Update and review of central retinal vein occlusion
Nikolas J.S. London and Gary Brown

Retina Service, Wills Eye Institute, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Correspondence to Nikolas J.S. London, MD, Wills Eye Institute, 840 Walnut Street, Suite 1020, Philadelphia, PA 19107, USA
Tel: +1 215 928 3300; fax: +1 215 825 2443;
e-mail: nik.london@gmail.com

Purpose of review
To review the clinical picture of central retinal vein occlusion (CRVO), with an emphasis on recent therapeutic developments.

Recent findings
The most significant advances with regard to CRVO relate to the establishment of the important role of intravitreal anti-vascular endothelial growth factor and corticosteroids in the treatment of macular edema associated with vein occlusion.

Summary
Important objectives on evaluation of a patient presenting with a CRVO include differentiation between ischemic and nonischemic types, identification of any complications, and establishment of a treatment and/or follow-up plan. Macular edema is one of the main causes of vision loss in CRVO, and for the first time we can have effective treatment options for affected patients.

Keywords
anti-vascular endothelial growth factor, ischemic, macular edema, nonischemic, vascular

Introduction

Central retinal vein occlusion (CRVO) is common retinal vascular disorder [1–3], and a frequent cause of visual morbidity in patients older than 50 years [4]. The 4-year incidence of retinal vein occlusion (RVO) is estimated to be 5/1000 persons aged 65 and older [5]. Although most patients with CRVO are over the age of 50, it can occur in younger patients, commonly termed papillophlebitis. Younger patients frequently have an associated inflammatory cause [6] or coagulopathy [7,8], and deserve particular attention.

Clinical features

CRVO is often a fairly straightforward diagnosis. Patient interview may reveal one or more associated risk factors, including systemic hypertension, diabetes mellitus, and open angle glaucoma [9,10]. Less frequently, patients will have a known coagulopathy [11]. Patients most often present on an urgent basis for sudden, unilateral, painless loss of vision, commonly noticed upon waking. Visual acuity is typically better than 20/200 in cases of nonischemic CRVO, and is 20/400 or worse in cases of ischemic CRVO. It is important to note the presence of an afferent pupillary defect, which is more consistent with an ischemic CRVO. The slit lamp examination is typically unremarkable in acute cases, whereas the fundoscopic examination is striking. A CRVO is characterized by what is often called a 'blood and thunder' appearance with extensive, widespread intraretinal hemorrhages radiating from the optic nerve head, and dilated and tortuous retinal veins (Fig. 1). The retinal hemorrhages may be superficial and flame-shaped, or deeper and dot-blot, and are often a combination of the two. Cotton-wool spots may be present, as well as edema of the optic nerve head and/or macula. Breakthrough vitreous hemorrhage may be present. In chronic cases, collateral vessels can develop on the optic nerve head, and are seen as a positive prognostic sign indicating compensatory perfusion.

Differential diagnosis

Although not always a necessary consideration, the differential diagnosis of CRVO includes ocular ischemic syndrome (OIS), hyperviscosity syndromes (e.g. polycythemia vera, sickle cell disease, leukemia, and multiple myeloma), severe anemia, and advanced hypertensive retinopathy. OIS is probably the most relevant consideration, and is typically associated with mid-peripheral blot-like hemorrhages, iris neovascularization, and ocular pain. OIS is associated with decreased arterial perfusion, a simple test for which consists of applying light digital pressure on the globe and looking for central retinal artery pulsations. Systemic conditions, on the other hand, commonly produce bilateral findings.

Perfusion status

CRVO is classified into two clinical types, and it is important to differentiate between the more common nonischemic CRVO and the less common ischemic CRVO [12,13]. Nonischemic CRVO accounts for approximately 75% of all cases, and is typically associated with less severe retinal findings, better visual acuity, the lack of an afferent pupillary defect, and a lack of cotton-wool spots [14,15]. The Central Vein Occlusion Study (CVOS) classified CRVOs into perfused, nonperfused, or indeterminate, based on the amount of amount of retinal nonperfusion on wide-field intravenous fluorescein angiography (IVFA) [14]. A CRVO was called perfused if there were fewer than 10 disc areas of retinal capillary nonperfusion. In contrast, ischemic CRVOs demonstrate more severe findings with extensive hemorrhages, cotton-wool spots, and edema of the macula and optic nerve head. Patients commonly have visual acuity worse than 20/400 as well as an afferent pupillary defect. IVFA reveals 10 or more disc areas of retinal nonperfusion. If the amount of retinal hemorrhage is extensive, it may be

Key points

- Central retinal vein occlusion is a common and dramatic cause of visual loss.
- Risk factors include age, systemic hypertension, open angle glaucoma, and diabetes mellitus.
- In younger patients, inflammatory causes and coagulopathy are considered.
- First-line management for macular includes monthly intravitreal anti-vascular endothelial growth factor injections.

difficult to determine the disc areas of angiographic nonperfusion. Such cases are often labeled 'indeterminate'. Whereas most practitioners go by the criteria described by the CVOS, the means of distinguishing between nonischemic and ischemic CRVO is somewhat controversial. Other methods include Goldmann perimetry in which eyes with nonischemic CRVO more frequently can see the I-2e target whereas eyes which see only the V-4e target or worse are likely ischemic, and electroretinography (ERG) in which eyes with an

Figure 1 Fundus photograph and fluorescein angiogram images
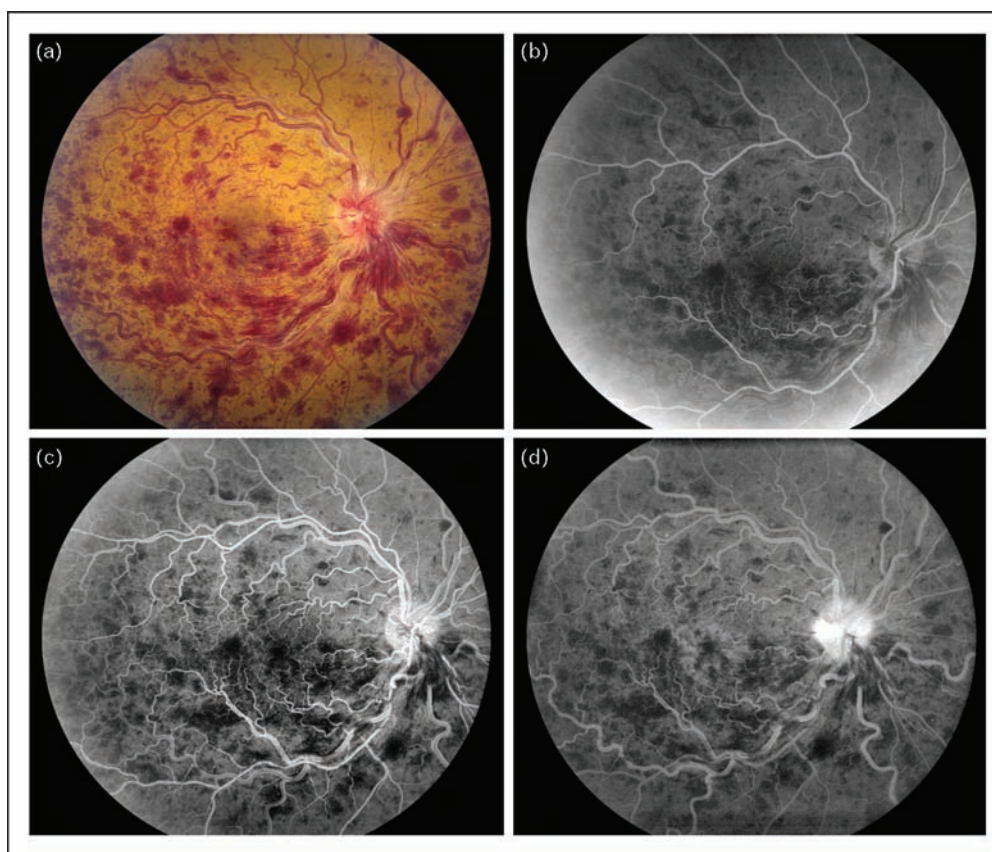
(a) Color fundus photograph and (b) early-phase, (c) mid-phase, and (d) late-phase fluorescein angiogram images of a patient with a central retinal vein occlusion. Note the diffuse intraretinal hemorrhages in all four quadrants, erythema and edema of the optic nerve head, dilated and tortuous retinal veins, and late cystoid leakage in the angiogram, consistent with macular edema. This figure shows a 68-year-old woman presenting with a visual acuity of count fingers at 6 ft.

ischemic often have a b-wave amplitude less than 60% of normal [13,16]. However, these modalities are rarely necessary to distinguish between CRVO types.

The distinction between ischemic and nonischemic CRVO is particularly important for patient counseling regarding the prognosis. Eyes with nonischemic CRVO do substantially better than eyes with ischemic CRVO with better visual outcomes. Although both types may develop macular edema, it is typically more severe and less responsive to treatment in ischemic CRVO. Moreover, only ischemic CRVOs are at risk for the development of one of the most devastating complications, rubeosis and neovascular glaucoma. Notably, however, in the CVOS approximately one-third of eyes that were initially labeled nonischemic converted to an ischemic CRVO at 3 years [17], termed an 'ischemic transformation'. This condition was most often seen in the first 4 months of follow-up [15,17].

Complications and causes of vision loss
The vast majority of vision loss associated with CRVO results from the main complications, macular edema and intraocular neovascularization. Macular edema results in vascular damage and is present to some degree in nearly all cases of CRVO. CRVO-associated macular edema can often be easily identified on clinical exam, and should be further documented and quantified using intravenous IVFA (Fig. 1b–d) and optical coherence tomography (OCT, Fig. 2). Recent recognition of the utility of intraocular anti-vascular endothelial growth factor (VEGF) has made the documentation of baseline macular edema even more important. Persistent macular edema can lead to profound, permanent loss of vision.

The more dramatic complication associated with CRVO is the development of intraocular neovascularization. Eyes with ischemic CRVO may develop neovascularization of the iris or angle, which may in turn lead to the development of neovascular glaucoma. There is a direct correlation between the severity of ischemia and the risk of developing neovascularization. In the CVOS, anterior segment neovascularization was defined as 2 or more clock hours of iris neovascularization or any angle neovascularization [15]. This condition developed in 16% of eyes with 10–29 disc areas of retinal nonperfusion, and in over half (52%) of eyes with 75 or more disc areas of nonperfusion [15]. Retinal or optic nerve head neovascularization is rare. It is important to differentiate between optic nerve head neovascularization and collaterals. Collaterals are compensatory channels that develop to provide blood supply from the choroidal or pial circulation to obstructed vessels on the nerve head. They appear as tortuous loops as opposed to a lacy frond of neovascular tissue, and typically do not leak on IVFA.

Figure 2 Fundus photographs and corresponding horizontal optical coherence tomography images
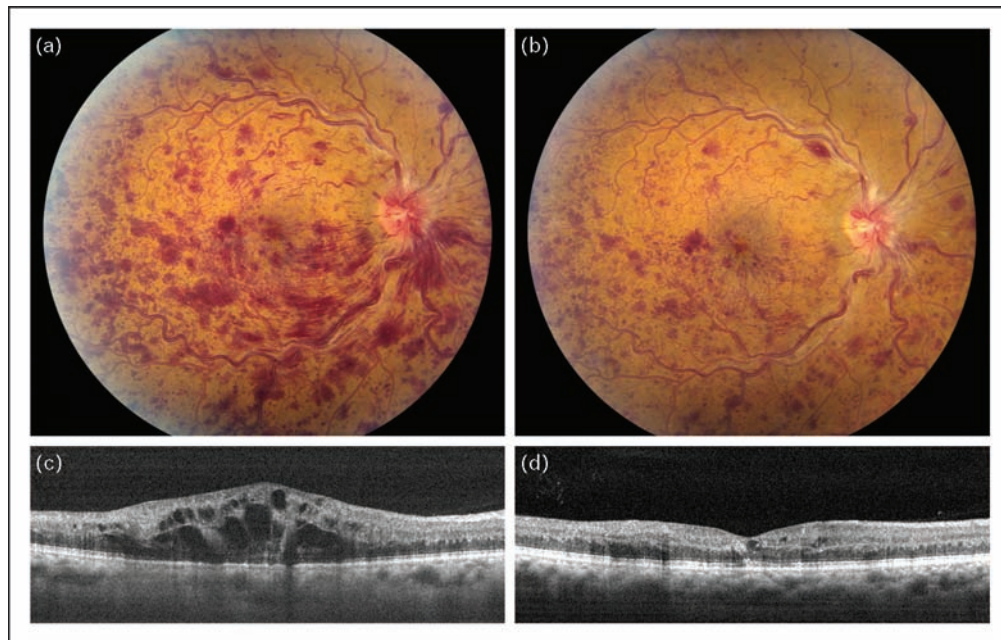
Color fundus photographs and corresponding horizontal OCT images of the same patient depicted in Fig. 1 at presentation (a and c) and 1 month later. The patient received an intravitreal injection of bevacizumab on presentation. Note the dramatic resolution of intraretinal hemorrhages (b) as well as intraretinal edema (d). Her visual acuity improved from count fingers at 6 feet at baseline to 20/100 at 1 month. OCT, optical coherence tomography.

Other causes of vision loss include epiretinal membrane formation and optic atrophy.

Pathophysiology

CRVO is believed to result from thrombotic occlusion of the central retinal vein at or just posterior to the lamina cribrosa [18]. The pathogenesis of this disease is not fully understood, is likely multifactorial, and varies according to the clinical scenario. At the lamina cribrosa, the central retinal vein and artery share a common adventitial sheath and any atherosclerotic change in the artery may result in a narrowing of the venous lumen. This is in addition to the baseline narrowing associated with passage through the lamina. Glaucomatous cupping, nerve head swelling, and orbital disorders may also contribute to mechanical compression of the vein. Additionally, hemodynamic abnormalities may also increase the risk of thrombus formation [19].

Whatever the cause, occlusion of the central retinal vein results in increased intravascular pressure, reduced retinal blood flow, and retinal ischemia. Retinal ischemia, in turn, leads to the production of inflammatory mediators, including VEGF, which increase capillary permeability and promote neovascularization.

Work-up and diagnosis

After a thorough history, paying particular attention to the duration of vision loss, presence of risk factors, and previous interventions, all patients should undergo a complete ocular examination, including visual acuity, intraocular pressure (IOP), pupillary reactions, undilated examination of the iris, gonioscopy, slit lamp examination of the anterior and posterior segments, and indirect examination of the posterior segment. Although often overlooked, gonioscopy is an important part of the examination [20]. Possible findings have been discussed above.

Most cases are easily diagnosed upon history and examination, and do not require further diagnostic evaluation. Patients under the age of 50 years, however, more commonly have an inflammatory or coagulopathic association which warrants a basic work-up including a complete blood count, lipid profile, basic metabolic panel, fasting serum glucose and/or glucose tolerance test, serum protein electrophoresis, and syphilis serologies. Work-up for a coagulopathy may include activated protein C resistance, lupus anticoagulant, antithrombin III, prothrombin 20210 gene mutation, protein C, protein S, and anticardiolipin antibodies.

In addition to examination findings, IVFA is important to help differentiate between ischemic and nonischemic CRVO. In cases with substantial retinal hemorrhage, IVFA may reveal little information. Such cases should be assumed to be ischemic until proven otherwise.

OCT is important to obtain in all patients where treatment is being considered. Most cases of CRVO are associated with some degree of macular edema. OCT enables you to document even subtle edema and to follow resolution with treatment.

Electroretinography is not typically obtained, but may be considered when the type of CRVO is in doubt and differentiation is desired. As CRVO primarily affects the circulation of the inner retina, the b-wave amplitude is decreased relative to that of the a-wave [13].

Management

CRVO treatment regimens are more directed toward the complications, if present, than toward the vein occlusion itself. It is important, however, to counsel patients on the importance of minimizing risk factors in order to minimize the risk of vein occlusion in the same or fellow eye. This includes appropriate management of open angle glaucoma, hypertension, and any underlying inflammatory disorder or coagulopathy. Treatment for the typical patient is variably advocated, and may include a daily aspirin, systemic anticoagulation, anti-inflammatory agents, isovolemic hemodilution [21,22], and plasmapheresis. Along with risk factor reduction, most providers advise a daily aspirin along with a healthy diet and daily exercise. During treatment, patients are typically followed on a 4–6-week basis, depending on the treatment modality as well as the clinical course.

Recent progress has drastically changed the management of macular edema associated with CRVO. On the basis of the recently published results of the SCORE and CRUISE trials, intravitreal anti-VEGF agents have been established as the front-line therapy for the treatment of macular edema associated with CRVO (Fig. 2) [23••,24•], followed by intravitreal triamcinolone acetonide [25••,26]. The newest addition to the armamentarium, the dexamethasone sustained-release implant (Allergan Inc., Irvine, California, USA) also shows promise in particular scenarios [27•]. These trials will be reviewed in detail.

CRUISE

CRUISE (Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety) compared ranibizumab with sham in patients with macular edema secondary to CRVO [23••]. In CRUISE, 392 patients were randomized to 6 monthly injections of ranibizumab 0.3 mg, ranibizumab 0.5 mg, or sham. Ranibizumab-treated patients fared significantly better than sham-treated patients, gaining an average of nearly three lines of visual

acuity at 6 months compared with less than a single letter. Adverse events were uncommon. Bevacizumab was not studied in CRUISE, but is felt to have similar efficacy.

In clinical practice, intravitreal anti-VEGF injections are the first-line of treatment offered to patients with macular edema associated with CRVO. The best treatment regimen has not been established. Many providers give a series of monthly injections until edema is resolved (a minimum of 3), followed by either as needed treatment as indicated by the reappearance of macular edema, a drop in visual acuity, or the development of neovascularization. The clinical effectiveness of a treat-and-extend compared with as-needed treatment is currently being investigated.

SCORE
The Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) trial was a phase III multicenter clinical trial that compared IVTA with the current standard of care (observation) for patients with macular edema associated with CRVO ($n = 271$) [25$^{\bullet\bullet}$]. Patients treated with IVTA were five times more likely to regain substantial vision after 1 year. At month 12, 7% of patients in the observation arm gained 15 or more ETDRS letters, compared with 27%, and 26% in the 1 and 4 mg IVTA groups, respectively. Interestingly, the rates of elevated IOP and cataract were similar for the observation and 1 mg groups, but higher in the 4 mg group.

In clinical practice, IVTA is a second-line agent, typically reserved for anti-VEGF nonresponders, for uninsured patients who cannot afford bevacizumab, or for those seeking a longer interval between injections. IVTA lasts on the order of 3 months, where bevacizumab is typically repeated every 6 weeks and ranibizumab is repeated every 4 weeks. IVTA is relatively contraindicated in patients with preexisting glaucoma because of the possibility of steroid-induced ocular hypertension, as well as in phakic patients because of the concern regarding the acceleration of cataract formation.

Ozurdex
The newest intravitreal option is the dexamethasone drug-delivery system (dex-DDS) marked by Allergan (Irvine, California, USA). The dex-DDS was recently approved by the FDA for the treatment of macular edema associated with retinal vein occlusion, based on the results of two simultaneous phase III trials [27$^{\bullet}$]. The trials enrolled 1267 patients with best-corrected visual acuity (BCVA) between 20/50 and 20/200 secondary to chronic intraretinal edema. In the 6-month primary phase, patients were randomized 1:1:1 to receive either a 700-μg dexamethasone implant ($n = 427$), a 350-μg dexamethasone implant ($n = 412$), or a sham injection ($n = 423$). Baseline and demographic characteristics were

similar for each of the groups. The dex-DDS produced significantly greater and more rapid improvement in vision compared with sham treatment. Compared with sham, patients treated with the dex-DDS experienced a three-line gain in BCVA by day 60 in 29% of patients compared with 11% of sham-treated patients ($P < 0.001$). The gain in acuity peaked at month 2 with nearly 30% of patients in the dexamethasone-treated groups gaining three or more lines compared with only 11% of sham-treated patients ($P < 0.001$). This difference between the dexamethasone and sham-treated groups persisted through month 3. For the most part, the dex-DDS was well tolerated.

In clinical practice, the dex-DDS is used infrequently. The general impression is that the benefits of the implant do not outweigh its high cost (approximately US$ 2000), particularly given a comparable duration of action comparable with intravitreal triamcinolone acetate (IVTA). The dex-DDS may hold promise in vitrectomized eyes where the clearance of other medications is relatively rapid. Other potential scenarios include use in patients with severe disease and/or in combination with other therapies.

Laser photocoagulation
The CVOS showed us that macular grid photocoagulation is not indicated for eyes with macular edema associated with CRVO [14,17]. Although effective in reducing angiographic edema, grid laser did not improve final visual outcome.

Panretinal laser photocoagulation (PRP) is useful for the treatment of neovascular complications associated with CRVO. However, the CVOS demonstrated that prophylactic PRP is not indicated and instead PRP should be administered after the onset of iris neovascularization to prevent neovascular glaucoma [14,15,17].

Surgical intervention
A variety of surgical approaches for the treatment of CRVO have been described, including chorioretinal venous anastomosis formation [28$^{\bullet}$,29–32], radial optic neurotomy [33–36,37$^{\bullet}$], and pars plana vitrectomy [38–40]. These approaches have met with variable success and do not have a prominent role in the management of CRVO. In the event of a nonclearing vitreous hemorrhage, pars plana vitrectomy may be offered [41].

Follow-up
Follow-up is variable depending upon the clinical scenario and treatment regimen. In general, all eyes with ischemic or indeterminate CRVO are followed monthly for at least 6 months, monitoring for the development of neovascularization. These patients should be monitored with undilated slit lamp examination and gonioscopy at each visit. Patients with very good initial visual acuity

($\geq$20/40) can be seen every 2 months for 6 months, and then yearly. Patients with acuity between 20/50 and 20/200 should be seen monthly for 6 months, increasing the interval between visits based on the clinical scenario. Any patient who experiences a significant visual decline should be monitored more closely. One exception to the above follow-up schedule regards patients being treated with intravitreal bevacizumab, who may be seen at 6-week intervals, if that is their treatment interval.

Conclusion

CRVO is an important case of visual loss, particularly in elderly patients with one or more risk factors. Both the symptoms and clinical picture can be dramatic, and the analogy made to patients is often that of a 'stroke' in the eye. Whether or not this analogy is appropriate, it underscores the unheralded, sudden nature of its onset, as well as the emotional impact on the patient. Although we still cannot predict, prevent, or directly treat CRVO with great clinical effect, we are fortunate to have recently gained several powerful means of treating the vision-threatening complications. In particular, anti-VEGF medications have drastically changed the visual outcome for affected patients. The future holds great promise as the most effective treatment regimens, modalities, and combinations of modalities are discovered.

Acknowledgements

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