Ophthalmol Ther (2012) 1:3
DOI 10.1007/s40123-012-0003-y

REVIEW

Practical Management of Retinal Vein Occlusions

Carlo La Spina · Umberto De Benedetto · Maurizio Battaglia Parodi · Gabriel Coscas · Francesco Bandello

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Received: June 19, 2012 / Published online: August 9, 2012

ABSTRACT

Retinal vein occlusion (RVO) is the second most common cause of visual impairment due to retinal disease after diabetic retinopathy. Nowadays, the introduction of new, powerful diagnostic tools, such as spectral domain optical coherence tomography, and the widespread diffusion of intravitreal drugs, such as vascular endothelial grow factor inhibitors or implantable steroids, have dramatically changed the management and prognosis of RVO. The authors aim to summarize and review the main clinical, diagnostic, and therapeutic aspects of this condition. The authors conducted a review of the most relevant clinical trials and observational studies published within the last 30 years using a keyword search of MEDLINE, EMBASE, Current Contents, and Cochrane Library. Furthermore, for all treatments discussed, the level of evidence supporting its use, as per the US Preventive Task Force Ranking System, is provided.

Keywords: Bevacizumab; Branch retinal vein occlusion; Central retinal vein occlusion; Cystoid macular edema; Management; Radial neurotomy; Ranibizumab; Retinal vein occlusion; Vascular endothelial growth factor

C. La Spina · U. De Benedetto · M. B. Parodi · F. Bandello (✉)
Department of Ophthalmology, Scientific Institute San Raffaele, University Vita-Salute, Via Olgettina, 60, 20132 Milan, Italy
e-mail: bandello.francesco@hsr.it

G. Coscas
Hôpital Intercommunal de Créteil, Service Universitaire d'ophtalmologie, Créteil, France

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INTRODUCTION AND PATHOPHYSIOLOGY

Retinal vein occlusion (RVO) is currently the second most common cause of visual impairment due to retinal disease after diabetic retinopathy [1]. It is defined as a vascular disorder characterized by engorgement and dilatation of the retinal

veins with secondary, mostly intraretinal hemorrhage, and retinal edema. Retinal ischemia, cotton wool spots, exudates, and macular edema can also be present [2]. The incidence of vein occlusion is 0.7% for the age group 49–60 years and 4.6% after 80 years of age, with no gender disparities [3].

RVOs are classically divided into two groups by their location: central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). In fact, although CRVOs involve the whole venous retinal system, in BRVO the venous engorgement involves only a branch of the retinal venous network. If only a hemisphere of the fundus is involved, the presumed site of the occlusion is one of the two trunks of an abnormally split intraneural central retinal vein. This entity (hemicentral RVO) is considered a variant of CRVO [1, 2]. When the arteriovenous crossing is located on or close to the optic disc, a hemispheric RVO can develop, extending to a hemiretina. CRVO is presumably determined by an increased venous outflow resistance located at the lamina cribrosa level; this resistance is more distal in a BRVO. CRVO can be limited to a small artery crossing a small macular vein, or involve a whole quadrant when occurring at the edge of the optic nerve. BRVO occurs at retinal arteriovenous crossing sites, where the vein shares the adventitia with the artery; thus, being vulnerable to its compression. Fluorescein angiography has demonstrated turbulent blood flow at these sites; thus, leading to a predisposition toward endothelial damage and thrombus formation [4]. In eyes affected by the advanced stages of CRVO, histopathologic studies show a thrombus placed at or just posterior to the lamina cribrosa [5]. The main hypothesis explains its formation as the central retinal vein is compressed by the central artery at the tract where a common fibrous sleeve is shared [6].

METHODS

The authors conducted a review of the most relevant clinical trials and observational studies published within the last 30 years using a keyword search of MEDLINE, EMBASE, Current Contents, and Cochrane Library. Furthermore, for all treatments discussed, the level of evidence supporting its use, as per US Preventive Task Force Ranking System, is provided.

SIGNS AND SYMPTOMS

CRVO is clinically characterized by marked dilatation and tortuosity of all retinal veins, disk edema, deep and superficial hemorrhages, cotton wool spots, and retinal edema. The presence or absence of widespread areas of capillary nonperfusion sets the distinction into “ischemic” and “nonischemic” CRVO. These two forms clearly differ in natural history, prognosis, and therapeutic approach and, as will be discussed ahead, a nonischemic CRVO may eventually turn into an ischemic form. BRVO presents similar features confined to a section of the retina [7]. The obstructed vein appears dilated and tortuous and, with time, the corresponding artery may become narrowed and sheathed.

Typically, a patient with CRVO complains of a progressive, painless, and severe decrease in visual acuity (VA), without other symptoms. The VA at presentation has been demonstrated to be a key prognostic factor: an initial VA of 20/40 or better is associated with a more favorable visual prognosis. Only 20% of eyes with an initial VA between 20/50 and 20/200 improve spontaneously to 20/50, while 80% of patients whose baseline vision is worse than 20/200 remain at this level or deteriorate further [8].

Loss of VA is usually more pronounced with ischemic compared with nonischemic CRVO, although vision also tends to be poor in eyes with nonischemic CVRO [2, 9].

At presentation, patients with BRVO complain of blurred vision from retinal hemorrhage or macular edema. Occasionally, subjective spots, strands, or curtains may occur due to vitreous hemorrhage. VA is generally worse than 20/40 [7–9].

RISK FACTORS

Major cardiovascular risk factors, such as diabetes, hypertension, and dyslipidemia, are more often associated with RVO, whereas minor risk factors, such as smoking and high body mass index, show a less consistent linkage to RVO [10, 11].

Open-angle glaucoma is the main ophthalmological risk factor; the increased intraocular pressure reduces the retinal venous outflow, leading to flow stasis. It is clearly associated with CRVO [12, 13], while only one study reveals a statistically significant linkage to BRVO [14].

To date, the role of thrombophilic defects is controversial. As revealed by two meta-analyses, the factor V Leiden mutation clearly increases the risk of RVO by approximately 50–60% [1, 15]. Interestingly, other rather common prothrombotic defects, such as deficiencies of antithrombin and protein C or S, are not associated with RVO [15]. The role of lupus anticoagulant factor and anticardiolipin antibodies have not been fully understood, but their relationship with RVO seems to be weak so far [7, 16].

Some studies suggest that patients suffering from RVO could have an underlying genetic predisposition [2, 7]. In fact, as RVO occurs where the blood flow is locally turbulent, changes in platelet activity due to polymorphisms in the platelet receptors may be important. Even though further studies are needed to reveal a possible genetic cause of RVO, the authors believe it is advisable to screen patients for family and personal history of major thrombotic events.

In younger patients, other factors, including the use of oral contraceptives and positive history for vasculitis, have been linked to RVO [17], even though some studies claim there is no significant association [18, 19]. Recently, an association with sleep apnea has also been reported [20]. Other rare associations include inflammatory diseases, myeloproliferative disorders (found in approximately 1% of RVO patients), and autoimmune disorders, such as Beçet's disease, systemic lupus, and Goodpasture's syndrome [2].

NATURAL HISTORY

After a CRVO has occurred, VA is usually poor and tends to remain impaired during follow-up, despite therapeutic efforts. It has been reported that at least 75% of eyes with CRVO (ischemic and nonischemic) had a VA of 20/40 or worse after 12 months [8]. As mentioned previously, the presence and the extension of nonperfused retinal areas are correlated with bad visual outcome and higher rates of complication, such as neovascular glaucoma. It is, thus, essential to regularly monitor CRVO patients for ischemic areas using fluorescein angiography. A nonischemic CVRO may convert into an ischemic CVRO, and such an irreversible event is known to happen in up to 34% of cases after 3 years of follow-up [2, 8], being more rapid during the first 4 months.

The development of anterior segment neovascularization is the most severe

complication of untreated CRVOs, leading to neovascular glaucoma and, less frequently, to vitreous hemorrhage. The strongest predictors of anterior segment neovascularization are VA and the extension of nonperfused areas. It has been reported that, of those eyes initially categorized as nonperfused or indeterminate, 35% developed iris or angle neovascularization, compared with 10% of eyes initially categorized as perfused [8]. Ischemic CVRO have been reported to lead to neovascular glaucoma in up to 23% of cases within 15 months [9]. A 10% rate of vitreous hemorrhages in ischemic CRVO patient at 9 months follow-up has also been reported [21].

Macular edema is another major complication of both ischemic and nonischemic CRVO, and is often already present at baseline. If left untreated, it tends to become chronic, leading to a poor visual prognosis. It has been stated in many studies that the longer the duration of edema, the greater the likelihood of permanent structural damage to the fovea [2, 8, 9]. Therefore, early treatment is justified and encouraged.

When a BRVO occurs, patients usually experience a VA improvement during the first months of follow-up, although improvements beyond 20/40 are rather uncommon [3]. Nevertheless, as reported by the Branch Vein Occlusion Study, 20% of untreated eyes experienced a significant visual deterioration over time [22]. Fortunately, the incidence of neovascularization is low and appears to be closely related to the retinal ischemic burden. In fact, patients showing nonperfused areas larger than five optic disc sizes may present neovascularization in up to 30% of cases [23]. Macular edema is more common after a BVRO and its incidence over a 1-year period is reported to be between 5–15% [22, 23].

Involvement of the contralateral eye has been reported in approximately 10% at 1-year follow-up, whereas 4–7% of cases show bilateral involvement at baseline, being often related to the coexistence of multiple risk factors [2, 23, 24].

MANAGEMENT

The first step after a RVO diagnosis is a careful medical investigation for underlying systemic risk factors. Treatment of systemic conditions, such as unknown diabetes or hypertension, is mandatory to prevent future nonocular life-threatening events. Furthermore, it is the only way to reduce risk for involvement of the contralateral eye [23, 24]. Ocular conditions, such as glaucoma, must be identified and treated, even though it is not clear to date if a prompt resolution of these predisposing factors is associated with a better visual prognosis.

The efficacy of anticoagulant, fibrinolytic, and antiplatelet drugs have been tested in many trials, but results remain disappointing [2]. The poor long-term results of such drugs in VA do not seem to support their use, considering the severity of local adverse effects (retinal and vitreous hemorrhages) and systemic adverse effects (major, life-threatening bleeding).

The only systemic treatment that has revealed beneficial effects is hemodilution (level II-1), if performed promptly after diagnosis of RVO. Recently, a prospective, multicenter study showed a positive result of erythrocytapheresis a as first-line therapy for RVO [25]. Despite that, many contraindications to this procedure (for example, ischemic CRVOs, diabetes, uncontrolled hypertension, cardiac or renal failure, and anemia) may limit the applicability of this treatment [25].

Ophthalmological Management of CRVO

The diagnosis of CRVO must be followed by the differentiation between the ischemic and nonischemic form. A fluorescein angiogram is an essential first step to detect nonperfused capillary areas, their extension, and presence of macular ischemia (seen as a foveal avascular zone enlargement). At early stages, these angiographic features are often difficult to recognize, but there are some clinical signs, typical of ischemic forms that may support the differential diagnosis: poor VA; relative afferent pupillary defect; presence of multiple dark, deep intraretinal hemorrhages; and the presence of multiple cotton wool spots [8]. Furthermore, functional tests, such as electroretinography and visual field, can help the clinician eliminate the presence of an ischemic form.

A major complication of both perfused and nonperfused forms is macular edema. The presence of cystoid macular edema has to be eliminated at baseline, and rechecked periodically during follow-up by performing spectral domain OCT (SD-OCT). This is another important tool in the management of patients with RVO as it helps to quantify the amount of edema and supplies additional information, such as whether the accumulated fluid is located mostly within the retinal layers or in the subretinal space [26]. SD-OCT can also detect a thinning of the nerve fiber layer due to an important ischemic component.

In cases of nonischemic CRVO with VA better than 20/40 at presentation, treatment is not recommended, as the prognosis is usually favorable. Strict monitoring for the first 3 months, and then every 2 months for the first year is advisable. The aim of such intensive follow-up is to identify and promptly treat visual-threatening complications, such as persistent macular edema and ischemic conversion.

In cases of nonischemic CRVO with VA less than or equal to 20/40 (almost always due to macular edema), and ischemic forms with macular edema and macula that is still perfused, early treatment should be considered. It is of interest that this management is in contrast to previous common suggestions of waiting at least 3 months before treatment of RVOs [27].

Grid laser photocoagulation as first-line therapy is not indicated, as it was not able to provide a statistically significant VA benefit, in spite of reducing macular edema [28]. Currently, the only indication for grid laser photocoagulation are patients non- or partially responding after multiple antivascular endothelial grow factor (VEGF) administrations and scatter treatment of nonperfused areas (level II-1).

The use of corticosteroids is based on their ability to reduce capillary permeability, and to inhibit the expression of the VEGF gene and the metabolic pathway of VEGF. Several formulations have been tested in randomized clinical trials (RCT). Triamcinolone acetonide 4 mg has been used for many years as an off-label treatment (level III), but has been now discontinued partly due to the lack of RTC supporting its benefit, and partly because of high rate of side effects [2]. Recently, in the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) trial [29], a new 1 mg preservative-free preparation revealed good results and an acceptable safety profile with a lower intraocular pressure increase rate (level I). Nonetheless, triamcinolone acetonide 1 mg is available only in the USA market so far, and cannot be used in Europe.

A dexamethasone intravitreal implant has been successfully tested in the Global Evaluation of Implantable Dexamethasone in Retinal Vein Occlusion with Macula Edema

(GENEVA) trial for RVO-related macular edema (level I). The biodegradable implant containing 0.7 mg dexamethasone revealed an improvement of VA, with a peak effect after 2 months and a progressive decline to baseline values at 6 months. On average, patients achieved a 10-letter gain at 60 days after implantation. VA improvement could be effectively achieved after a second injection at month 6 over a 1-year follow-up [27]. Due to its good safety profile, dexamethasone intravitreal implant is currently approved by the US Food and Drug Association (FDA) and EU.

Another promising approach is anti-VEGF intravitreal administration. Pegaptanib, a selective anti-$VEGF^{165}$ blocker, has been the first to be explored. A single RTC supports its use [2], but long-term efficacy is still controversial (level II-1).

Bevacizumab, a pan-VEGF blocker, is being widely used due to its relatively-low cost. Due to the lack of RTCs, RVO treatment remains an off-label indication, even if several uncontrolled case series have reported promising results [30, 31] (level II-3).

Ranibizumab, a pan-VEGF blocker, is an anti-VEGF that has been approved for RVO-related macular edema treatment in USA (level I). The Clinical Trial of Subjects with Macula Edema Secondary to Central Retinal Vein Occlusion (CRUISE) trial revealed the efficacy of ranibizumab at 6 months and the VA gain could be sustained up to a 12-months follow-up [32]. VEGF Trap-Eye is a 115 kDa recombinant fusion protein with portions of the VEGF receptor 1 and 2, and the Fc region of human immunoglobulin G (IgG), binding all VEGF-A isoforms. Encouraging 1-year results, still unpublished to date, come from the phase 3 General Assessment Limiting Infiltration of Exudates in Central Retinal Vein Occlusion with VEGF-Trap Eye (GALILEO) study: 60.2% of patients receiving monthly VEGF Trap-Eye 2 mg gained at least 15 letters of vision from baseline, compared to 22.1% of those receiving sham injections (level II-1).

In cases of ischemic CVRO (defined as more than 10-disk diameter of retinal nonperfusion), pan-retinal photocoagulation (PRP) should be considered to avoid neovascularization. If during follow-up visits (that must be scheduled at least monthly), anterior or posterior segment neovascularization is noted, prompt PRP should be suggested. Several case series studies reveal the beneficial effect of combining anti-VEGF and PRP, especially in cases of neovascular glaucoma [2, 33]. Unfortunately, no RTC currently support these data (level II-2).

Ophthalmological Management of BRVO

A BRVO with perfused periphery and normal VA requires only a careful follow-up. If significant macular edema is detected, the treatment should be started as soon as possible. If VA is deteriorated at baseline or the patient complains of a loss during follow-up, significant macular edema is likely to be present. Grid laser therapy has been the reference standard therapy for BVRO-related macular edema for many years. It remains a valid option when the patient has a VA of 20/40 or less, persistent edema lasting for 4 months or longer, and the permanence of macular hemorrhages (level I).

Similarly to CRVO treatment, intravitreal drug administration is the latest breakthrough. Dexamethasone intravitreal implant has already been FDA and EU approved, based on results from the GENEVA trial (level I). Interestingly, a recent analysis of the GENEVA results [27] has shown that treating edema secondary to BRVO of short duration has a

better effect than delaying the treatment. Furthermore, the efficacy and acceptable safety profile of the triamcinolone acetonide 1 mg dosage have been shown in the SCORE trial [29] (level I).

Among anti-VEGF medications, the off-label use of bevacizumab is common for BRVO macular edema treatment even in the absence of RCT data. Ranibizumab is the only anti-VEGF treatment that has received FDA approval for both BRVO and CRVO-related macular edema. In the Branch Retinal Vein Occlusion (BRAVO) study, a 0.5 mg dose (repeated almost monthly) gained significantly better 6-month results compared to sham and laser treatment [34].

In cases of ischemic areas with a well-perfused macula, laser coagulation should be considered only if the area is extensive (level II-1). Otherwise, the complication rate of BRVO remains very low.

With regards to CRVO, in case of macular ischemia, intravitreal treatment should be contemplated as outlined above, with informed consent of patients as the prognosis can be poor.

SURGICAL OPTIONS

Many surgical treatments have been proposed for RVO. In radial optic neurotomy (RON), an incision into the nasal side of the optic nerve, radial to the nerve itself, is performed to induce a surgical decompression of the vein and a postoperative development of optociliary venous anastomosis [35–39]. Pilot studies have reported transient improvement of VA, but randomized, prospective trials did not show beneficial effects of this procedure [40] (level II-3). Recently, safety concerns have been raised after some studies reported acute optic nerve ischemia and visual loss after the procedure [40].

Other possible complications of this procedure are laceration of central retinal artery or vein, globe perforation, retinal detachment, vitreous hemorrhage, neovascular glaucoma, or choroidal neovascularization (CNV) [36, 41, 42]. Consequently, benefits of RON appear to be controversial and its efficacy remains to be proven in prospective, RCTs.

In chorioretinal venous anastomosis, a shunt is created between the retinal vein, and the choroid to bypass the occluded vein and to improve retinal outflow. It can be induced either by laser or surgery (level III). In the former case, frequent serious complications have been reported, such as CNV, segmental retinal ischemia, or retinal detachment [36, 43–45]. In the latter case a pars plana vitrectomy is followed by a Mersilene™ (Ethicon, Inc., Somerville, NJ, USA) suture insertion beneath the retina adjacent to the major retinal veins [44] or by an Er:YAG (erbium doped yttrium–aluminum-garnet) laser [46]. Although performing a surgically-induced chorioretinal venous anastomosis does not lead to reperfusion of the areas with capillary nonperfusion, it is thought to reduce the ischemia of para and perifoveal areas, leading to VA improvement resulting from the improved venous outflow and reduced macular edema. Nevertheless, these procedures are still considered experimental. Furthermore, pars plana vitrectomy with or without internal limiting membrane (ILM) peeling has been proposed in RVO cases. Some studies have reported a reduction of the macular edema [47, 48], but the exact mechanism is still unknown. It has been proposed that the removal of vitreous cytokines and VEGF, and the enhancing oxygen transport to the retina could play an important role [49, 50]. However, many studies did not confirm the benefits of

this kind of surgery and the long-term effects are unknown [51].

Some studies have promoted the administration of tissue plasminogen activator (t-PA) directly to the affected retinal vein to obtain a rapid lysis of the thrombus with a precise visualization of the occlusion site, and with the administration of a very small dose of drug [52] (level III). Visual improvement after this technique was reported in 54% of the 28 treated eyes [53], but results still remain controversial.

Another proposed approach consists of the dissection of the common adventitial sheath at the level of the arteriovenous blockage site in patients affected by BRVO. Unfortunately, until now, most studies have failed to show a convincing improvement on outcomes in BRVO that could justify the risks of the surgical procedure [54, 55]. In conclusion, many different surgical treatments have been proposed but, to date, results remain inconsistent and controversial. New prospective RCTs are necessary to confirm a possible role of these surgical approaches in the management of patients affected by RVO.

ACKNOWLEDGMENTS

Dr. Bandello is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Conflict of interest. Dr. Bandello is an advisory board member for Allergan, Novartis Pharmaceuticals Corporation, Farmila-Thea, Bayer Schering Pharma, Pfizer, Alcon, Bausch & Lomb, Genentech, Alimera Sciences, Sanofi Aventis, and Thrombogenics.

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