Central Retinal Vein Occlusion: Current Management Options

Tahir Mahmood

Central retinal vein occlusion (CRVO), a common retinal vascular disorder, remains an important cause of visual loss. Patients generally present with painless visual loss in the affected eye. The clinical appearance typically demonstrates 4 quadrants of intraretinal hemorrhages with dilated and tortuous retinal veins. Macular edema, optic disc edema, and cotton-wool spots may be present to a variable degree. CRVO is broadly divided into 2 clinical subtypes, based on the degree of ischemia: Nonischemic CRVO is typically associated with relatively better vision and a better prognosis for spontaneous visual improvement; ischemic CRVO is typically associated with more profound visual loss on presentation, a relative afferent pupillary defect, and a relatively higher risk for neovascular glaucoma. Nonischemic CRVO may progress to ischemic CRVO, typically within the first 3-9 months.

CRVO generally affects people over age 50 years. Its pathogenesis is uncertain, although constriction of the central retinal vein at the level of the lamina cribrosa has been implicated. Many additional associated risk factors have been proposed, including hyperhomocysteinemia, various coagulation disorders (Protein C deficiency, Protein S deficiency, Anti-thrombin III deficiency, Factor V Leiden deficiency) and inflammatory mediators (C-reactive protein) and vascular factors (Hypertension, Diabetes mellitus). The evidence for these risk factors is not conclusive.

The most common cause of visual loss in patients with CRVO is macular edema. Other causes of visual loss include macular ischemia and neovascular glaucoma. At this time, there is insufficient evidence to support any specific treatment to improve vision in CRVO.

Reported Treatment Options for CRVO

Systemic therapy
- Systemic anticoagulation
- Systemic immunosuppression

Photocoagulation
- Panretinal photocoagulation (PRP)
- Chorioretinal venous anastomosis

Pharmacotherapy
- Intravitreal triamcinolone acetonide/other corticosteroids
- Intravitreal anti-VEGF agents (eg, bevacizumab)
- Pharmacotherapies combined with PRP

Surgical therapy
- Pars plana vitrectomy (PPV) with removal of posterior hyaloid and/or internal limiting membrane
- PPV with radial optic neurotomy/laminar puncture
- PPV with retinal endovascular surgery
- PPV with chorioretinal venous anastomosis

Treatment of CRVO
**Systemic Therapy**

To date, no systemic intervention has been demonstrated to favorably affect the natural history of CRVO. CRVO has been reported in patients receiving chronic, therapeutic levels of warfarin, implying that this medication may be ineffective as prophylaxis. Similarly, other vascular agents, including streptokinase, ticlopidine, and pentoxifylline, have been studied but have not shown significant efficacy. Treatment with systemic tissue plasminogen activator (tPA) was reported in 96 patients, of whom 42% gained 3 or more lines of vision but 1 died of stroke. Many investigators have attempted treatment with hemodilution without convincing efficacy.

Due to the suspected inflammatory association, several authors have attempted treatment with various immunosuppressive agents, particularly in younger patients. These have included systemic corticosteroids, cyclosporine, azathioprine, and alemtuzumab. Results to date are inconclusive.

**Photocoagulation**

The Central Vein Occlusion Study (CVOS) was a randomized clinical trial that found that macular grid photocoagulation did not improve visual acuity in patients with nonischemic CRVO. In this study, final median visual acuity was 20/200 in treated eyes and 20/160 in control eyes. In eyes with at least 10 disc areas of retinal capillary nonperfusion, prophylactic scatter photocoagulation did not prevent the development of anterior segment neovascularization. The CVOS concluded that it was safe to observe these eyes until early neovascularization of the iris or angle developed. Neovascularization regressed after treatment in 56% of photocoagulation-naive eyes and 22% of eyes treated previously with scatter photocoagulation.

Laser-induced chorioretinal venous anastomosis has been proposed to reduce macular edema and improve vision. In a recent report using combinations of wavelengths, anatomic success was achieved in up to 77% of cases. Among eyes in which an anastomosis was achieved, visual acuity improved 2 or more lines 82% of the time. Other investigators, however, have reported significant complications with this technique, including vitreous hemorrhage and choroidal neovascularization.

**Pharmacologic Therapy**

There are currently no US Food and Drug Administration (FDA)-approved pharmacologic therapies for CRVO, but in the last several years triamcinolone and bevacizumab are used for CRVO. Although there are no randomized, controlled trials confirming their efficacy and safety, there have been a significant number of case series suggesting promise. Triamcinolone acetonide is a corticosteroid that, in addition to its anti-inflammatory effects, may cause downregulation of vascular endothelial growth factor (VEGF). Bevacizumab is a full-length recombinant humanized antibody, active against VEGF, and approved for use in colorectal cancer. In several case series both triamcinolone and bevacizumab were reported to improve macular edema associated with CRVO, at least in the short term. In addition, bevacizumab appears to have activity against anterior segment neovascularization. Therefore, either triamcinolone or bevacizumab may be effective to treat complications of nonischemic CRVO, while bevacizumab may be effective to treat complications of ischemic CRVO as well.

Intravitreal triamcinolone has also been administered for posterior segment diseases as exudative age-related macular degeneration (AMD), diabetic macular edema, pseudophakic macular edema, and cystoid macular edema due to other causes, such as uveitis.

Major risks of intravitreal triamcinolone include cataract progression, elevation of intraocular pressure (IOP), and endophthalmitis. Intravitreal triamcinolone may cause visually significant cataract in about half of treated eyes within 1 year. Elevation of IOP to 24 mm Hg occurs in about 40% of patients, typically within about 3 months. Elevated IOP in response to intravitreal triamcinolone may be severe or intractable, leading to glaucoma surgery in some patients. The incidence of endophthalmitis following intravitreal triamcinolone has been estimated to be between 0.099% and 0.87% per injection. Pseudoendophthalmitis, which may be caused by migration of triamcinolone particles into the anterior chamber or an inflammatory reaction to the drug or a component in the vehicle of the drug, has also been reported.

Peribulbar, rather than intravitreal, triamcinolone acetonide appears to confer a lower risk for endophthalmitis and perhaps other complications, although intractable glaucoma requiring trabeculectomy has been reported following treatment with peribulbar triamcinolone for CRVO.
The use of anti-VEGF agents in retinal disease has become increasingly common since the approval of pegaptanib and ranibizumab for AMD in 2004 and 2006, respectively. These agents are currently being studied for efficacy against macular edema due to CRVO. The anti-VEGF agent that is most studied in regard to CRVO is bevacizumab. Intravitreal injection of bevacizumab was first reported as a potential therapy for macular edema secondary to CRVO in 2005.

Recurrence macular edema may occur in patients with CRVO following treatment with bevacizumab; in some cases, the recurrent macular edema may be more severe than the pretreatment macular edema ("rebound" macular edema). Bevacizumab does not appear to increase the risk for IOP elevation or cataract progression. The incidence of endophthalmitis following intravitreal bevacizumab injection has been reported at 0.014% per injection.

Intravitreal tPA has been studied, with mixed results. Several studies reported improvement in visual acuity in some patients with CRVO, although other investigators reported no significant benefit.

Surgical Therapy
Pars plana vitrectomy (PPV) - which involves not only removal of the vitreous but also removal of the posterior hyaloid and/or internal limiting membrane - has been associated with improvement in vision in 60% to 79% of patients in small, nonrandomized series of both ischemic and nonischemic CRVO.

Radial optic neurotomy (RON) represents an attempt to treat the proposed constriction of the central retinal vein at the level of the lamina cribrosa. RON has been reported to have favorable anatomic and visual outcomes in several nonrandomized series. Combining RON with intravitreal triamcinolone does not appear to improve outcomes over RON without intravitreal triamcinolone. Better visual results appear correlated with younger age (under 50 years). Major adverse events include visual field loss and, rarely, significant intraocular hemorrhage or central retinal artery occlusion. A related procedure, lamina puncture, was not shown to be effective in patients with CRVO.

Retinal endovascular surgery (REVS) involves PPV, followed by cannulation of a branch retinal vein and infusion of tPA. The procedure has been reported to improve vision by 3 or more lines in 54% to 72% of patients with nonischemic CRVO, but does not appear effective for patients with ischemic CRVO.

An alternative surgical approach is PPV with creation of a chorioretinal venous anastomosis using a microvitreoretinal blade, sometimes followed by placement of suture material to stimulate vascularization. This technique was reported to improve vision in 60% to 80% of patients in 2 small, nonrandomized series.

GUIDELINES FOR TREATMENT
Diagnosis
I. Complete ophthalmic examination
   a. Special attention to the presence of neovascularization of the iris (NVI) or neovascularization of the angle (NVA), including gonioscopy.
II. Consider fundus photography, fluorescein angiography, and/or optical coherence tomography (OCT)

Treatment
I. Ischemic CRVO
   a. If NVA or at least 2 clock-hours of NVI are present, consider panretinal photocoagulation (PRP)
   b. If unable to perform PRP (corneal edema, poor papillary dilation, media opacity), consider intravitreal injection of anti-VEGF agent (such as bevacizumab)
II. Nonischemic CRVO
   a. If significant macular edema, consider intravitreal injection of triamcinolone acetonide or bevacizumab

Follow-up
I. Follow-up examinations, including gonioscopy, for 6-9 months following CRVO
II. OCT if monitoring treatment of macular edema

While there is no proven treatment for macular edema associated with CRVO to date, patients with nonischemic CRVO and visual loss due to macular edema may be considered for treatment with either intravitreal triamcinolone or intravitreal bevacizumab. Patients with ischemic CRVO and signs of anterior segment neovascularization are managed with scatter photocoagulation, with or without adjunctive intravitreal bevacizumab.
REFERENCES