Optimal Treatment of Retinal Vein Occlusion: Canadian Expert Consensus

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\textbf{Key Words}
Retinal vein occlusion \cdot Neovascularization \cdot Retina \cdot Laser \cdot Vascular endothelial growth factor \cdot Algorithms \cdot Canadian expert consensus

\textbf{Abstract}
Background: The availability of new therapeutic approaches, particularly intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapies, has prompted significant changes to the established treatment paradigms for retinal vein occlusion (RVO). Better visual outcomes and significantly lower rates of adverse events have been noted in multiple large randomized clinical trials and have led to a new standard of care for this sight-threatening condition. \textbf{Objective:} To develop an expert consensus for the management of RVO and associated complications in the context of recent clinical evidence. \textbf{Methods:} The development of a Canadian expert consensus for optimal treatment began with a review of clinical evidence, daily practice, and existing treatment guidelines and algorithms. The expert clinicians (11 Canadian retina specialists) met on February 1, 2014, in Toronto to discuss their findings and to propose strategies for consensus. \textbf{Results:} The result of this expert panel is a consensus proposal for Canadian ophthalmologists and retina specialists treating patients presenting with RVO. Treatment algorithms specific to branch and central RVO (BRVO and CRVO) were also developed. \textbf{Conclusions:} The consensus provides guidelines to aid clinicians in managing RVO and associated complications in their daily practice. In summary, laser remains the therapy of choice when neovascularization secondary to RVO is detected. Adjunctive anti-VEGF could be considered in managing neovascularization secondary to RVO in cases of vitreous hemorrhage. Intravitreal anti-VEGF should be considered for symptomatic visual loss associated with center-involving macular edema on optical coherence tomography. Patients with BRVO and a suboptimal response to anti-VEGF could be treated with grid laser, and those with CRVO and an inadequate response to anti-VEGF may be candidates for intravitreal steroids.

\textbf{Introduction}
Retinal vein occlusion (RVO) is a sight-threatening retinal vascular disorder that is often associated with macular edema and neovascularization. The recent deve-
Development of intravitreal pharmacotherapy has significantly expanded treatment options and has changed the standard of care for treatment of the disease. To that end, Canadian retina specialists perceived a need for concise recommendations and guidance to assist their colleagues in treating RVO and associated complications, and, to address this need, formed an expert panel.

Following a careful review of the medical literature and data from recent clinical trials, the expert panel drafted practical consensus recommendations based on the best available scientific evidence for the clinical approach to the management of RVO, including treatment algorithms for branch (BRVO) and central (CRVO) RVO. This document presents a suggested standard of practice for patients with RVO and was created to optimize the likelihood of best visual and medical outcomes for individuals with RVO. The outlined recommendations are not intended to be a replacement for clinical judgment, but rather to inform patterns of practice. When considering therapeutic approaches for patients presenting with RVO, the treating clinician must individualize therapy, giving consideration to the patient’s personal health needs.

**Methods**

An English-language literature search using the PubMed Library was performed with the term ‘retinal vein occlusion’ to identify studies published from January 2008 to January 2014. This was followed by a manual search of references cited in selected papers published in peer-reviewed journals. Thus, some of the supporting references date back to the 1980s. These older publications and trials were taken into consideration if deemed relevant and applicable to current practice and/or in cases where recently published evidence was insufficient to make sound conclusions. Meta-analyses, systematic reviews, and randomized clinical trials with at least 1 year of follow-up were selected as preferred sources.

References identified by the literature searches were further reviewed by the expert panel members. Each member was assigned a specific topic, which they presented to the entire group during a consensus meeting that took place on February 1, 2014, in Toronto. During this meeting, the experts reviewed the evidence and formulated consensus recommendations with consideration of the health benefits, risks, and adverse effects of interventions. Consensus was sought on all recommendation points. Table 1 lists categories used to rank the quality of evidence in support of each consensus statement.

**Treating RVO in Canada: Unmet Needs, Treatment Gaps, and Drug Coverage**

Access to pharmacotherapies for RVO in Canada varies from province to province (table 2), and the access to these drugs is further influenced by patient age, family income, extent of the disease, and previous therapies. Furthermore, while budgetary limitations in some provinces significantly influence clinician prescribing decisions, budgetary silos (hospital vs. private practice) add to already complicated reimbursement protocols.

**Consensus**

- The Canadian expert panel supports optimal access to medical care for all Canadians. Access to appropriate treatment and clinician prescribing decisions should ideally be based on best evidence, and should not be influenced by provincial budgetary limitations. Co-payment by patients for pharmacotherapy should not be a barrier to access for medications that are already on provincial formularies (level III).

**Epidemiology, Etiology, and Pathogenesis**

RVO is the second most common cause (after diabetic retinopathy) of vision loss due to retinal vascular disease [1]. Depending on the area affected, RVO is broadly divided into CRVO and BRVO. BRVO is about 3–6 times more common than CRVO [2–4].

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**Table 1. Categories used to rank the quality of evidence in support of each consensus statement**

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>Level I</td>
<td>Evidence gathered from at least one properly designed randomized controlled trial</td>
</tr>
<tr>
<td>Level IIa</td>
<td>Evidence gathered from well-designed controlled trials without randomization</td>
</tr>
<tr>
<td>Level IIb</td>
<td>Evidence gathered from well-designed cohort or case-control analytic studies</td>
</tr>
<tr>
<td>Level III</td>
<td>Evidence based on opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees</td>
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Berger et al.
Determining the true incidence of RVO is not straightforward as many patients are asymptomatic and, furthermore, the condition is often detected incidentally. The Blue Mountains Eye Study found that the 10-year cumulative incidence of RVO was 1.6% [2]. The Beaver Dam Eye Study reported that the 15-year cumulative incidences of CRVO and BRVO were 0.5 and 1.8%, respectively [3]. Pooled data from 11 population-based studies from the US, Europe, Asia, and Australia reported prevalence rates of about 0.52% for any RVO, 0.44% for BRVO, and 0.08% for CRVO [4]. Prevalence varies by ethnicity and increases with age, but does not appear to be affected by gender.

Although the pathogenesis of RVO is multifactorial, arterial disease is a predominantly pathogenetic mechanism in the majority of cases. As central retinal veins and arteries are present within the same adventitial sheath within the lamina cribrosa, arterial stiffness can affect neighboring veins, leading to CRVO [5, 6]. BRVO may be the result of a combination of vein compression at arteriovenous crossings, degenerative changes within venous walls, and hypercoagulability [5, 7]. It has also been suggested that endothelin-1 produced by atherosclerotic arteries may diffuse across to the neighboring vein, stimulating venous vasoconstriction. The role of inflammation in the progression and outcome of vitreoretinal disease including RVO is also well recognized [8]. Significantly elevated vitreous levels of the soluble cytokines interleukin (IL)-6 and 8, monocyte chemotactrant protein-1, and vascular endothelial growth factor (VEGF) are found in patients with RVO [9]. Furthermore, the levels of VEGF and IL-6 correlate with both the severity of macular edema and extent of retinal nonperfusion [10–13]. VEGF is produced by the retinal pigment epithelium, endothelial cells, and Müller cells [9]. A close correlation between aqueous VEGF levels and the course of iris neovascularization and vascular permeability in patients with ischemic CRVO has been observed [14]. Furthermore, it has been suggested that the initial vein occlusion acts as a precipitating event that causes baseline ischemia and release of VEGF, which then contributes to the progression of retinal nonperfusion (RNP) and thus worsening of ischemia [15]. The excessive vascular permeability induced by VEGF is also likely to contribute to the macular edema. Due to a self-perpetuating cycle of VEGF-induced vascular permeability, edema can persist even after the resolution of the primary venous obstruction. This can lead to chronic macular edema, capillary damage, and retinal ischemia. Thus, timely, aggressive blockade of VEGF can prevent the worsening of nonperfusion, promote reperfusion, and eliminate a positive feedback loop [15].

In summary, retinal vascular disease progresses by 2 major pathways: (1) damage to the inner blood-retinal barrier that leads to increased vascular permeability and edema; and (2) vessel closure leading to ischemia and the development of abnormal neovascularization [16]. These pathways are also closely associated with an abnormal inflammatory repair process.

Table 2. Provincial coverage of recently approved pharmacological treatments for RVO in Canada

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Ozurdex (intravitreal implant)</th>
<th>Lucentis® (ranibizumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia</td>
<td>Not listed</td>
<td>Listed but under budgetary restrictions</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>Not listed</td>
<td>Listed</td>
</tr>
<tr>
<td>Alberta</td>
<td>Not listed</td>
<td>Not listed</td>
</tr>
<tr>
<td>Manitoba</td>
<td>Not listed</td>
<td>Listed</td>
</tr>
<tr>
<td>Ontario</td>
<td>Listed for CRVO</td>
<td>Listed for CRVO</td>
</tr>
<tr>
<td>Quebec</td>
<td>Capped at a maximum of 2 implants per year</td>
<td>Can be obtained through special access for BRVO when other therapies have failed</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td></td>
<td>Listed</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>Not listed</td>
<td>Not listed</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td></td>
<td>Listed</td>
</tr>
<tr>
<td>Newfoundland/Labrador</td>
<td></td>
<td>Listed</td>
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</table>

1 As of February 1, 2014.
In an attempt to better understand the etiology of RVO, many investigators tend to examine risk factors involved in the occurrence of systemic venous thrombosis and compare them to those found in RVO. Although these 2 entities may share some common cardiovascular and hypercoagulation risk factors, it is important to understand that they are separate entities requiring different management strategies and leading to different complications. Moreover, several studies have suggested that carrying out exhaustive tests for thrombophilia in RVO in the absence of a suggestive medical history is not necessary [1, 28, 29]. Rehak et al. [29] suggested that the role of thrombophilic disorders is much more important in patients without acquired risk factors, i.e. hypertension, diabetes, and hyperlipidemia. In this study, 37.9% of RVO patients (n = 29) without acquired risk factors tested positive for at least 1 thrombophilic risk factor compared with 7.6% of patients (n = 92) with acquired risk factors (p < 0.001) and 8.3% of the controls (n = 60; p < 0.001). These findings suggest that there are possible differences in the etiology of RVO in different groups of patients.

In RVO patients with acquired disorders, changes in the vascular walls are important in the etiology of the disease. In patients without acquired risk factors, it is likely that a hypercoagulable state leads to thrombosis. A trend in the prevalence of thrombophilic disorders (factor V Leiden) according to age (≤50 and >50 years) was also observed. The prevalence of factor V Leiden in patients ≤50 years of age was 14.3%, and in individuals over 50 it was 6.3% (p = 0.314). The prevalence of at least one of the investigated thrombophilic disorders was 23.8% in younger patients and 10.1% in older patients (p = 0.06). Based on these results, the investigators suggested that screening for the abovementioned acquired risk factors should be done in all patients with RVO [29]. In patients without acquired risk factors, the investigation of thrombophilic disorders is indicated, regardless of their age [29]. See table 3 and Brown [30] for potential laboratory workup.

**Consensus**

- Extensive assessment and workup for systemic disease are unnecessary in the vast majority of patients with RVO, especially those with known acquired risk factors that require medical attention (level I [25–27, 29]).
- However, functional inquiry (systemic review) may be used to identify the need for further workup. Anything considered ‘unusual’ such as a personal or familial history of thromboembolism or simultaneous bilateral presentation should warrant additional examination, especially in younger patients (consensus/level III).

### Table 3. Potential laboratory workup for patients with RVO

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>Activated protein C resistance</td>
</tr>
<tr>
<td>Glucose tolerance test</td>
<td>Lupus anticoagulant</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Anticardiolipin antibodies</td>
</tr>
<tr>
<td>Serum protein electrophoresis</td>
<td>Protein C</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>Protein S</td>
</tr>
<tr>
<td>Thrombophilia screening</td>
<td>Antithrombin III</td>
</tr>
</tbody>
</table>

Reproduced with permission from Brown [30].

**Ocular and Systemic Risk Factors**

Numerous systemic and ocular conditions are considered to predispose an individual to the development of RVO. Ocular factors include glaucoma, optic disc drusen, ocular hypertension, hyperopia, and orbital compression of the optic nerve [17]. It has also been demonstrated that developing RVO in one eye predisposes to development in the fellow eye [18, 19].

The common cardiovascular predisposing systemic risk factors for RVO include hypertension, diabetes mellitus, and dyslipidemia [20–24]. According to a meta-analysis of 21 studies by O’Mahoney et al. [24], hypertension and hyperlipidemia were most significantly associated with RVO; the odds ratios (ORs) were 3.5 [95% confidence interval (CI): 2.5–5.1; p < 0.05] and 2.5 (95% CI: 1.7–3.7; p < 0.05), respectively. The association between RVO and diabetes was less pronounced but still significant (OR 1.5; 95% CI: 1.1–2.0; p < 0.05). Therefore, it is not surprising that RVO patients might be at higher risk of cardiovascular and cerebrovascular events. In a retrospective cohort study that involved 4,500 RVO patients and 13,500 controls, patients with RVO had an almost 2-fold higher incidence of cerebrovascular accidents than controls [25]. Event rates for myocardial infarction (MI) were similar in patients with RVO and controls, although there was a trend toward an increase in MI in certain RVO subgroups (e.g. males, patients younger than 65 years). The efficacy of anticoagulant therapy with low-molecular-weight heparin in the treatment of acute RVO suggests the presence of a hypercoagulable state in these patients and systemic hypercoagulability as another risk factor [26, 27]. Thus, over recent years there has been great interest in the potential role of thrombophilia in the development of RVO, particularly CRVO. Thrombophilia can be congenital or acquired and is more important in younger patients.
Standardized communication between family doctors, internists, and ophthalmologists is needed. Hypertension, diabetes, and hyperlipidemia need to be addressed and treated (consensus/level III). Ophthalmologists should be aware that RVO might be a manifestation of hypertensive crisis. These at-risk patients should be managed and referred for urgent follow-up (consensus/level III).

Smoking cessation and the use of hormonal birth control should also be addressed (consensus/level III).

Clinical Features and Classification

The classification of RVO is derived from the fundoscopic appearance of the eye and the location of venous occlusion. It includes 3 main groups: BRVO, CRVO, and hemiretinal vein occlusion (HRVO). Table 4 provides an overview of RVO types as defined in the Standard Care versus Corticosteroid in Retinal Vein Occlusion (SCORE) study [31].

Fluorescein angiography (FA) is used to further differentiate CRVO into nonischemic (‘perfused’ or ‘venous stasis retinopathy’) and ischemic (‘nonperfused’ or ‘hemorrhagic’) types. Ischemic CRVO is the less common but more severe of the subtypes [32, 33]. Ischemic CRVO is defined in the Central Vein Occlusion Study (CVOS) as more than 10 disc diameters of retinal capillary nonperfusion. It is characterized by the presence of more striking fundus findings, including more pronounced intraretinal hemorrhages, nerve fiber layer infarcts, optic disc edema, and more commonly shows evidence of poorer vision (<20/200) and a relative afferent papillary defect. The prognosis for visual recovery is poor, and complications such as persistent macular edema and anterior segment neovascularization (in 40–70% of cases) are common. Nonischemic CRVO demonstrates less dense retinal hemorrhage and fewer cotton wool spots; however, vision is often impaired due to edema. There is minimal capillary nonperfusion on FA. Although over 75% of CRVOs are nonischemic, during the CVOS 3-year follow-up, 34% of nonischemic cases converted to the ischemic type [33].

HRVO differs from CRVO as it represents the occlusion of 1 of the 2 trunks of the central retinal vein. Similar to CRVO, it can also be divided into ischemic and nonischemic subtypes [33]. Nonischemic HRVO usually has a good visual outcome after resolution of edema [34]. Although HRVO is a variant of CRVO, its clinical course can follow either that of CRVO or BRVO, depending on its origin.

In addition to ischemic and nonischemic subtypes, BRVOs are also classified according to their anatomical location either as major (when one of the major first-order branch veins is involved) or as macular (when one of the smaller second-order veins within the macula is blocked) [35]. The risk of BRVO at each vein-posterior crossing is about 12 times higher than each vein-anterior crossing [36]. Occlusion in inferotemporal branches occurs in 22–43% of cases, macular branches in 24%, and nasal branches in 0.5–2.6% [37]. As nasal BRVOs are associated with fewer complications and better vision than other types, they are often underdetected [35].

BRVO symptoms depend on the site and severity of the occlusion. The condition may also be asymptomatic. Median visual acuity (VA) at presentation for major BRVO is 20/60 and for macular BRVO is 20/40 [38].
While macular BRVO presents with a central visual field defect, major BRVO presents with a peripheral visual field defect corresponding to the retinal quadrant that the affected vein drains [39]. Longstanding occlusion leads to absolute scotomas, and short-term occlusion causes relative scotomas in areas of capillary nonperfusion [40].

Acute BRVO can be detected by fundoscopy, and fundus examination findings include some or all of the following: dilated tortuous veins, flame-shaped hemorrhages, dot and blot hemorrhages, cotton wool spots, hard exudates, retinal edema, and hemorrhage at an arteriovenous crossing (Bonnet sign) [7, 41, 42]. These findings should respect the horizontal raphe (i.e. are either superior only or inferior only). In addition to these features, chronic BRVO is also characterized by the appearance of venous collateral formation, vascular sheathing and/or lipid exudates [7, 43]. While the extent of macular edema and the amount of capillary nonperfusion can be detected by FA [44], optical coherence tomography (OCT) is a critical diagnostic test to confirm and quantify the macular swelling, and to qualitatively assess the health of the inner segment/outer segment (IS/OS) junction (see treatment algorithms: fig. 1, 2). Ota et al. [45] have demonstrated that even when macular edema is resolved and there is a decrease in foveal thickness, VA remains poor in eyes with an incomplete or missing third high reflectance band (IS/OS junction). It is hypothesized that severe ischemia or severe swelling during acute or chronic BRVO could lead to photoreceptor cell death or disarrangement of the photoreceptor cells. A recent study by Hayreh et al. [46] that investigated the effect of the cup-to-disk (C/D) ratio in various types of...
RVO demonstrated that the C/D ratio is not implicated in the severity of retinopathy, visual outcome, or resolution of retinopathy.

**Natural History and Complications**

The natural history of RVO can be examined by assessment of VA and visual field. The complications of the disease include macular edema, retinal pigment epithelium changes, epiretinal membrane, neovascularization, and fellow eye involvement.

A study conducted by the CVOS Group [47] in the late 1990s found VA at baseline to be a strong predictor of VA at 3 years for eyes with good and with poor vision but a poor predictor for patients with intermediate acuities. VA was also found to be an accurate predictor of the development of iris and angle neovascularization.

A recent study by Hayreh et al. [48] investigated the natural history of visual outcome in 667 patients with CRVO of ≤3 months’ duration. At the initial visit, VA was 20/100 or better in 78% of patients with nonischemic CRVO and in only 1% with ischemic CRVO (p < 0.0001). Visual field defects were minimal or mild in 91 and 8% of nonischemic and ischemic CRVO, respectively (p < 0.0001). Final VA, on resolution of macular edema, was 20/100 or better in 83% of patients with nonischemic CRVO and in 12% with ischemic CRVO (p < 0.0001). Visual field defects were minimal or mild in 95 and 18% of nonischemic and ischemic CRVO, respectively (p < 0.0001). These results demonstrate that the differences in initial presentation are strongly predictive of the overall
visual outcome for the 2 types of CRVO. In ischemic CRVO, it appears that the primary cause of poor VA and visual fields is ischemic damage of the macula, while in nonischemic CRVOs, the poor VA is caused, most commonly, by macular edema. Eyes with poorer initial VA were more likely to develop retinociliary collaterals. In these eyes, resolution of macular edema took longer than in the eyes without collaterals. Eyes without collaterals tended to have better VA outcomes. Age also had a significant impact on change in VA, with younger patients being more likely to improve and less likely to worsen.

In the CVOS [47], neovascularization was rare in the nonischemic form (<2%). Up to 60% of eyes with the ischemic form developed neovascularization at a mean 3–5 months after onset of the occlusion. Neovascularization is usually found in the anterior segment. VA was a strong predictive factor for neovascularization. Neovascular glaucoma developed in 30% of eyes with the ischemic form. The risk of an RVO in the fellow eye is about 1% per year.

In the Branch Vein Occlusion Study (BVOS) [49], 34% of eyes with BRVO had VA 20/40 or better with a mean VA of 20/70 after 3 years of follow-up. In ischemic cases, neovascularization of the disc or elsewhere formed in 30–40% of eyes. Of those, 60% will have a vitreous hemorrhage. Anterior segment neovascularization is found in 1% of eyes with BRVO. Hayreh and Zimmermann [38] found that for eyes with initial VA of 20/60 or better, VA improved or remained better in 75% for major BRVO and 86% for macular BRVO. In those with initial VA of 20/70 or worse, VA improved in 69% for major BRVO and 53% for macular BRVO, with a median final VA of 20/60 for both BRVO types. Median time to macular edema resolution was 21 months in those with major BRVO and 18 months in those with macular BRVO. The study also demonstrated better visual outcomes in younger patients.

Burden of Disease

Impact on Quality of Life

Two US studies assessed the impact of CRVO and unilateral BRVO on vision-related quality of life (VRQoL) using the National Eye Institute 25-Item Visual Function Questionnaire with 25 questions (VFQ-25) [50, 51]. Both BRVO and CRVO were found to have a detrimental effect on VRQoL. Patients with CRVO scored significantly lower than a control group without ocular disease and had similar scores to a cohort of patients with diabetic retinopathy [51]. For patients with unilateral BRVO, the detrimental effect on VRQoL was significant even when VA in the fellow eye was 20/25 or better [50].

Impact on Mortality

Data from a pooled cohort of the Beaver Dam Eye Study and the Blue Mountains Eye Study showed no association between RVO and mortality secondary to cardiovascular [hazard ratio (HR) = 1.2; 95% CI: 0.8–1.8] or cerebrovascular causes (HR = 0.9; 95% CI: 0.4–2.1) after adjustment for age, gender, body mass index, hypertension, diabetes, and other factors [52]. Thus, despite the documented association between RVO and systemic risk factors for cardiovascular diseases, RVO has not been shown to predict overall mortality.

Economic Burden

Data regarding treatment patterns and the economic burden associated with RVO are sparse. A retrospective cohort study of US Medicare beneficiaries compared the 1- and 3-year costs for BRVO and CRVO patients with the costs for individuals with hypertension and glaucoma [53]. BRVO patients had 16% higher 1-year direct medical costs and 12% higher 3-year costs than hypertension patients. Compared with glaucoma patients, BRVO patients incurred 18% higher costs at 1 year and 13% higher costs at 3 years. The increases in direct medical costs for individuals with CRVO over hypertension patients were 22 and 15% at 1 and 3 years, respectively, and 24 and 16% higher costs compared with glaucoma patients at 1 and 3 years. The estimated annual direct cost related to managing RVO in the US in 2006 was USD 5.8 billion: USD 4.5 billion for BRVO and USD 1.3 billion for CRVO.

Consensus

- Proper and accurate clinical diagnosis and classification of RVO should include measurements of best corrected VA (BCVA), undilated pupillary and slit lamp examination, measurement of intraocular pressures (IOP), gonioscopy, and dilated ophthalmoscopy (consensus/level III).
- Fundus photography is recommended for documentation purposes and it is also useful for patient education (consensus/level III).
- OCT is recommended at baseline to establish the presence or absence of cystoid macular edema and to assess the IS/OS junction. OCT testing is also critically useful for determining treatment success or failure, and to help in determining the need for continued retreatment (consensus/level III).
• FA should be considered at baseline for diagnosis and classification of RVO. Wide-angle FA may offer more accurate documentation of peripheral capillary non-perfusion. Studies are currently evaluating whether wide-angle FA-directed sectoral or panretinal photocoagulation (PRP) may lead to improved outcomes (consensus/level III).

The Role of Anti-VEGF in the Management of RVOs

Abnormally elevated levels of the cytokine VEGF have been found in the vitreous and aqueous of eyes with RVO. Several of the anti-VEGF drugs currently available have been used in patients with RVO in clinical trials of varying size. The consensus treatment algorithms outline proposed approaches for first-line use of this class of agents and treatment consideration after 3 monthly injections.

Bevacizumab

Small-scale clinical trials have demonstrated the efficacy of bevacizumab in the treatment of CRVO and BRVO [54–57]. In these trials, treatment with bevacizumab improved BCVA and reduced central macular thickening (CMT) when compared to sham in CRVO [54, 55], or when compared to steroids [56] or grid laser photocoagulation [57] in BRVO.

Epstein et al. [54, 55] assessed the efficacy of bevacizumab in 60 patients with macular edema secondary to CRVO. Patients were randomized 1:1 to receive intraocular injections of bevacizumab or sham every 6 weeks for 6 months [54]. At month 6, 18 of 30 patients (60.0%) treated with bevacizumab gained ≥15 letters compared with 6 of 30 patients (20.0%) in the sham group (p = 0.003) [54]. From month 6, all patients received intraocular injections of bevacizumab every 6 weeks for 6 months [55]. At month 12, the BCVA improved by 16.0 letters in the patients treated with bevacizumab from the beginning of the trial compared with 4.6 letters in the patients switched from sham to bevacizumab at month 6 (p < 0.05) [55]. An unplanned retrospective analysis revealed that patients aged >70 years had a significantly worse outcome when receiving delayed treatment, losing 1.4 letters (95% CI: −9.7 to 8.4) compared with a gain of 20.1 letters (95% CI: 13.9–26.3) in patients aged <70 years who were initially randomized to bevacizumab (p < 0.003) [55].

In another randomized clinical trial, 86 eyes with recent-onset (<12 weeks) BRVO were assigned to monthly intravitreal bevacizumab (43 eyes; 1.25 mg), or intravitreal triamcinolone acetonide (IVTA) every 2 months (43 eyes; 2 mg) [56]. At month 6, mean BCVA improved significantly in both groups, from 0.68 ± 0.25 to 0.31 ± 0.21 logMAR (logarithm of minimum angle of resolution) in the bevacizumab group and from 0.67 ± 0.29 to 0.46 ± 0.31 logMAR in the IVTA group (p < 0.001 for both). However, between-group differences reached a significant level at months 4 (p = 0.013) and 6 (p < 0.001) in favor of intravitreal bevacizumab. At all visits, mean IOP rise was significantly higher in patients treated with IVTA versus bevacizumab.

In a study that included 30 eyes with perfused BRVO, eyes randomized to bevacizumab had better BCVA and lower CMT values at 1, 3, 6, and 12 months (p < 0.05) compared to those treated with grid laser photocoagulation [57].

Ranibizumab

Two large double-masked, multicenter, randomized, controlled phase 3 trials – BRAVO (Ranibizumab for the Treatment of Macular Edema after Branch Retinal Vein Occlusion) [58] and CRUISE (Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion) [59] – assessed the efficacy of ranibizumab for the treatment of macular edema secondary to BRVO (397 eyes) and CRVO (392 eyes). Patients with BCVA using Early Treatment Diabetic Retinopathy Study (ETDRS) charts of 20/40 to 20/400 (BRVO) or 20/40 to 20/320 (CRVO) were included in these studies and those with relative afferent papillary defect and diabetic retinopathy were excluded.

In the BRAVO trial, the comparison groups included a monthly sham injection arm, a monthly 0.3 mg ranibizumab injection arm, and a monthly 0.5 mg injection arm [58]. These injections were administered every month for 6 months. Rescue laser was permitted after 3 months if evidence of progressive vision loss or increase in CMT was noted. Six-month analysis indicated that the monthly intravitreal ranibizumab arms gained 16.6 (0.3 mg) to 18.3 letters (0.5 mg) compared with a gain of 7.3 letters in the sham group (table 5). Furthermore, 55 (0.3 mg) to 61% (0.5 mg) of ranibizumab–treated eyes gained ≥15 letters from baseline compared to 28.8% of the eyes receiving sham treatment.

In the CRUISE trial, the comparator groups were similar to the BRAVO trial. In the CRUISE trial, the ranibizumab arms gained 12.7 (0.3 mg) to 14.9 letters (0.5 mg) compared to a 0.8-letter gain in the sham group at 6 months [59]. In addition, 46.2 (0.3 mg) to 52.6% (0.5 mg) of ranibizumab–treated eyes gained ≥15 letters from baseline compared with only 19.2% in the sham group. In
both trials, improvements in VA were accompanied by statistically significant reductions in foveal thickness.

After 6 months of treatment, the percentage of patients with CRVO without RNP was significantly greater in patients treated with ranibizumab (0.3 mg, 82.0%, p = 0.0067) versus those receiving sham (67.0%) [15]. Reperfusion of nonperfused retina was rare (1%) in sham-treated CRVO patients, but occurred in 6–8% of CRVO patients treated with ranibizumab. Results in patients with BRVO mirrored those in patients with CRVO (sham 32.7%; 0.3 mg, 48.1%, p = 0.023; 0.5 mg, 51.0%, p = 0.0044). Crossover to 0.5 mg ranibizumab from sham at month 6 halted the progression of RNP in these patients and resulted in improvement in both CRVO and BRVO [15].

Following the initial 6-month study periods, all patients received prn ranibizumab for macular edema. The benefits with ranibizumab observed in the first 6 months were generally maintained at 12 months (table 5) [60, 61]. Although the patients who were initially in the sham group also showed marked improvement in vision after receiving ranibizumab, the improvements did not reach the same level of benefit as in patients who were treated with ranibizumab from the beginning of the trial.

In the BRAVO and CRUISE trials, rescue laser therapy was initiated in patients with one or more of the following conditions: Snellen score ≤20/40, <5 letters gained, mean CMT ≥250 μm, and ≥50-μm decrease in CMT in the previous 2 months. Approximately 20% of patients received 0.5 mg ranibizumab monthly during the first 6 months of treatment, and 24% received 0.5 mg ranibizumab during the prn treatment phase.

The HORIZON trial [62] is an open-label, multicenter, 2-year extension study in patients who completed the 12-month BRAVO and CRUISE studies. The mean changes from baseline BCVA letter scores at month 24 in BRVO patients were +0.9 (sham/0.5 mg), −2.3 (0.3/0.5 mg), and −0.7 (0.5 mg). The mean changes from baseline BCVA at month 24 in CRVO patients were −4.2 (sham/0.5 mg), −5.2 (0.3/0.5 mg), and −4.1 (0.5 mg), as shown in figure 3. Thus, while reduced follow-up and fewer ranibizumab injections in the 2nd year of treatment were associated with a decline in vision in CRVO patients, vision remained stable in BRVO patients. In addition, at 24 months, previous sham-treated subjects who received ranibizumab after 6 months did not gain as much VA as those who were treated with ranibizumab from the outset. These results suggest that during the second year of ranibizumab treatment of RVO patients, follow-up and injections should be individualized and that, on average, CRVO patients may require earlier intervention and follow-up more frequently than every 3 months. CRVO patients who reached CMT ≤250 μm and resolution of macular edema within 3 months of treatment (rapid responders) experienced a statistically significant improvement in vision during the first 12 months versus those who did not achieve this outcome after 3 months of treatment [63].

Subgroup analyses of the BRAVO and CRUISE trials also demonstrated substantial improvements in visual function [64] and reading speed [65]. Significant differences in the VFQ-25 composite score and near and distance activities subscales compared with sham patients were observed as early as 1 month after the first ranibizumab injection [64]. At 6 months, the difference in mean correctly read words per minute (wpm) between ranibizumab (0.5 mg) and sham was 16.3 wpm (p = 0.007) for BRVO patients and 12.4 wpm (p = 0.01) for CRVO patients [65].

The recently presented phase 3b BRIGHTER trial evaluated the impact of concomitant laser on visual outcome and treatment frequency in patients with BRVO
receiving prn ranibizumab [66, 67]. BRIGHTER participants were randomized to the 3 treatment groups: ranibizumab 0.5 mg (n = 183), ranibizumab 0.5 mg plus adjunctive laser (n = 180), and laser alone (n = 92). After 6 months of prn treatment, there was a statistically significant difference in mean change in BCVA from baseline in patients treated with ranibizumab versus laser (+14.8 and +14.1 letters for ranibizumab monotherapy and ranibizumab plus laser, respectively, vs. +6.0 letters for laser, p < 0.0001 for both ranibizumab groups vs. laser alone comparisons). An average of 4.8 (ranibizumab monotherapy) and 4.5 (ranibizumab plus adjunctive laser) injections were administered, 3 of which were mandatory by the treatment protocol. Furthermore, while patients with >10 disc areas of nonperfusion were excluded from the BRAVO trial, approximately 45% of patients enrolled in the BRIGHTER trial had ischemia. Thus, the BRIGHTER study demonstrated that ranibizumab treatment is equally effective in both ischemic and nonischemic patients [66, 67].

Similarly, the CRYSTAL trial will provide additional efficacy and safety data on ranibizumab 0.5 mg in patients with CRVO presenting with ischemia. Baseline characteristics of 357 enrolled patients indicate a higher proportion of patients with ischemic lesions compared to the CRUISE trial (15.4 vs. 2%) [68].

**Afibercept**

The efficacy of VEGF-Trap (afibercept) in the treatment of CRVO was evaluated in the COPERNICUS [69] (n = 189 US patients) and GALILEO [70] (n = 171 patients from Europe, Asia, and Australia) trials. In these trials, the dose and frequency of afibercept injections was 2 mg every 4 weeks. In the GALILEO trial, the control group received sham for 12 months, and in the COPERNICUS trial, the sham patients were allowed to receive
Aflibercept on a prn basis after 6 months. In the GALILEO trial, more patients receiving aflibercept (60.2%) gained ≥15 letters after 6 months of treatment compared with those receiving sham injections (22.1%; p < 0.0001) [70]. Aflibercept patients gained a mean of 18.0 letters compared with 3.3 letters with sham injections (p < 0.0001). At the 52-week mark, 55.3% of aflibercept-treated eyes gained >15 letters compared with those receiving sham treatment (p < 0.001) [71]. Figure 4 displays mean change in vision (ETDRS letters) in the GALILEO [70] and COPERNICUS [72] trials. In the COPERNICUS trial, although the patients who were initially in the sham group also showed marked improvement in vision after receiving aflibercept in the second 6-month ‘prn period’, the improvements did not reach the same level of benefit as in patients who were treated with aflibercept from the beginning of the trial. At the end of the 12-month period, the monthly treated arm had a 12.4-letter advantage in letters gained (+16.2 to +3.8; fig. 4b) [72].

The recently presented VIBRANT trial [73], a multicenter, double-masked, active-controlled, randomized, phase 3 trial, indicated superiority of intravitreal aflibercept versus laser in BRVO. After 6 months of treatment, significantly more patients treated with aflibercept 2 mg every 4 weeks gained ≥15 letters from baseline compared to those treated with laser (53 vs. 27%; p < 0.001). The mean improvement in BCVA from baseline to week 24 was 17.0 letters with aflibercept and 6.9 with laser (p < 0.0001). The mean reduction in central retinal thickness from baseline to week 24 was 280.5 μm with aflibercept versus 128.8 μm with laser (p < 0.0001).

**Consensus**
- There is level I evidence to support the use of ranibizumab [58–62] and aflibercept [69–72] treatment for nonischemic RVOs accompanied by visual loss from macular edema.
- Clinicians should judiciously consider the results of clinical trials when deciding when and whether to initiate anti-VEGF treatment for patients with RVO. The treatment should be considered in symptomatic patients with visual loss associated with center-involving macular edema on OCT (consensus/level III).
- Treatment could also be considered in patients with relatively good functional vision (better than 20/30) and OCT evidence of minimal subclinical macular edema (1–2 small intraretinal cysts). These are patients that would not have been trial eligible due to their initial VA being better than 20/40 (consensus/level III).
- Intravitreal anti-VEGF therapy should be considered as first-line therapy for BRVO-associated macular
• Intravitreal anti-VEGF therapy should be considered as the first-line therapy for CRVO-related macular edema (level I for ranibizumab [58, 60, 62], level IIb for bevacizumab [56, 57]).

• Intravitreal anti-VEGF therapy should be considered as the first-line therapy for CRVO-related macular edema (level I for ranibizumab [59, 61, 62], level I for aflibercept [69–72], level IIb for bevacizumab [54, 55]).

• The treatment is considered successful if, after 3–4 monthly injections, vision is stable or is progressively improving and OCT shows reduction in retinal fluid. In this case, the clinician should consider prn treatment with frequent (ideally monthly) monitoring, or a treat-and-extend approach. Patients should be followed for at least 3 years (consensus/level III).

• CRVO patients should be followed and monitored more frequently than BRVO patients. Monthly follow-up is recommended until they present with relatively stable vision and reduced fluid on OCT (level I [60]).

• Laser (scatter or PRP) is the therapy of choice when neovascularization secondary to RVO is detected (level I [19, 33, 49, 74]). Anti-VEGF agents should be considered in cases where anterior segment neovascularization is present or before the initiation of laser treatment (consensus/level III).

• Anti-VEGF therapy should also be considered in cases of vitreous hemorrhages, associated with anterior or posterior segment neovascularization, following detailed B-scan imaging to rule out tractional changes (consensus/level III).

**Role of Steroids in the Management of RVO**

The increase in retinal capillary permeability that results in macular edema in patients with RVO may be caused by a breakdown of the blood retina barrier mediated in part by VEGF. We know that VEGF is upregulated in eyes with CRVO. It has been demonstrated that corticosteroids inhibit the expression of VEGF and therefore may be an effective therapy for RVO-related macular edema [75, 76]. Inflammation may also contribute to the pathology of CRVO, and the anti-inflammatory properties of corticosteroids may play a role in the mitigation of the disease [77]. In addition, it has been suggested that corticosteroids may have a neuroprotective effect that may be beneficial in eyes with CRVO [78].

**Triamcinolone**

The SCORE trial investigators compared intravitreal injection of 1 or 4 mg of preservative-free intravitreal triamcinolone (IVTA; Trivaris®) versus observation in the treatment of CRVO (271 eyes) [79] or grid-pattern laser in BRVO (411 eyes) [80]. Eyes were retreated every 4 months during the 12-month study period. No significant improvement in the VA of BRVO patients was observed with IVTA therapy compared to laser [80]. Although the 4 mg IVTA group had significantly greater improvement in VA scores compared to the other 2 groups at month 4, it was not maintained throughout the study. At month 12, the mean changes from baseline in VA letter scores were 4.2, 5.7, and 4.0 for laser, 1 mg IVTA, and 4 mg IVTA, respectively. A subgroup analysis also demonstrated no statistically significant difference at month 12 among treatment groups in patients with pseudophakic eyes (p = 0.44). However, after month 12, mean change from baseline in VA letter score was greater in the laser group compared with the 2 IVTA groups (p < 0.05 at months 16, 20, 24, and 32). This demonstrates a disadvantage of long-term IVTA compared to laser in patients with BRVO [80].

In CRVO patients, however, treatment with IVTA showed significant VA improvement compared to observation. At 1 year, 27% of eyes in the 1 mg IVTA group and 26% of eyes in the 4 mg IVTA group gained ≥ 15 letters (primary outcome) compared to 7% of untreated eyes (p = 0.001 for both IVTA groups against control) [79]. Mean change in VA was a loss of 1.2 letters in either the 1 mg or 4 mg IVTA group compared with a loss of 12.1 letters with observation. At 1 year, pseudophakic eyes gained a mean of 2 letters with 1 mg IVTA, compared with losses of 1 letter with 4 mg IVTA and 14 letters among untreated eyes.

Primary ocular adverse events associated with IVTA in the SCORE studies included cataracts and elevated IOP. At 1 year, 20 and 35% of eyes treated with 1 mg and 4 mg IVTA, respectively, in the SCORE-CRVO trial required IOP-lowering treatment versus 8% in the observation group. Iris neovascularization or neovascular glaucoma was present in 13 patients (9 out of 92 in the 1 mg group and 4 out of 91 in the 4 mg group). Cataract surgery was performed in 26 and 33% of patients in the 1 mg and 4 mg arms, respectively, after 1 year of treatment with IVTA. In eyes with BRVO, elevated IOP was observed in 8% (1 mg) and 41% (4 mg) of IVTA-treated eyes compared to 2% in the laser group.

1 Trivaris is not available in Canada. Preservative-free Triesence® is available, and it is indicated for visualization during vitrectomy.
The Diabetic Retinopathy Clinical Research Network (DRCRnet) study [81] demonstrated a significant increase in cataract rates in patients with diabetic macular edema receiving 4 mg IVTA – from about 7% at year 1 to 83% at year 3.

It is important to note that several small-scale studies demonstrated benefits of the anti-VEGF inhibitor bevacizumab over IVTA with regard to these ocular adverse events [56, 82–85]. Although intravitreal bevacizumab and IVTA were both associated with a comparable gain in VA [84], none of the bevacizumab-treated patients experienced neovascular glaucoma or significant increases in IOP.

**Ozurdex® (Sustained-Release Dexamethasone Intravitreal Implant)**

Ozurdex is a sustained-release dexamethasone intravitreal implant (0.7 mg). It is composed of a biodegradable copolymer of polyactic-co-glycolic acid containing micronized dexamethasone. The Ozurdex device has been approved by Health Canada for the treatment of macular edema secondary to CRVO [86]. This approval
was based on favorable results of an international study (GENEVA trial) [87] investigating the effect of a single 0.35- or 0.7-mg injection compared with sham injection for the treatment of macular edema in eyes with BRVO or CRVO. At baseline, patients received dexamethasone implants at doses of either 0.7 mg (n = 421) or 0.35 mg (n = 412), or sham (n = 423) in the study eye (masked phase of the study). At day 180, patients could receive the 0.7 mg dexamethasone implant if their BCVA was <84 letters (Snellen equivalent of 20/20) or retinal thickness was >250 μm (open-label extension). Figure 5a shows the mean change in BCVA in CRVO eyes treated with 0.7 mg dexamethasone at baseline and day 180 (retreated) or at day 180 only (sham group).

The mean change in BCVA in BRVO eyes treated with dexamethasone in the GENEVA trial is shown in figure 5b [87]. However, it is important to note that 25.5% of patients who received the 0.7 mg dexamethasone implant at baseline began treatment with IOP-lowering medication during the masked phase of the study. In the subgroup that qualified for retreatment and received a second 0.7 mg dexamethasone implant at day 180, an additional 10.3% of patients began treatment with IOP-lowering medication during the open-label phase of the study. Thus, after 1 year of follow-up, 35% of the patients required IOP-lowering medications. Furthermore, the incidence of cataracts after the first year of treatment was recorded in 29.8% (90/302) of phakic study eyes in the retreated dexamethasone 0.7/0.7 mg group, 10.5% (31/296) of phakic study eyes in the delayed-treatment was recorded in 29.8% (90/302) of phakic study eyes in the retreated dexamethasone 0.7/0.7 mg group, 19.8% (56/283) of phakic study eyes in the retreated dexamethasone 0.35/0.7 mg group, and 10.5% (31/296) of phakic study eyes in the delayed-treatment group (p < 0.001).

Efficacy and safety results observed in the GENEVA trial were confirmed by several smaller retrospective [88, 89] and prospective studies [90].

In a study that assessed efficacy and safety of Ozurdex in patients with diabetic macular edema, the rate of cataract surgery during the study was 59.2% for patients treated with 0.7 mg Ozurdex dexamethasone intravitreal implant versus 7.2% in patients receiving sham [91]. Furthermore, the incidence of cataract-related adverse events increased after the 1st year of the study, and over three quarters of the cataract surgeries in the patients treated with the Ozurdex implant were performed between 18 and 30 months.

In addition, the areas under the curve (fig. 5) clearly demonstrate that Ozurdex is not a 6-month duration drug for many RVO patients. According to the retrospective chart review of 102 patients with cystoid macular edema secondary to BRVO (n = 54) or CRVO (n = 48) treated with Ozurdex at 8 centers, approximately 41% of BRVO eyes required reinjection after 17.5 ± 4.2 weeks and 50% of CRVO eyes needed to be retreated after 17.68 ± 4.2 instead of 24 weeks [89].

Consensus

- Currently available evidence supports the role of steroids in CRVO but not BRVO (consensus/level III [79, 80, 87]).
- If steroids are to be used in the management of nonischemic CRVO with visual loss due to macular edema, a lower dose (1–2 mg) of IVTA should be considered as clinical trials demonstrated equivalent efficacy and fewer side effects compared to the 4-mg dose (level I [79]).
- In patients treated with intravitreal steroids, IOP should be monitored every 4–6 weeks (consensus/level III).
- Gonioscopy is recommended frequently during CRVO follow-up, as neovascular glaucoma should be managed differently (laser or anti-VEGF) from ocular hypertension (consensus/level III).
- Increases in IOP, cataracts, and glaucoma present significant concerns with intravitreal steroids. Steroids can be considered in specific situations and with specific patient subgroups such as pseudophakic patients (level IIb [79, 80, 87, 91]).

Surgical and Laser Management of RVO

Thermal Laser Treatment for RVO

Until recently, treatment for RVO was based on the findings of the BVOS [50] and CVOS [74] that were conducted in the 1980s and in the 1990s, respectively. In BVOS, treatment of eyes with nonischemic BRVO and VA <20/40 due to perfused macular edema with grid-pattern laser led to 2-line improvement in VA compared to the control group (65 vs. 37%) at 3 years. This finding led to the recommendation that persistent BRVO-related perfused macular edema and VA 20/40 to 20/200 should be treated with grid-pattern laser. The BVOS group also demonstrated that treatment with sector PRP to nonperfused areas prevents development of neovascularization and vitreous hemorrhage [19]. Based on these findings, the BVOS group recommended that sector PRP treatment should be applied after the development of neovascularization.
The CVOS did not demonstrate VA benefit of macular grid laser over observation for nonischemic CRVO with macular edema despite reduction of macular edema following laser. Thus, until recently, observation has been the standard of care for CRVO-related macular edema. Prompt regression of neovascularization in response to PRP was more likely to occur in eyes that have not been treated previously. Thus, the group recommended careful observation with frequent follow-up examinations and prompt PRP of eyes in which neovascularization develops [33]. Recently, there have been several reports of the beneficial effects of combination therapy with laser and intravitreal anti-VEGF injections on improving VA [92, 93]. This combination also provides durable response with less therapeutic interventions. Although the pathophysiology of HRVO mimics CRVO, its clinical findings and complications are found to be intermediate between CRVO and BRVO. Most clinicians manage macular edema following HRVO similarly to BRVO [94]. For example, a focal laser is often used for the treatment of recalcitrant macular edema.

Chorioretinal Venous Anastomosis Treatment for RVO

McAllister et al. [95] showed the effectiveness of laser in inducing chorioretinal venous anastomosis (CRA) and its potential for the treatment of CRVO. Laser-induced CRA occurred in 76.4% of eyes (42/55) with nonischemic CRVO in this study. Eyes that developed an anastomosis had a significant improvement (11.7 letters) in final VA after 18 months compared with eyes in the control (observation – no laser) group (p = 0.004). CRA treatment was associated with many complications. Choroidal neovascularization developed in 10 of 55 treated eyes (18.2%) at the site of the laser-induced CRA, and vitrectomy surgery was required in 5 of 55 treated eyes (9.1%) because of macular traction or nonresolving vitreous hemorrhage.

Vitrectomy Surgery for RVO

Several reports have indicated that surgical decompression of BRVO via arteriovenous crossing sheathotomy is a technically feasible procedure that can result in favorable outcomes [96, 97]. Resolution of macular hemorrhage, edema, and ischemia may improve visual prognosis. Opremcak et al. [98] performed pars plana vitrectomy with radial optic neurotomy on 117 consecutive patients with CRVO and severe loss of vision (defined as 20/200 or worse). Anatomical and clinical improvements were found in 95% of patients. VA improved by an average of 2.5 lines in 71% of patients, with ≥2 lines gained in 53% of patients and ≥4 lines gained in 25%. Anterior-segment neovascularization was found in 6% of patients with CRVO.

Pars plana vitrectomy with internal limiting membrane peeling has also been investigated for treatment of RVO-associated macular edema with variable outcomes [50, 74, 91–104]. There is a need for further documentation of the effectiveness and safety of these therapies via randomized, controlled clinical trials, particularly in the era of effective and less invasive intravitreal pharmacotherapies.

Vitrectomy does have an important role in RVO cases where there is nonclearing vitreous hemorrhage, retinal detachment (tractional and rhegmatogenous) and significant epiretinal membrane.

Consensus

- Due to better visual outcomes and tolerability profile, macular focal/grid laser is the preferred second-line option over intravitreal steroids for BRVO patients with suboptimal response to anti-VEGF (consensus/level III).
- Macular grid laser can be considered in patients with suboptimal response (persistent edema and vision <20/40) after 3–4 monthly injections of anti-VEGF (level I [58, 60, 62]). In this instance, FA should be performed to determine the degree and location of ischemia and to identify areas of leakage that might benefit from laser treatment (consensus/level III).
- In eyes with RVOs with evidence of nonclearing vitreous hemorrhage, visually significant epiretinal membrane, or vitreomacular traction threatening or affecting the central retinal area, vitrectomy surgery should be considered (consensus/level III).
- All cases described above should be referred to a retina specialist (consensus/level III).

Emerging Therapies

Although current pharmacological therapies (i.e. anti-VEGF agents) have greatly improved clinical outcomes in patients with RVO, there are issues related to these treatments. These include the burden of the large number of visits and intravitreal injections required for most patients, as well as the risk of frequent treatment (i.e. endophthalmitis, etc.). In addition, not all patients respond to intravitreal anti-VEGFs. Thus, the search for better...
therapeutic approaches continues. Emerging treatment modalities can be divided into those aimed to resolve the obstruction of venous outflow (endovascular fibrinolysis [105–107], endovascular cannulation [108], and systemic thrombolitics [109]) and those aimed at the sequelae of RVO (macular edema and macular ischemia). Therapies aimed at the latter can be grouped into those that minimize reperfusion injury [110], provide hemodilution [111], modify retinal vascular permeability [112], and offer neuroprotection [113] and pharmacologic vitreolysis [113–117].

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Although aimed to provide ophthalmologists with a practical guide for management of RVO, these recommendations should not be interpreted as legal standards. Furthermore, these recommendations are not meant to replace clinical judgment of trained retina specialists acting according to the patient needs and/or the unique clinical circumstances. The recommendations are based on the highest level of evidence available at the time of the panel’s last review.

References


Optimal Treatment of RVO: Canadian Expert Consensus


