Latin American consensus on retinal vein occlusion

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Key words: Retinal vein occlusion, Anti-VEGF therapy, surgical treatment, neovascular glaucoma.

Introduction

The introduction of anti-VEGF agents has allowed unprecedented progress in the management and treatment of ophthalmologic conditions characterized by an increased vascular permeability and intraocular neovascularization. One of these conditions is retinal vein occlusion (RVO). RVO is one of the most common causes of reduced vision due to retinal vascular disease. Without timely treatment, macular edema, macular ischemia, neovascularization and other potential sequelae of RVO can lead to photoreceptor cell death and consequently to irreversible vision loss.

Treatments for this indication that have been recently approved by several regulatory agencies throughout the world include: the VEGF inhibitor ranibizumab (Lucentis, Genentech), the VEGF and placental growth factor inhibitor aflibercept (Eylea, Regeneron Pharmaceuticals and Bayer HealthCare), and a slow release intravitreal implant of dexamethasone (Ozurdex, Allergan). In addition bevacizumab (Avastin, Genentech) has been used extensively in an off-label manner.
These new treatments allow us to preserve vision for many RVO patients who could not have expected such favorable results just 5 or 6 years ago. However, not every treatment is effective for every patient, and whether one option is superior to another or a combination of options is superior to monotherapy, have yet to be definitively determined.

A growing body of literature with strong evidence supports the use of these new treatments. However, in several instances the literature is not conclusive to support unified management of RVO. This document is a summary analysis on RVO assembled by a group of specialists summoned by the Pan-American Vitreo-Retinal Society (SPRV) to participate in this Latin American consensus.

CONSENSUS METHODOLOGY

The Pan-American Vitreo-Retinal Society (SPRV) summoned a group of Latin American experts during the Pan-American Congress of Ophthalmology held in Rio de Janeiro in August 2013. The main objective for this meeting was to review the literature, discuss the review and summarize the discussion as consensus statements for different aspects of RVO.

The experts that participated in the Latin American Consensus Meeting in RVO are all members of the SPRV. These experts represented Argentina, Brazil, Colombia, Costa Rica, Mexico, Peru and Venezuela. The document resulting from this consensus meeting is the outcome of a systematic and judicious review of the currently available literature for RVO.

The topics reviewed included epidemiology and risk factors for RVO; natural history, pathophysiology, classification and clinical course; diagnosis; treatment (corticosteroids, laser, surgical, anti-VEGF and combined modalities); and neo-vascular glaucoma. Before the meeting, the participants reviewed the literature by topic and produced a summary with suggested consensus statements.

At the meeting, each participant presented the review to the peers and the group discussed all statements until reaching a consensus. All reviews and consensus statements are presented in this document.

Epidemiology Consensus Statements

1. There are no population-based data in LATAM on the prevalence or risk factors for RVO
2. There is a need to identify specific populations in LATAM, whose risk is higher for the development of RVO

Risk Factors Consensus Statements

1. Systemic arterial hypertension, diabetes mellitus and hyperlipidemia are the principal systemic risk factors.
2. The condition is frequently observed in patients in their 60’s and 70’s.
3. Open angle glaucoma is the most important ocular risk factor associated with RVO, particularly CRVO and HRVO.
4. Screening for thrombophilia is not justified in the majority of patients (including younger patients), except for those with a history of recurrent thrombosis or a family history of thrombosis.

Pathophysiology and Natural History Consensus Statements

1. The main risk factor for a RVO is an anatomic predisposition that leads to clot formation.
2. Inflammatory cytokines and growth factors such as VEGF are released and are responsible for the complications seen in RVO (macular edema and intraocular neovascularization).
3. Baseline visual acuity is an important prognostic indicator.

Diagnosis (FA and OCT) Consensus Statements

1. FA should be performed to assess retinal perfusion.
2. In patients with extensive hemorrhages, FA could be postponed until there is clearing of the hemorrhage to confirm retinal perfusion.
3. The use of a 50-degree lens with peripheral sweeps or a wide-field angiogram is important to assess peripheral retinal perfusion status.
4. Periodic FA should be done to monitor the retinal perfusion status. Even if the macular edema resolves the eyes, it could still be at risk of progressive retinal non-perfusion.
5. The OCT is an essential tool for the initial evaluation of the degree and extent of macular edema secondary to RVO. It should be done prior to the beginning of and during pharmacological treatment for macular edema secondary to RVO.

RVO Treatment – Consensus Statements

Steroid treatment Consensus Statements

1. Corticosteroids are beneficial for the treatment of macular edema secondary to RVO:
   a. 1mg of intravitreal triamcinolone is more effective than the natural course of macular edema secondary to CRVO and safer than the 4mg dose.
   b. Macular grid laser photocoagulation is preferred over intravitreal triamcinolone in eyes with macular edema secondary to BRVO. Similar visual outcomes are obtained with both, but the safety profile is better with laser.
   c. An intravitreal extended-release implant of dexamethasone improves the visual acuity in eyes with macular edema secondary to RVO.
d. An intravitreal extended-release implant of dexamethasone has a peak effect at 3 months after implantation.
e. Common secondary effects associated to steroid treatment include cataract formation and elevation of intraocular pressure.
f. Vitrectomized eyes may benefit from a slow release dexamethasone intravitreal implant.

Laser Photocoagulation Consensus Statements

1. Macular laser grid photocoagulation improves the visual acuity and macular edema in eyes with macular edema secondary to perfused BRVO, compared to the natural course of the disease.
2. Macular laser grid photocoagulation has demonstrated to be superior to intravitreal triamcinolone in the treatment of macular edema secondary to perfused BRVO.
3. Macular laser grid photocoagulation is not indicated in the treatment of macular edema secondary to CRVO.
4. Currently there is not enough information to recommend FA guided scatter retinal photocoagulation to decrease the injection burden or to improve the visual outcomes in eyes with macular edema secondary to RVO.
5. The best treatment for intraocular neo-vascularization is the ablation of the ischemic retina.

Anti-VEGF treatment Consensus Statements

1. There is strong evidence that anti-VEGF agents should be considered first line treatment for macular edema due to RVO.
2. Treatment should be strongly considered upon diagnosis since a delay in treatment has been shown to severely affect the potential visual benefits from treatment.
3. There is considerable variability among patients with RVO. Some stabilize after a few consecutive monthly injections and require a few injections thereafter but the vast majority, particularly patients with CRVO, require frequent follow-up and multiple injections to control macular edema.
4. Once treatment has been initiated with an anti-VEGF agent, patients with macular edema secondary to CRVO need to be followed on a regular basis with OCT scans.
5. Reinjection criteria are based on OCT findings of persistent or recurrent macular edema.
6. Persistent macular edema in eyes with CRVO as detected by OCT at month 3 is a poor prognostic indicator and indicates probable need for more injections and continuous monitoring.
7. Periodic fluorescein angiograms should be performed to monitor perfusion status.

Combined Treatments Consensus Statements

1. The outcomes following a combination of corticosteroids with anti-VEGF agents are inconsistent.
2. Macular laser grid photocoagulation may be used as an adjuvant treatment for anti-VEGF in eyes with macular edema secondary to BRVO.

Surgical Treatment Consensus Statements

1. There is no indication at this moment to perform primary vitreous surgery for either central or branch retinal vein occlusion.
2. Pars plana vitrectomy may be considered a salvage treatment for those eyes with macular edema that have failed pharmacological treatment.
3. Surgery is indicated in cases of vitreous hemorrhage and in retinal detachment secondary to RVO.

Neovascular Glaucoma Consensus Statements

1. Successful management of NVG involves controlling IOP by any means and reducing the stimulus for VEGF secretion.
2. Retinal ablative therapy with either pan retinal photocoagulation (PRP) or cryotherapy is the mainstay of therapy for VEGF down regulation.
3. In eyes with synechiae angle closure, surgical control of IOP is required.
4. The long-term success of filtering surgeries with antimetabolites and glaucoma drainage devices are variable.
5. Adjunctive anti-VEGF drugs appear to improve the outcomes in NVG.

Introduction

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Treatments for this indication that have been recently approved by several regulatory agencies throughout the world include the VEGF inhibitor ranibizumab (Lucentis, Genentech), the VEGF and placental growth factor inhibitor aflibercept (Eylea, Regeneron Pharmaceuticals), and a slow release intravitreal implant of dexamethasone (Ozurdex, Allergan). In addition bevacizumab (Avastin, Genentech) has been used extensively in an off-label manner.

These new treatments allow us to preserve vision for many RVO patients who could not have expected such favorable results just 5 or 6 years ago. However, not every treatment is effective for every patient, and whether one option is superior to another or a combination of options is superior to monotherapy, have yet to be definitively determined.

A growing body of literature with strong evidence supports the use of these new treatments. However, in several instances the literature is not conclusive to support unified management of
RVO. This document is a summary analysis on RVO assembled by a group of specialists summoned by the Pan-American Vitreo-Retinal Society (SPRV) to participate in this Latin American consensus.

**CONSENSUS METHODOLOGY**

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The experts that participated in the Latin American Consensus Meeting in RVO are all members of the SPRV. These experts represented Argentina, Brazil, Colombia, Costa Rica, Mexico, Peru and Venezuela. The document resulting from this consensus meeting is the result of a systematic and judicious review of the currently available literature for RVO.

The topics reviewed included epidemiology and risk factors for RVO; natural history, pathophysiology, classification and clinical course; diagnosis; treatment (corticosteroids, laser, surgical, anti-VEGF and combined modalities); and neo-vascular glaucoma. Before the meeting, the participants reviewed the literature by topic and produced a summary with suggested consensus statements. At the meeting, each participant presented the review to the peers and the group discussed all statements until reaching a consensus. All reviews and consensus statements are presented in this document.

1. **Epidemiology**

Retinal vein occlusion (RVO) which includes central retinal vein occlusion (CRVO), hemi retinal vein occlusion (HRVO) and branch retinal vein occlusion (BRVO) are some of the most common acquired retinal vascular abnormalities in adults, only exceeded by diabetic retinopathy. HRVO are considered to be variants of CRVO so they should be treated as such. RVO typically occurs in middle-aged and elderly individuals (older than 50 years), with an equal gender distribution. The reported prevalence of RVO varies between 0.3% and 1.6%. It is reported to be 0.7% for the 49- to 60-year-old group and 4.6% after the age of 80. It is currently estimated that there are about 520 new RVO cases per million people, of which 442 are BRVO cases and 80 CRVO cases. The presence of bilateral disease varies according to the type of RVO. The incidence of BRVO in the fellow eye may be as high as 10%. Approximately 5–10% of CRVO cases were reported to develop RVO in the fellow eye over a one year period.

The effect of ethnicity on the prevalence of RVO is difficult to assess since the vast majority of published studies on RVO prevalence included subjects from a single ethnic group. Of note there isn’t a single population based study of RVO in Latin America.

Epidemiology Consensus Statements

1. There are no population-based data in LATAM on the prevalence or risk factors for RVO.
2. There is the need to identify specific populations in LATAM whose risks are higher for the development of RVO.

2. **Risk Factors for RVO**

RVOs are multifactorial in nature. Abnormalities of the vessel wall, blood flow, blood viscosity and coagulation all play a role in the pathogenesis of a RVO. Of these, the most important factor is the degenerative changes of the vessel wall. Systemic hypertension, diabetes mellitus and hyperlipidemia are the major systemic risk factors associated with RVO. Primary open angle glaucoma is strongly associated to CRVO and HRVO but only weakly associated to BRVO. Optimizing the systemic and ocular factors that influence RVO is prudent, since it may reduce the risk of subsequent RVO in the same or the fellow eye, and may also reduce the severity of subsequent problems in the affected eye.

Given that the most important precipitating and predisposing factor in the development of a RVO is an anatomic one (degenerative changes of the vessel wall), an extensive medical work-out is unnecessary. In general, patients should be evaluated for diabetes mellitus, systemic arterial hypertension and dislipidemia. Patients should not be routinely screened for thrombophilia, unless there is a family history of blood dyscrasias, thrombosis or systemic evidence of clinical abnormalities suggestive of hematological disease.

Risk Factors Consensus Statements

1. Systemic arterial hypertension, diabetes mellitus and hyperlipidemia are the main systemic risk factors.
2. The condition is frequently observed in patients in their 60’s and 70’s
3. Open angle glaucoma is the most important ocular risk factor associated with RVO, particularly CRVO and HRVO.
4. Screening for thrombophilias is not justified in the majority of patients (including younger patients), except for those with a history of recurrent thrombosis elsewhere or a family history of thrombosis.
3. Pathophysiology and Natural History of RVO

3a. Pathophysiology

The retinal veins and arteries share a common fibrous adventitia. BRVO most commonly occurs at arteriovenous crossings where the artery lies on top of the vein.7 The artery is usually sclerotic as a consequence of systemic hypertension or atherosclerotic disease. The vein is pressed by the thickened arteriole, generating a decrease in blood circulation and turbulence that leads to thrombus formation.7 The tissue responds with inflammation and liberation of cytokines and growth factors, such as vascular endothelial growth factor (VEGF), interleukins and migration of activated microglia.

In CRVO, a similar phenomenon occurs at the level of the lamina cribrosa.9 At the lamina cribrosa, the lumen of the central retinal vein narrows. Compression of the adjacent sclerotic artery facilitates thrombus formation. The location of the thrombus with respect to the lamina cribrosa will determine the degree of ischemia. If the thrombus is located more posteriorly, there will be less ischemic occlusion. This is due to the presence of collateral circulation which allows blood flow to bypass the thrombus;18,19

3b. Natural History of RVO

Central Retinal Vein Occlusion

Visual Acuity

The Central Vein Occlusion Study (CVOS) 19, 20, 21 has identified visual acuity (VA) at baseline as a key prognostic factor. Eyes with an initial VA of ≥ 20/40 had a more favorable visual prognosis than those with a worse initial VA. For instance, 65% of eyes that had a VA ≥ 20/40 at baseline remained within those parameters. Only 10% of these eyes lost vision to a level of ≤20/200. In eyes with a baseline VA between 20/50 and 20/200, 19% improved to ≥20/40, 44% remained within 20/200, and 37% lost vision to ≤20/200. In eyes with a baseline VA of ≤20/200, only 1.5% of eyes regained VA to a level of ≥20/40; 19% improved to a VA between 20/50 and 20/200 and 79% remained with a VA ≤ 20/200.20 Other groups have reported similar findings.21, 22

The CVOS arbitrarily defined an eye as ischemic if there were ≥ 10 disc areas of capillary non-perfusion.23 CRVO of all types may evolve into an ischemic form, and thus classification is dependent on time. The CVOS showed that approximately one third of the non-ischemic cases become ischemic (15% in the first 4 months, an additional 19% over the next 32 months of follow-up, for a total of 34% in three years). The development of non-perfusion or ischemia was most rapid in the first 4 months and progressed continuously throughout the entire duration of follow-up.20 A meta-analysis reported that the mean decrease in VA after 12 months or longer follow-up for ischemic CRVO was 35 letters, compared to a decrease of an average of 3 letters in non-ischemic CRVO.20

Branch Retinal Vein Occlusion

Visual Acuity

Vision with BRVO is generally worse than 20/40. Although it generally improves, progression beyond 20/40 is rare.24 The Branch Vein Occlusion Study (BVOS) reported that 20% of untreated eyes experienced significant visual deterioration over time.25 Approximately 50% of untreated eyes with BRVO retained a VA of 20/40 or better, while in 25% of cases, final VA was less than 20/200.25,26 A meta-analysis assessed the natural history and clinical course of vision and ocular complications of untreated symptomatic BRVO cases.24 They showed that overall VA is poor at baseline, ranging from 20/40 to less than 20/200. Over time, VA generally improves, with between 33% and 75% of eyes with BRVO showing at least a 2-line improvement in VA, and mean VA improving by 1 letter at 3 months to 15 letters over 18 months.24

Pathophysiology and Natural History

Consensus Statements

1. The main risk factor for a RVO is an anatomic predisposition that leads to clot formation.
2. Inflammatory cytokines and growth factors such as VEGF are released and are responsible for the complications seen in RVO (macular edema and intraocular neovascularization).
3. Baseline visual acuity is an important prognostic indicator.

4. Diagnosis of RVO

In most cases, the diagnosis of CRVO is straightforward and based on clinical findings. Acutely varying degrees of intraretinal hemorrhage, tortuosity and dilation of the retinal veins in the four quadrants, optic disc edema and macular edema may be seen. In more chronic cases, the hemorrhages and the venous tortuosity may have cleared, leaving macular edema as the only finding. Close examination of the optic disc may reveal the presence of collateral vessels. In BRVO, the findings are limited to a sector of the retina that follows the distribution of a retinal vein. Evaluation with fluorescein angiography (FA) and optical coherence tomography (OCT) are mandatory and necessary for the proper management of patients with RVO.

Retinal Fluorescein Angiography

Retinal fluorescent angiography (FA) is critical to assess retinal perfusion. The use of a 50-degree lens with peripheral sweeps or a wide-field angiogram is
recommended. The frequency at which the FA should be done is subject to the classification, initial treatment and the patient’s clinical course. In general, if there is a clinically significant change, it should be evaluated by angiography to determine the nature of the underlying vascular variation.

**Optical Coherence Tomography**

The OCT is important for the initial evaluation of the degree and extent of macular edema secondary to CRVO. It should be performed at the time of diagnosis. The non-invasive nature of the procedure can be safely repeated, as necessary, to evaluate the response to treatment or to assess a clinically significant change on the clinical course or the visual acuity.

**Diagnosis (FA and OCT) Consensus Statements**

a. FA should be performed to assess retinal perfusion.

b. In patients with extensive hemorrhages, FA could be postponed until there is clearing of the hemorrhage to confirm retinal perfusion.

c. The use of a 50-degree lens with peripheral sweeps or a wide-field angiogram is important to assess peripheral retinal perfusion status.

d. Periodic FA should be done to monitor the retinal perfusion status. There could still be risk of progressive retinal non-perfusion even if the macular edema resolves the eyes.

e. The OCT is an essential tool for the initial evaluation of the degree and extent of macular edema secondary to RVO; it should be done prior to the beginning of and during pharmacological treatment for macular edema secondary to RVO.

5. RVO Treatment

5a. Laser Photocoagulation

Different modalities of laser photocoagulation have been explored as treatment options for RVOs. Pan-retinal photocoagulation (PRP) is the mainstay of therapy for the treatment of intraocular neovascularization. Grid macular photocoagulation and micro pulse laser have been used in the treatment of macular edema secondary to RVOs.

Presumably, PRP destroys photoreceptors and thus diminishes the oxygen consumption of the ischemic retina. This leads to VEGF down regulation and control of the neovascular process.

**CRVO and Panretinal Photocoagulation**

The CVOS study concluded that early PRP in ischemic CRVO does not prevent the development of iris or angle neovascularization. If anterior segment neovascularization is detected, PRP should be performed promptly. In the CVOS, neovascularization regression occurred in >90% of cases treated with PRP and lowered the risk of neovascular glaucoma to 1%.

**CRVO and Grid Laser Photocoagulation**

The CVOS investigated the effectiveness of macular grid laser photocoagulation in improving VA in eyes with perfused macular edema secondary to CRVO. It must be noted that this study pre-dated the use of OCT and FA was used to determine treatment and re-treatment criteria. Although there was a large reduction in macular edema on a fundus fluorescein angiogram at 1 year (69% of the treated group vs. 0% of control eyes), no difference was seen between treated (20/200) and untreated (20/160) eyes in VA at any point during the follow-up period. In conclusion, there was no significant VA benefit from macular grid laser photocoagulation.

**Laser in Branch Retinal Vein Occlusion**

The Branch Vein Occlusion Study (BVOS Group evaluated whether grid laser macular photocoagulation improved VA in patients with VA of 20/40 or worse, resulting from macular edema secondary to BRVO. The grid laser group had statistically significant improvements in VA with 65% (28/43) of treated eyes versus 37% (13/35) of controls gaining ≥2 lines of vision over consecutive visits (P=0.014). This study concluded that grid laser photocoagulation is recommended as an effective treatment to reduce macular edema and to improve VA in BRVO.

In 40% of eyes with BRVO with ≥5 disc areas of capillary non-perfusion on FA, neovascularization will develop. And in 60% of those eyes that develop neovascularization, vitreous hemorrhage will ensue. Scatter laser photocoagulation to the areas of capillary non-perfusion will decrease the incidence of vitreous hemorrhage to 30%. It is recommended that scatter laser photocoagulation be performed only when neovascularization is present, otherwise unnecessary treatment in 60% of eyes will be performed.

**FA Guided Scatter Retinal Laser Photocoagulation**

Many eyes are non-responsive to anti-VEGF agents and despite multiple injections, the macula remains edematous. Since VEGF is a major player in the pathogenesis of macular edema, the question arises as to where the VEGF is coming from. Some have proposed to eliminate regions of ischemic retina that may be a source of VEGF contributing to macular edema. However, the results to date do not appear promising at all.
Laser Photocoagulation

Consensus Statements

1. Macular laser grid photocoagulation improves the visual acuity and macular edema in eyes with macular edema secondary to perfused BRVO, compared to the natural course of the disease.

2. Macular laser grid photocoagulation has demonstrated to be superior to intravitreal triamcinolone in the treatment of macular edema secondary to perfused BRVO.

3. Macular laser grid photocoagulation is not indicated in the treatment of macular edema secondary to CRVO.

4. There is currently not sufficient information to recommend FA guided scatter retinal photocoagulation to decrease the injection burden or to improve the visual outcomes in eyes with macular edema secondary to RVO.

5. The best treatment for intraocular neovascularization is the ablation of the ischemic retina.

5b. Steroid Treatment in Macular Edema Secondary to RVO

The pathogenesis of macular edema secondary to RVO is multifactorial. And although VEGF plays a central role, other inflammatory cytokines have been implicated as well. Thus intravitreal triamcinolone, an intravitreal fluocinolone acetonide implant and a slow release intravitreal implant of dexamethasone have been evaluated as possible therapeutic agents for this condition.

The Standard Care versus Corticosteroid for Retinal Vein Occlusion Study (SCORE) studied the effects of 1 mg and 4 mg of intravitreal triamcinolone, in comparison to the natural history in eyes with macular edema secondary to CRVO, and in comparison to macular grid laser photocoagulation in eyes with macular edema secondary to CRVO. In the BRVO arm of the study, the visual outcomes were similar across all groups. However, the rate of complications, such as cataract and elevation of IOP was higher in the triamcinolone groups. In the CRVO arm of the study, both triamcinolone groups were superior to the natural history. Both doses of triamcinolone had similar functional outcomes but the complications were greater in the eyes treated with 4 mg of triamcinolone. In summary, macular grid laser photocoagulation is preferred over triamcinolone in eyes with macular edema secondary to BRVO. In eyes with macular edema secondary to CRVO, 1 mg of intravitreal triamcinolone was preferred over the natural history of the disease.

Randomized clinical trials have shown that a slow release intravitreal implant of dexamethasone reduced macular edema and improved visual acuity in eyes with RVO in comparison to sham injections. The cumulative response rate was 41% in the 0.7 mg dexamethasone implant group, 40% in the 0.35 mg dexamethasone implant group, and 23% in the sham group (P<0.001). No difference in this primary endpoint was found when comparing the 0.35 and 0.7 mg dexamethasone implant groups.

Although the proportion of eyes achieving at least a 15-letter improvement from baseline, best-corrected visual acuity was significantly greater in the treatment groups from day 30 (21% in the 0.7 mg group vs. 18% in the 0.35 mg group vs. 8% in the sham group; P<0.001) to day 90 (22% in the 0.7 mg group vs. 23% in the 0.35 mg group vs. 13% in the sham group; P<0.001), this effect was not maintained by day 180, when no significant difference from the sham group was identified.

The decrease in mean OCT measured central subfield retinal thickness was significantly greater in both the 0.7 mg and 0.35 mg dexamethasone implant groups (208±201µm and 177±197 µm respectively) than in the sham group (85±173µm) at day 90 (P<0.001), but neither at day 180 nor at any other time point. There was no significant difference between the 0.7 mg and 0.35 mg dexamethasone implant groups in any of the efficacy analyses in this study. In terms of safety measures, ocular hypertension was reported more frequently in the 0.7 mg and 0.35 mg dexamethasone implant groups than in the sham group (P<0.002). Between the 0.7 mg and 0.35 dexamethasone implant groups, five eyes underwent a surgical procedure for IOP lowering. The incidence of cataract was not significantly different for participants randomized to the 0.7 mg (4.1%) or 0.35 mg (4.5%) dexamethasone implant group, compared with participants randomized to the sham procedure group (4.5%) (P=0.079).

It is well known that vitrectomy alters the pharmacokinetics of intravitreal drugs and hastens the clearance of most drugs such as corticosteroids and anti-VEGF agents. The slow release intravitreal implant of dexamethasone has been studied in vitrectomized eyes with diabetic macular edema and has shown promising results. This implies that the pharmacokinetics of the slow release intravitreal implant of dexamethasone is not affected by vitrectomy.

Steroid Treatment

Consensus Statements

Corticosteroids are beneficial for the treatment of macular edema secondary to RVO:

1. 1 mg of intravitreal triamcinolone is more effective than the natural course of macular edema secondary to CRVO and safer than the 4mg dose.
2. Macular grid laser photocoagulation is preferred over intravitreal triamcinolone in eyes with macular edema secondary to BRVO since similar visual outcomes are obtained with both. Nevertheless, the safety profile is better with laser.

3. An intravitreal extended-release implant of dexamethasone improves the visual acuity in eyes with macular edema secondary to RVO.

4. An intravitreal extended-release implant of dexamethasone has a peak effect at 3 months after implantation.

5. Common secondary effects associated to steroid treatment include cataract formation and elevation of intraocular pressure.

6. Vitrectomized eyes may benefit from a slow release dexamethasone intravitreal implant.

**5c. Anti-VEGF for RVO**

There is increasing evidence that VEGF plays a key role in the pathogenesis of macular edema and intraocular neovascularization secondary to retinal vein occlusions (RVO). Experimental models have shown that hypoxia triggers VEGF up-regulation. Increased aqueous VEGF levels have been reported in human eyes with retinal cells to the ischemic regions of the retina. Up-regulation. In enucleated human eyes with neovascular glaucoma secondary to central retinal vein occlusion (CRVO), in situ hybridization techniques localized the VEGF, producing retinal cells to the ischemic regions of the retina. Increased aqueous VEGF levels have been reported in human eyes with both CRVO and BRVO.

There are currently four commercially available anti-VEGF agents in the world. Namely, Pegaptanib sodium (Macugen, Valeant Ophthalmics, Bridgewater, NJ, USA), Ranibizumab (Lucentis, Genentech, South San Francisco, CA, USA), Bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) and Afiblercept (Eylea, Pharmaceuticals Inc, Tarrytown, NY, USA; Regeneron, Bayer HealthCare, Berlin, Germany). Pegaptanib is an aptamer against the VEGF-A 165 isoform. Bevacizumab is a humanized, recombinant monoclonal IgG antibody that binds and inhibits all VEGF-A isoforms. Ranibizumab is the humanized recombinant monoclonal IgG antibody fragment that binds and inhibits all VEGF-A isoforms. Afiblercept is a fusion protein that combines the second domain of human VEGF receptor 1, the third domain of receptor 2 and the Fc domain of IgG 1. It binds VEGF-A and placental growth factor (PIGF).

Several clinical trials have shown the value of VEGF suppression in the management of macular edema secondary to RVO. Pivotal trials include the BRAVO (BRVO) for macular edema associated to BRVO and CRUISE (CRVO) for ranibizumab and GALILEO and COPERNICUS (CRVO) for afiblercept.

In BRAVO, patients with macular edema due to BRVO were randomly assigned to receive monthly injections of 0.3 mg, 0.5 mg or sham injections of ranibizumab for 6 consecutive months. At the sixth month, patients were followed monthly and re-injected as needed. In the first 6 months, a rapid improvement in BCVA (+18.3 for the 0.5 mg group, +16.6 for the 0.3 mg group and +7.3 letters for the sham group; p<0.05) that was statistically significantly different from the sham group was observed in both ranibizumab groups. It was noted that at month 12, both ranibizumab groups maintained the visual acuity gains of the first 6 months.

In the HORIZON extension trial, despite a less frequent follow-up with fewer injections, eyes maintained the gains from the BRAVO trial. The use of macular grid laser may have contributed to the stability of these eyes.

The RETAIN study was an extension study of the patients that completed the HORIZON study. Only 34 patients from the BRAVO Study were enrolled in the RETAIN Study. Patients were followed monthly during the first year of the study and at least every 3 months during the second year of the study. Reinjections were performed if intraretinal fluid was identified. On average, patients had a follow-up of 4 years. The results from this study demonstrate the excellent long-term outcomes of eyes with macular edema secondary to a BRVO. Fifty percent of eyes had resolution of macular edema. Resolution of macular edema was defined as the absence of intraretinal fluid for at least 6 months from the last injection. At the last visit, 62% of eyes had an improvement of ≥ 3 lines from the BRAVO trial baseline and 80% of eyes had a BCVA ≥ 20/40.

In the CRUISE trial, the only difference was that no macular laser treatment was allowed. In the first 6 months, a rapid improvement in BCVA (+14.9 for the 0.5 mg group, +12.7 for the 0.3 mg group and +0.8 letters for the sham group; p<0.05) that was statistically significantly different from the sham group was observed in both ranibizumab groups. At month 12, both ranibizumab groups maintained the visual acuity gains of the first 6 months.

At the end of the HORIZON-CRUISE trial, the BCVA gains were not sustained and patients lost an average of 4 letters. These results indicate that PRN quarterly dosing is not sufficient to treat macular edema due to CRVO. It appears that some eyes stabilize after a few consecutive monthly injections and require a few injections thereafter but the vast majority requires frequent follow-up and multiple injections to control macular edema. Findings from TD-OCT may be used to predict visual outcomes. Persistent macular edema at month 3 as measured by TD-OCT indicates a worse prognosis and probable need for more injections and continuous monitoring.

In the RETAIN-CRVO study, 32 patients were enrolled and had an average follow-up of 4 years. Unlike the BRVO patients, the long-term outcomes in CRVO are more guarded. Results from this study showed that 44% of eyes had resolution of macular edema, 53% had an improvement of ≥ 3 lines from the CRUISE trial baseline and 44% of eyes had a BCVA ≥ 20/40. Eyes that had resolution of macular edema had a statistically significantly greater improvement in BCVA (25.2 vs 4.3 letters) and a statistically significantly greater proportion of eyes with BCVA ≥ 20/40 (64.3% vs 27.8%) as compared to those eyes without resolution. Results from another small study indicate that progression of retinal non-perfusion continues, particularly in eyes where macular edema has not resolved and anti-VEGF injections are given sporadically. The authors from this study state that in eyes with macular edema secondary to RVO, the resolution of macular edema...
aqueous VEGF levels have been reported in human eyes with months. At the sixth month, patients were followed monthly and 0.5 mg or sham injections of ranibizumab for 6 consecutive
Valeant Ophthalmics, Bridgewater, NJ, USA),38 Ranibizumab neovascularization secondary to retinal vein occlusions (RVO). for ranibizumab and GALILEO and COPERNICUS (CRVO) for third domain of receptor 2 and the Fc domain of IgG 1. It binds inhibits all VEGF-A isoforms. Aflibercept is a fusion protein that recombinant monoclonal IgG antibody fragment that binds and is an aptamer against the VEGF-A 165 isoform.38 Bevacizumab is USA; Regeneron, Bayer HealthCare, Berlin, Germany). Pegaptanib treatment was allowed. 61 In the first 6 months, a rapid improvement an improvement of ≥ 3 lines from the BRAVO trial baseline and 80% of Fifty percent of eyes had resolution of macular edema. Resolution of term outcomes of eyes with macular edema secondary to a BRVO. The results from this study demonstrate the excellent long-

Vitrectomized eyes may benefit from a slow release 4. An intravitreal extended-release implant of different from the sham group was observed in both ranibizumab groups. It (+18.3 for the 0.5 mg group, +16.6 for the 0.3 mg group and +7.3 dexamethasone has a peak effect at 3 months with macular edema secondary to RVO. dexamethasone improves the visual acuity in eyes outcomes are obtained with both. Nevertheless, edema secondary to BRVO since similar visual

In the RETAIN Study. Patients were followed with macular edema secondary to RVO, the resolution of macular edema

In the HORIZON-CRUISE trial, the BCVA gains were not 3. There is considerable variability among patients with RVO. Some stabilize after a few consecutive monthly injections and require a few injections thereafter but the vast majority, particularly patients with CRVO, require frequent follow-up and multiple injections to control macular edema

In the HORIZON extension trial, despite a less frequent follow-up with an average follow-up of 4 years. Unlike the BRVO patients, the long-

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secondary to BRVO, the addition of grid laser to intravitreal bevacizumab reduced the number of injections compared to bevacizumab monotherapy.\textsuperscript{42} The outcomes following a combination of corticosteroids with anti-VEGF agents are inconsistent.

The combination of intravitreal triamcinolone and bevacizumab does not seem to improve the visual outcomes of eyes with macular edema secondary to RVO over bevacizumab monotherapy.\textsuperscript{43, 44} In contrast, combination therapy of intravitreal bevacizumab and the intravitreal implant of dexamethasone appear to be promising.\textsuperscript{45, 46}

**Combined Treatments Consensus Statements**

1. The outcomes following a combination of corticosteroids with anti-VEGF agents are inconsistent
2. Macular laser grid photocoagulation may be used as an adjuvant treatment for anti-VEGF in eyes with macular edema secondary to BRVO.

**5e. Surgical Treatment**

The role of vitreous surgery remains controversial in the management of macular edema secondary to CRVO and BRVO.

Vitrectomy improves oxygenation of the vitreous cavity and removes growth factors such as VEGF and IL-6.\textsuperscript{47-50} However, there have been no randomized clinical trials evaluating the role of vitrectomy in the management of macular edema secondary to RVO. Several uncontrolled series have shown that vitrectomy consistently improves macular edema, but the effects on visual acuity are more variable.\textsuperscript{51-53}

Several adjuvant surgical techniques such as internal limiting membranes,\textsuperscript{54, 55} arteriovenous sheathotomy,\textsuperscript{56, 57} trans-vitreous optic disc surgeries\textsuperscript{58, 59} and retinal vein canulation and thrombolysis,\textsuperscript{60} have been attempted in the hopes of improving the outcomes. Transvitreal optic disc and arteriovenous sheathotomies have been abandoned for their lack of effect and high complication rate.\textsuperscript{58}

**Surgical Treatment Consensus Statements**

1. There is no indication at this moment to perform primary vitreous surgery for either central or branch retinal vein occlusion.
2. Pars plana vitrectomy may be considered a salvage treatment for those eyes with macular edema that have failed pharmacological treatment.
3. Surgery is indicated in cases of vitreous hemorrhage and in retinal detachment secondary to RVO.

**6. Neovascular Glaucoma**

NVG is a potentially devastating sequel to various ocular and systemic diseases such as CRVO that are characterized by profound retinal ischemia. Anterior segment neovascularization (ASNV) occurs as a consequence of retinal ischemia. Ischemia is one of the most important up-regulators of VEGF secretion. The amount of VEGF secreted is proportional to the degree of ischemia. Thus ASNV is rarely seen following BRVO. The VEGF produced by the ischemic retina eventually makes its way into the anterior segment where it induces neovascularization of the angle and iris. If this ASNV is not controlled in a timely manner, peripheral anterior synectiae with obstruction of the trabecular meshwork will lead to an elevation of intraocular pressure and neovascular glaucoma (NVG).

The CVOS showed that approximately one third of the non-ischemic cases become ischemic (15% in the first 4 months, an additional 19% over the next 32 months of follow-up, for a total of 34% in three years). Therefore all cases of CRVO, whether or not ischemic at baseline, must be carefully monitored over time.\textsuperscript{20, 23} Only ischemic cases will develop ASNV. Approximately 35% of eyes with ischemic CRVO will develop ASNV.\textsuperscript{19, 61-67} In approximately 75% of cases that develop ASNV, the ASNV will develop by 3 months. An additional 10% will develop by 1 year and the remaining 15% will occur in the following 2 years. In order to detect early signs of anterior segment neovascularization, the CVOS has recommended a monthly undilated slit lamp exam coupled with gonioscopy in eyes with CRVO during the first 6 months of the disease.\textsuperscript{23} Not all cases of ASNV go on to develop NVG. Up to a third of eyes that develop ASNV do not develop NVG.\textsuperscript{18}

Successful management of NVG involves controlling IOP by any means and reducing the stimulus for VEGF secretion. Retinal ablative therapy with either PRP or cryotherapy is the mainstay of therapy for VEGF down regulation. Cryotherapy should be reserved for cases with media opacities that don’t allow adequate PRP because cryotherapy causes more inflammation and pain than PRP.\textsuperscript{23} In cases where synectiae angle closure from neovascularization of the angle has occurred, IOP needs to be controlled surgically.\textsuperscript{68} Severe inflammation limits the long-term success of filtering surgeries even with adjunctive 5-fluorouracil or mitomycin c.\textsuperscript{69}

Glucomatous drainage devices have become popular options in this setting since their success is less dependent on the control of inflammation. However, long-term results remain variable.\textsuperscript{71, 72} Additional options for eyes with limited visual potential are cyclo-destructive procedures with either cryotherapy or laser.\textsuperscript{73} Precise intraocular pressure control is more difficult to obtain with cyclodestructive procedures. In many cases, more than one treatment is needed to obtain adequate IOP control. Excessive treatment may lead to hypotonic and phthisis bulbi.\textsuperscript{74}

Anti-VEGF agents have gained widespread clinical acceptance as adjuncts in the treatment of NVG. Rapid disappearance of the neovessel in the retina and iris after a single Intravitreal bevacizumab application has been reported.\textsuperscript{75} Adjuvative anti-VEGF drugs appear to improve the outcomes in NVG.\textsuperscript{76-78}

**Neovascular Glaucoma Consensus Statements**

1. Successful management of NVG involves controlling IOP by
any means and reducing the stimulus for VEGF secretion.

2. Retinal ablative therapy with either PRP or cryotherapy is the mainstay of therapy for VEGF downregulation.

3. In eyes with synchiae angle closure surgical control of IOP is required.

4. The long-term success of filtering surgeries with anti-metabolites and glaucoma drainage devices are variable.

5. Adjunctive anti-VEGF drugs appear to improve the outcomes in NVG.