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Treatment of retinal vein occlusion – current state of knowledge

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Summary: Retinal vein occlusion is the second most common retinal vascular disease. Branch retinal vein occlusion is the most frequent form and differs significantly from central retinal vein occlusion in terms of epidemiology, clinical course, risk of complications, and therapeutic management. The disease shows a strong association with cardiovascular risk factors, and its occurrence is linked to increased mortality.

The pathogenesis of the occlusion corresponds to the classic Virchow's triad and includes endothelial damage, venous stasis, and hypercoagulability. Vessel closure leads to retinal ischemia, which induces overexpression of vascular endothelial growth factor and inflammatory mediators, potentially resulting in macular edema and neovascular complications, including neovascular glaucoma.

Therapeutic management of retinal vein occlusion focuses on treating complications responsible for vision deterioration. The treatment of choice for macular edema secondary to retinal vein occlusion is intravitreal anti vascular endothelial growth factor therapy. Retinal laser therapy remains the primary method for managing neovascular complications; however, it is not used prophylactically. Intravitreal steroids serve as second-line treatment for patients with an insufficient response or contraindications to anti vascular endothelial growth factor therapy. Vitrectomy is reserved for selected complications, particularly in cases of massive or recurrent vitreous hemorrhage.

Key words: retinal vein occlusion (RVO), vascular endothelial growth factor (VEGF), laser therapy, vitrectomy (PPV), RVO drug program.

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease, second only to diabetic retinopathy [1, 2].

Branch retinal vein occlusion (BRVO) represents a clinically distinct form of retinal venous occlusion, differing clearly from central retinal vein occlusion (CRVO) in terms of prevalence and population burden [1, 3]. In the European population, BRVO is the most frequent subtype of retinal venous occlusion. The five-year cumulative incidence of BRVO is approximately 0.35%, compared with 0.043% for CRVO, while the ten-year incidence reaches 0.64% for BRVO and 0.14% for CRVO. The prevalence of RVO in the European population is lower than in the populations of North America and the Western Pacific region, suggesting significant geographic variation and the potential influence of environmental and demographic factors. RVO shows a significant association with classic cardiovascular risk factors, such as dyslipidemia, diabetes, and a positive family history of stroke or myocardial infarction [1, 4]. Age represents another significant independent risk factor for the development of RVO [4]. Additional risk factors include tobacco smoking, open-angle glaucoma, hypercoagulable states, and hypothyroidism. Both BRVO and CRVO are associated with an increased risk of all-cause mortality, independent of traditional cardiovascular risk factors, underscoring the systemic significance of the disease.

Pathomechanism

The pathogenesis of RVO corresponds to the classic Virchow's triad, which includes endothelial damage, venous stasis, and hypercoagulability. Close proximity between the artery and vein within a shared adventitial sheath causes a stiffened and dilated artery – such as in the course of arterial hypertension – to exert pressure, leading to deformation and loss of elasticity of the venous wall [1, 3]. This promotes turbulent blood flow within the affected vein and contributes to a prothrombotic state. When a thrombus forms and RVO occurs, retinal ischemia induces local overexpression of hypoxia-dependent factors, particularly vascular endothelial growth factor (VEGF), and inflammatory mediators [1, 2, 5].

Venous occlusion leads to an increase in venous pressure within the retinal bed, resulting in intraretinal hemorrhages, edema, and ischemia. This initiates a complex molecular cascade involving the overexpression of hypoxia-dependent factors, specifically VEGF and pro-inflammatory mediators responsible for the further progression of vascular changes. VEGF is a potent proangiogenic factor. By acting on vascular endothelial cells, it induces their proliferation, resulting in pathological neovascularization, and increases vascular wall permeability, leading to the breakdown of the blood-retinal barrier. Chronic, persistent ischemia results in continuous overexpression of VEGF within the intraocular environment and the progression of neovascular changes in both the retina and the filtration angle and iris. Anti vascular endothelial growth factor (anti-VEGF) therapy, through the direct inhibition of the VEGF factor, limits endothelial cell proliferation and reduces pathological vascular permeability, thereby inhibiting the neovascularization process. Therapeutic management in RVO focuses on treating secondary complications that lead to the loss of visual functions, particularly macular edema, retinal neovascularization, and anterior segment neovascularization, which can result in the development of neovascular glaucoma [6, 7].

Treatment

The treatment of BRVO/ CRVO can be divided into two categories. The first involves the optimal reduction of cardiovascular risk factors, including control of arterial blood pressure, glycemia, and lipid levels, as well as smoking cessation. In this regard, close cooperation with a primary care physician, cardiologist, and diabetologist is crucial. The second treatment approach lies primarily within the domain of ophthalmology and focuses on minimizing complications resulting from BRVO or CRVO. A key role in this process is played by anti-VEGF therapy (e.g., bevacizumab, ava-

ilable in Poland through the national drug program). In the case of neovascular changes involving the retina, iris, or optic nerve, effective retinal photocoagulation is essential [2, 5, 6]. Vitrectomy is most commonly performed in vein occlusions complicated by an epiretinal membrane, vitreous hemorrhage, or when panretinal photocoagulation cannot be carried out (due to a narrow pupil, hemorrhages preventing visualization and assessment of the retina, or lack of patient cooperation during laser treatment).

1. Anti-VEGF injections

VEGF plays a crucial role in the pathophysiology of macular edema in RVO, exerting two fundamental biological effects on retinal microcirculation. First, by activating VEGFR-2 (vascular endothelial growth factor receptor 2) on endothelial cells, VEGF induces phosphorylation of tight junctions, disrupts the blood–retina barrier, and increases vascular wall permeability, clinically manifesting as macular edema. Second, VEGF acts as a potent mediator of angiogenesis, stimulating endothelial cell proliferation and migration, and promoting the formation of pathological vessels in areas of chronic ischemia [1]. Intravitreal anti-VEGF agents act by directly binding free VEGF-A isoforms (and, in the case of certain molecules, also VEGF-B and placental growth factor (PlGF)), thereby preventing their interaction with receptors on the surface of endothelial cells. This results in rapid inhibition of VEGF-dependent signaling, leading to normalization of capillary permeability, reduction of intraretinal exudation, and regression of macular edema. These effects translate directly into improved anatomical parameters visible on optical coherence tomography (OCT) and, in many cases, enhanced visual function. At the same time, anti-VEGF therapy exerts a significant, though usually transient, effect on neovascularization processes. By suppressing angiogenic stimuli, it inhibits the proliferative activity of pathological vessels and reduces the risk of hemorrhagic complications. However, it must be emphasized that anti-VEGF therapy does not eliminate the primary proangiogenic stimulus resulting from ischemia but merely modulates its molecular consequences. As a result, this treatment is not a causal therapy for retinal ischemia, and neovascular activity may recur after discontinuation of the drug. An additional aspect of anti-VEGF therapy is its indirect anti-inflammatory effect. Inhibition of VEGF leads to a secondary decrease in the expression of inflammatory mediators, limited leukocyte activation, and reduced endothelial damage, which further stabilizes the vascular barrier [1]. This effect is particularly important in chronic macular edema, where an inflammatory component contributes to the persistence of pathological vascular permeability.

Anti-VEGF therapy is of particular importance and represents the treatment of choice for macular edema secondary to retinal vein occlusion. It reduces vascular permeability resulting from VEGF overexpression in the retinal endothelium. Anti-VEGF therapy significantly improves the prognosis in RVO, leading to reduction of macular edema, improvement in visual acuity, and a lower incidence of neovascular complications. The indication for initiating anti-VEGF treatment is macular edema confirmed by OCT imaging, manifested by the presence of intraretinal fluid (IRF) and/ or subretinal fluid (SRF), as well as an increase in central retinal thickness (CRT) [1, 6].

CRT is a key parameter for assessing disease activity and monitoring treatment response. Extensive retinal hemorrhage may initially prevent accurate evaluation of ischemia on angiography [2, 5]. The actual area of non-perfusion is often assessable after the hemorrhage has regressed following intravitreal anti-VEGF treatment. However, it should be noted that the presence of extensive hemorrhage is not a contraindication to treatment; on

Inclusion criteria	Exclusion criteria	Drug dosing
– age ≥ 18 years; – macular edema secondary to RVO diagnosed within 9 months of RVO onset; – mean central subfield retinal thickness >250 μm on OCT; – best corrected visual acuity (BCVA) in the treated eye between 0.05 and 0.8 on the Snellen chart (or ETDRS equivalent); – patient consent for intravitreal injections; – absence of active fibrovascular tractions that may contract and lead to retinal detachment or adversely affect treatment prognosis within the program; – absence of retinal detachment associated with proliferative retinopathy; – absence of vitreous hemorrhage requiring surgical treatment; – absence of iris neovascularization; – absence of neovascular glaucoma; – controlled intraocular pressure; – absence of cataract that would interfere with monitoring treatment effectiveness within the program; – absence of significant and permanent macular retinal abnormalities that have a poor prognosis for improvement with anti-VEGF therapy or steroid treatment, such as: – extensive photoreceptor atrophy (outer retinal layer loss on OCT), – DRIL in the subfoveal region, – ischemic maculopathy, – patient consent to use contraception in accordance with the current SmPC.	– hypersensitivity to bevacizumab or any excipient; – active ocular or periocular infection; – active severe endophthalmitis; – pregnancy or breastfeeding; – occurrence of adverse reactions preventing further drug use; – rhegmatogenous retinal detachment or stage 3/4 macular hole; – disease progression defined as: – deterioration of BCVA to ≤0.05 on the Snellen chart (or ETDRS equivalent) persisting for more than 2 months or – permanent structural damage to the fovea preventing functional stabilization or improvement; – no active treatment with bevacizumab injections for 4 months after the last dose; – no disease activity or evidence from functional and anatomical assessment indicating lack of benefit from continued bevacizumab therapy; – lack of patient cooperation with the physician in charge (e.g., failure to attend at least 2 consecutive scheduled follow-up visits without justification).	1.1. Recommended dosage The recommended dose of bevacizumab for a single intravitreal injection is 1.25 mg, corresponding to 50 μl (0.05 ml) of solution per injection. 1.2. Treatment initiation – loading phase Treatment with bevacizumab begins with one injection per month (i.e., at intervals of at least 28 days but no later than 7 days after this period) for 3 consecutive months. 1.3. Maintenance phase Based on the physician's assessment of visual and/ or anatomical parameters, the interval between doses after the loading phase may remain monthly or may be extended according to the treat-and-extend regimen, in which intervals are lengthened by 2 or 4 weeks as long as the response in visual and/ or anatomical parameters is maintained. If the patient's visual and/ or anatomic outcomes worsen, the interval between consecutive doses should be reduced accordingly. If treatment effectiveness is confirmed according to the criteria described in section 4 after the first 5 bevacizumab injections, the interval between doses may be extended to maintain anatomical and functional disease control; if these parameters worsen, the interval must be shortened.

Tab. I. Inclusion and exclusion criteria and the drug dosing schedule under the RVO Drug Program.

the contrary, it supports early initiation of therapy [2, 5]. Based on the results of the COPERNICUS and GALILEO studies, intravitreal aflibercept was approved for the treatment of macular edema associated with CRVO in the United States in 2012 by the FDA (Food and Drug Administration) and in Europe in 2013 by the EMA (European Medicines Agency).

In Poland, a drug program is available for patients with macular edema resulting from a previous RVO. The inclusion and exclusion criteria, as well as the dosing regimen based on the Announcement of the Minister of Health, are presented in Table I [8].

2. Intravitreal steroid injections

Intravitreal steroids (primarily the sustained-release dexamethasone implant, Ozurdex) are indicated for the treatment of macular edema secondary to BRVO or CRVO; however, they are not used as first-line therapy but rather as an alternative or adjunct to anti-VEGF treatment [5, 6]. The primary indication for intravitreal steroid use is an insufficient response to anti-VEGF therapy, defined as persistent macular edema and a lack of significant improvement in visual acuity despite an adequate number of injections.

Steroid therapy should be considered in particular in patients with contraindications to anti-VEGF treatment, especially those with significant cardiovascular conditions (e.g., recent myocardial infarction or stroke), where minimizing systemic exposure to anti-VEGF agents is clinically important. Another indication includes situations where a reduction in injection frequency is required, such as in patients who have difficulty attending regular follow-up visits. In these cases, the steroid implant provides a longer-lasting therapeutic effect [6].

Steroids may be preferred in patients with features of chronic, inflammatory macular edema, particularly with long disease duration and in cases where the anatomical response to anti-VEGF is poor despite multiple injections. This therapy is acceptable in both BRVO and CRVO, regardless of the degree of ischemia, provided the treatment goal is macular edema control rather than the prevention of neovascularization.

The guidelines emphasize, however, that the use of steroids requires careful patient selection due to known adverse effects, including increased intraocular pressure (IOP) and acceleration of cataract progression. Therefore, patients with well-controlled IOP and those who have undergone cataract surgery are preferred candidates for this therapy. Regular monitoring of IOP is mandatory [6].

In summary, intravitreal steroids in RVO are primarily recommended as second-line therapy for patients with an inadequate response to or contraindications for anti-VEGF treatment, with careful consideration of their individual ocular and systemic risk profile.

3. Retinal laser therapy

In RVO, laser therapy should not be used prophylactically, even in the presence of extensive areas of non-perfusion (>5 DD) [3]. Overtreatment should be avoided in patients who might never develop neovascularization. In RVO, indications for laser therapy include the presence of neovascularization of the retina (NVE), the optic disc (NVD), or the iris (NVI) [6]. The laser should be applied to the ischemic areas within the affected vascular sector in BRVO, or to the entire retina excluding the macula in cases of NVE/NVD/NVI secondary to CRVO. Macular laser (grid laser) currently plays a secondary role in RVO, as anti-VEGF therapy has become the treatment of choice for macular edema. Contemporary guidelines do not specify fixed laser parameters; the therapeutic goal remains effective ablation of ischemic areas without damaging the central retina.

Table II summarizes the indications for retinal laser therapy in BRVO/ CRVO according to the Euretina guidelines.

Key points of the EURETINA guidelines

- Laser therapy is not a first-line treatment for macular edema (it has been replaced by anti-VEGF injections).
- Panretinal photocoagulation (PRP) remains the gold standard for treating neovascular complications in both BRVO and CRVO.
- Prophylactic PRP in CRVO is only applicable in exceptional cases where regular patient follow-up cannot be guaranteed.

4. Vitrectomy

Vitrectomy (Pars Plana Vitrectomy – PPV) involves the surgical removal of the vitreous body, often performed alongside the detachment of the posterior vitreous cortex, removal of epiretinal membranes, and intraocular laser therapy. In the context of CRVO, vitrectomy is generally not a first-line treatment; rather, it is reserved for complicated cases or those refractory to conservative management [6, 7].

One of its primary indications is massive or recurrent vitreous hemorrhage, which prevents adequate fundus evaluation and precludes effective laser therapy. Removal of blood from the vitreous cavity improves the clarity of the optical media, enables the performance of panretinal photocoagulation, and reduces the risk of further hemorrhage by removing the scaffold for vascular proliferation [7, 9].

Disease entity	Indication for laser therapy	Type of laser	Clinical remarks (according to EURETINA)
CRVO (central retinal vein occlusion)	Overt neovascularization of the iris, angle, or retina	panretinal photocoagulation (PRP)	Treatment of choice for neovascular complications
	Prophylactically in extensive ischemia when close follow-up is not feasible	(early) panretinal photocoagulation (PRP)	Routine prophylactic PRP is not recommended unless follow-up is impossible
	Ischemic CRVO without neovascularization	–	Observation with frequent check-ups (laser deferred until neovascularization appears)
BRVO (branch retinal vein occlusion)	Neovascularization of the retina or optic disc	Sectoral laser in the ischemic area	Standard of care for proliferative complications
	Macular edema (historically)	Focal/ grid laser	Effective, but currently 2nd line (after anti-VEGF therapy)
	Refractory macular edema or lack of access to injections	Focal/ grid laser	Alternative or adjunctive option
	BRVO without neovascularization, with possibility of follow-up	–	Observation; no indications for prophylactic laser

Tab. II. Indications for retinal laser therapy in BRVO/ CRVO according to Euretina.

Another important indication is the management of tractional complications, including epiretinal membranes, vitreoretinal proliferation, and tractional retinal detachment. Chronic macular edema and ischemia promote the development of proliferative changes that can further impair retinal function. Vitrectomy with membrane removal can lead to anatomical stabilization and, in some cases, improvement in visual acuity [9–11].

The literature also describes a potential role for vitrectomy in improving retinal oxygenation. Removal of the vitreous body enhances oxygen diffusion from the anterior segment to the retina, which may theoretically reduce ischemia and the production of proangiogenic factors such as VEGF. This mechanism may explain the reduction in macular edema observed in some studies following vitrectomy, even without direct macular intervention [9, 12].

Nevertheless, functional outcomes after vitrectomy in CRVO are variable. Better prognosis is observed in patients without extensive macular ischemia, without advanced optic nerve atrophy, and with a shorter disease duration [6, 13]. In severe ischemic CRVO, vitrectomy primarily serves a palliative role, preventing serious complications such as neovascular glaucoma [6, 7].

At the same time, it is worth noting that in selected cases where retinal vein occlusion coexists with neovascular glaucoma, PPV may be considered a first-line treatment [6, 7]. The rationale for this approach is that during PPV it is possible to simultaneously:

- ✓ perform complete panretinal photocoagulation [6],
- ✓ clear the macula via macular peeling [9, 11],
- ✓ administer anti-VEGF agents to prevent macular edema and reduce retinal ischemic changes [7, 13],
- ✓ perform simultaneous cyclophotocoagulation or cyclocryotherapy to lower and stabilize elevated IOP [6, 7].

It should be noted that these procedures are technically demanding and carry a higher risk. However, accelerated PPV should be considered in complex situations if outpatient treatment with anti-VEGF injections, lasers, or anti-glaucoma procedures is not feasible, or if the waiting time for such treatment is unacceptably long [7].

In summary, vitrectomy has a limited but clearly defined role in the treatment of central retinal vein occlusion. Its primary purpose is to address CRVO complications and facilitate further effective therapeutic interventions. Careful patient selection and consideration of the degree of retinal ischemia are crucial for achieving optimal treatment outcomes [6, 7].

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