO. Current treatment centers on prompt control of the inflammatory cascade and avoidance of the potential complications of ME.
- Approved pharmacologic therapy may be considered a first-line option for ME due to BRVO and CRVO.



Figure 1. Acute superotemporal BRVO, left eye.

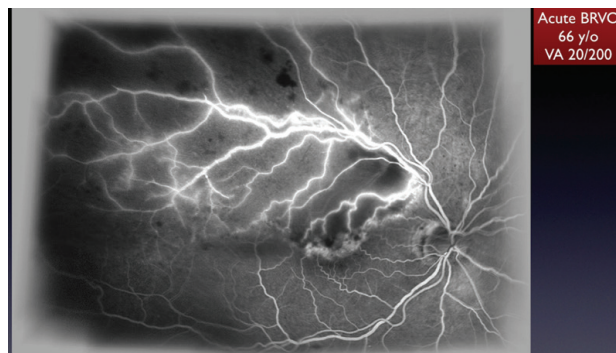


Figure 2. A 66-year-old patient with acute BRVO in the right eye; FA shows capillary closure.

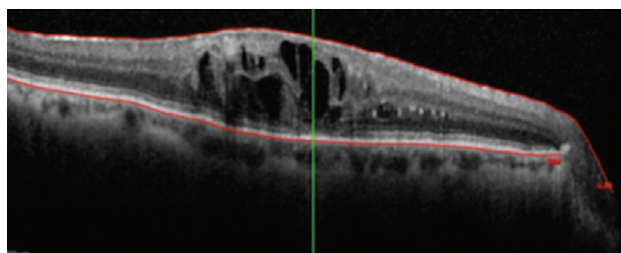


Figure 3. Same patient as seen in Figure 2. OCT shows cystoid macular edema. Visual acuity is 20/200.

CRVO

CRVO (Figures 4 and 5) is less frequent than BRVO, but it can be more severe, with a greater risk of serious complications and vision impairment. Causes can be local (glaucoma), and/or systemic (hematologic abnormalities such as hypercoagulability, among others). The incidence of CRVO is eight per 10,000 per year.^{9,10}

CRVO can take different clinical forms. Nonischemic or venous stasis CRVO (65% of cases) has a 5% risk of associated neovascularization and neovascular glaucoma. Ischemic or hemorrhagic CRVO (30% of cases) has a 40% to 85% risk of associated neovascularization and neovascular glaucoma. CRVO of undetermined cause occurs in 5% of cases, and conversion from nonischemic to ischemic CRVO occurs in 30% of cases.⁷⁻⁹

In some cases, functional tests such as visual acuity, visual field, afferent pupillary defect assessment, and electroretinography, or anatomic tests such as retinal examination and fluorescein angiography (FA) can help to distinguish the clinical form of CRVO.

PATHOPHYSIOLOGY

In the early stage of RVO there are changes in blood flow and in the dynamics of circulation. This generates the release of inflammatory mediators such as interleukin (IL)-1, IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), VEGF, and intracellular adhesion molecule-1 (ICAM-1), causing an increase in vascular permeability, leukocyte infiltration, and tissue remodeling. In the tissues that are the substrate of the inflammation, endothelial malfunction and the development of edema occur. ME can undergo acute or chronic evolution.¹¹

MANAGEMENT OF RVO

There is no single therapy for all subtypes of RVO. Current treatment of RVO centers on prompt control of the inflammatory cascade and avoidance of the potential complications of ME, which can include permanent retinal damage and irreversible vision loss due to cystic degeneration, lamellar macular hole formation, and



Figure 4. Fundus photo of a 70-year-old patient with acute CRVO in the right eye. Visual acuity was 20/200.

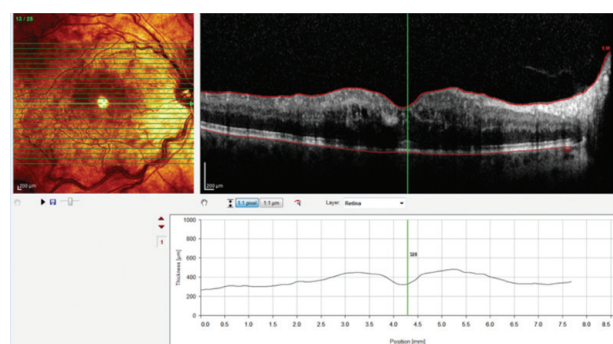


Figure 5. Same patient as seen in Figure 4. OCT shows cystoid macular edema.

epiretinal membrane formation and retinal atrophy.¹² As a consequence, prompt treatment of ME is called for. Four options are available: watchful waiting (ie, observation), pharmacologic therapies, laser photocoagulation, and surgery.

Among pharmacologic therapies, two classes of drug are in common use: anti-VEGF agents and steroids. In comparison with anti-VEGF agents, steroids have the advantage of targeting the three components of the pathophysiology of RVO. They reduce ME through inhibition of multiple inflammatory mediators (in addition to VEGF), they stabilize the blood-retina barrier, and they decrease vascular permeability and edema (Table).

In the real world of clinical retina, there are three options for steroid treatment of RVO: triamcinolone acetonide, dexamethasone, and fluocinolone acetonide.

Triamcinolone Acetonide

Triamcinolone acetonide bolus intravitreal injection is an off-label use of triamcinolone. The optimal dose is unknown. Intravitreal injection of triamcinolone is known to be associated with development of increased intraocular pressure and cataract, and repeated treatment is needed to maintain efficacy.^{22,23}

Dexamethasone

The efficacy of the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) lasts for up to 6 months. It is approved for treatment of ME secondary to BRVO or CRVO by regulators in the European Union, the United States, and other countries worldwide. This implant offers a potent corticosteroid therapy that suppresses inflammation, an important event in the pathophysiology of RVO, by inhibiting key inflammatory mediators that are associated with disease severity. Multiple prospective and retrospective studies have described the morphologic and functional results with the implant, in combination or as monotherapy, and have evaluated the safety and efficacy of this treatment for RVO.^{5,24-30}

Fluocinolone Acetonide

The fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences) is approved by the US Food and Drug Administration for the treatment of diabetic ME, not for ME secondary to RVO. Its use for RVO is an off-label indication.

RVO TREATMENT TIPS: CUSTOMIZE AND DELIVER EARLY

Treatment for RVO must be individualized because there is interindividual variability in presentation. Current treatment for ME secondary to RVO is aimed at the prompt control of the inflammatory cascade and avoidance of

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potential complications. The goal of RVO management is to reduce retinal complications while improving patients' vision and quality of life.

Among the available steroid therapies for RVO, dexamethasone has been shown to lead to significant improvement in BCVA in patients with ME associated with RVO, with similar results in both BRVO and CRVO. Earlier treatment is associated with better visual acuity outcome and is well tolerated. Increases in intraocular pressure return to baseline by 6 months and 1 year, and side effects are similar after a second injection.

Approved pharmacologic therapy may therefore be considered a first-line option for ME due to BRVO and CRVO. Use of the dexamethasone intravitreal implant reduces the number of injections needed when compared with anti-VEGF injections, and it addresses the ME in RVO through multiple mechanisms of action. ■

TABLE: COMPARISON OF THE MECHANISMS OF ACTION OF STEROIDS AND ANTI-VEGF AGENTS

Inflammatory Mediator	Physiologic Role	Steroids Inhibit? (Y/N) ^{19,20}	Anti-VEGF Agents Inhibit? (Y/N) ²¹
ICAM-1	Increased vascular permeability ¹³	Y	N
MCP-1	Increased vascular permeability, altered tight junctions, ¹⁴ increased cell recruitment ¹⁵	Y	N
VEGF	Increased vascular permeability ¹⁶	Y	Y
IL-6	Potentially increased vascular permeability ¹⁷	Y	N
IL-8	Increased vascular permeability, ¹⁴ stimulation of inflammatory proteins ¹⁵	Y	N
TNF-alpha	Increased vascular permeability ¹⁸	Y	N
Abbreviations: ICAM-1, intracellular adhesion molecule-1; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; N, no; TNF, tumor necrosis factor; Y, yes			

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