

## Bevacizumab in the treatment of acute central/hemicentral retinal vein occlusions

Călugăru Dan\*, Călugăru Mihai\*\*, Țălu Ștefan\*\*\*

\*Department of Ophthalmology, University of Medicine and Pharmacy, Cluj-Napoca, Romania

\*\*OcuCenter Ophthalmological Clinic, Cluj-Napoca, Romania

\*\*\*Department of AET Discipline of Descriptive Geometry and Engineering Graphics, Faculty of Mechanical Engineering, Technical University, Cluj-Napoca, Romania

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**Correspondence to:** Mihai Călugăru, MD, PhD,  
OcuCenter Ophthalmological Clinic, Cluj-Napoca,  
11 Brâncoveanu Street, Code 400012, Cluj-Napoca, Romania,  
Mobile phone: +40741 165 094, Fax: +40264 591 468, E-mail: mihai.calugaru@mail.dntcj.ro

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### Abstract

Even if bevacizumab is unlicensed, a majority of retina specialists still currently recommends it in retinal vein occlusion-related macular edema. For the first time, the results of our studies showed evidence suggesting that an early treatment administered immediately after the onset of venous occlusion, provided a significant and sustained improvement in visual acuity and foveal thickness, with inactive disease (dry retina and stable visual acuity for at least 6 months after the last injection) in most phakic patients with acute central/ hemicentral retinal vein occlusions, making this treatment option a rational and viable therapeutic strategy. Central/ hemicentral retinal vein occlusion has to be considered an ophthalmic emergency. The highlighting of the ocular conditions most frequently associated with central/ hemicentral retinal vein occlusion (ocular hypertension, primary open angle glaucoma, primary angle closure suspect, primary angle closure, and primary angle closure glaucoma) is mandatory. Regardless of the anti-vascular endothelial growth factor agents used (bevacizumab/ ranibizumab / aflibercept/), and regardless of the treatment approaches chosen (treat-and-extend/ pro re nata algorithm), the efficacy of therapy depends primarily on the precociousness of the therapy after the diagnosis of central/ hemicentral retinal vein occlusion. Any delay in the treatment will adversely influence the restoration of visual functions, which are difficult to correct even with subsequent treatment.

**Keywords:** central/ hemicentral retinal vein occlusion, intravitreal bevacizumab, vascular endothelial growth factor

### The rationale of the treatment

Retinal vein occlusion (RVO) is a second most common retinal vascular disorder following diabetic retinopathy and is often associated with visual loss. RVOs have an estimated prevalence of 0.5% in individuals over 40 years old [1]. A recent population-based

study estimated the 15-years cumulative incidence of RVOs to be 2.3% [2]. The most common age range is from the 6<sup>th</sup> to the 7<sup>th</sup> decade. RVOs are relatively uncommon in individuals under age 40. Central retinal vein occlusion (CRVO) is generally reckoned as one of the major threats to vision because many patients suffer irreversible visual loss even in the

face of several therapeutic alternatives. Main causes of visual impairment include macular edema (ME), retinal neovascularization with secondary neovascular glaucoma, epiretinal membrane formation, rubeosis iridis, retinal hemorrhages, vitreous hemorrhage, and retinal tissue destruction due to the retinal ischemia [3-5]. Various treatments for CRVO have been advocated over the last decade. These include medical therapy with anticoagulants, fibrinolytics, corticosteroids, acetazolamide, and isovolemic hemodilution. Panretinal or sectorial retinal laser photocoagulation should only be considered for the treatment of neovascularization [3,6]. Surgical options, including pars plana vitrectomy, surgically induced retinochoroidal anastomoses, direct venous cannulation, and radial optic neurotomy, may provide a potential benefit in RVO related ME. The evidence for the justification of these modalities has remained unproven or at least unclear for most of them. More recently, the intravitreal anti-vascular endothelial growth factor (VEGF) injections with bevacizumab (Avastin; Genentech Inc., San Francisco, CA, USA), ranibizumab (Lucentis; Genentech, Inc.) and aflibercept (Eylea; Regeneron Pharmaceuticals, Inc, Tarrytown, New York, USA) quickly became incorporated into the clinical management of CRVO representing its front-line therapy [7-10]. Even if bevacizumab is unlicensed, it is still currently recommended in CRVO-related ME over ranibizumab (22.2%) and aflibercept (15.1%;  $P < 0.0001$ ), by a majority of retina specialists (56.7%) [11]. Bevacizumab is a humanized antibody that binds all the subtypes of VEGF-A. We believe that eyes receiving therapy immediately after CRVO diagnosis may benefit more than those receiving a delayed treatment. Visual outcomes are better the sooner the treatment is performed after the occlusion forms. A few studies have investigated the use of anti-VEGF therapy in CRVOs during the acute phase of the disease (< 3-months duration of symptoms of a venous occlusive event) [7,12,13]. However, most of the currently available studies included only patients with intermediate (3-12 months) or late (> 1 year) stages of venous occlusions associated with ME. These patients with intermediate and late stages of venous occlusions associated with ME, most likely had a permanent retinal capillaropathy

(e.g. pigmentary changes in the fovea, poorly controlled severe recurrent macular edema, telangiectatic vessels with leakage, epiretinal membranes), that was temporarily relieved by a reduction of the edematous component with bevacizumab, ranibizumab or aflibercept. However, the pathology was incurable due to irreversible ischemic changes to the macular ganglion cell complex, close to the foveola, with macular edema being a minor factor. That is why the visual and anatomic results were poor [7,8,15-17]. For the first time, the results of our studies [5,7,9,17,18] showed evidence suggesting that the early treatment administered immediately after the onset of venous occlusion, provided significant and sustained improvement in the visual acuity and foveal thickness (FT), with inactive disease (dry retina and stable visual acuity for at least 6 months after the last injection) in most phakic patients with acute central/ hemicentral retinal vein occlusions (central/ hemicentral RVO), making this treatment option a rational and viable therapeutic strategy.

The rationale for administering early intravitreal bevacizumab treatment [7] to patients with acute occlusions included the following: initial abrogation of the increased VEGF levels in the acute phase, which are responsible for the main symptoms and complications, most of which occur in the natural clinical course during the first 7-8 months of the disease (ME, retinal capillary nonperfusion, neovascularization and neovascular glaucoma); binding of the bevacizumab to all VEGF-A isoforms, preventing their attachment to receptors situated on the endothelial cell surface; rapid, effective, and direct blocking of the neovascular process and its complications; reversal of increased vascular permeability mediated by VEGF, ensuring the stability and integrity of the inner blood retinal barrier; maintenance of a relatively normal or almost normal foveal anatomy during the acute phase of occlusion, when the VEGF levels are increased, until improvement of the draining circulation; prevention of acute functional curable retinal capillaropathy, that is present immediately after the onset of occlusion, to develop into a permanent capillaropathy, with limited reversal; and normalization of the long term physiological VEGF expression, which is essential for vascular

endothelial homeostasis, blood pressure homeostasis, and neuroprotection of the retinal ganglion cells.

## The presentation of the concepts used in practice

### The concept of central/ hemicentral RVO diagnosis

Central/ hemicentral RVOs were divided into two groups: nonischemic and ischemic forms. The criteria for acute nonischemic central/ hemicentral RVOs are the following [7,20,21]: a best corrected visual acuity (BCVA) score  $> 20/400$  Snellen equivalent in the affected eye; normal peripheral visual field with or without a relative central scotoma; mild to moderate intraretinal hemorrhages and venous tortuosity involving 4 (CRVO) or 2 (hemicentral retinal vein occlusion [hemicentral RVO]) retinal quadrants; rare ( $\leq 4$ ), if any, cotton wool spots; perfused retinal capillaries or small and very limited focal retinal capillary dropouts ( $< 10$  disc areas of retinal capillary nonperfusion); and optic disc edema and varied grades of macular edema. The criteria for the ischemic type [7,15,20] of acute central/ hemicentral RVOs are determined based on the angiography result. In cases with an angiographically clear evidence of retinal capillary nonperfusion zones, the criteria included 10 or more disc areas of nonperfusion. If intraretinal hemorrhages prevented a clear angiographic evaluation of the retinal capillary nonperfusion, the following parameters were considered: a BCVA score  $\leq 20/400$  Snellen equivalent; ability to see  $\leq V/4e$  of the isopter, based on the Goldmann perimeter; the presence of relative afferent pupillary defects in patients with a normal fellow eye; and an intraocular pressure (IOP) reduction in the occluded eye of  $\geq 4$  mmHg, compared with the congener eye. An eye was classified as having ischemic central/ hemicentral RVO by the presence of at least 4 of these 5 parameters.

### The concept of ocular hypertension (OH) associated with unilateral central/ hemicentral RVO (investigation of the contralateral uninvolved eye) [22]

1) IOP without treatment  $> 21$  mmHg in at least 3 successive measurements; 2) Normal visual field (defined as a mean deviation and pattern standard deviation within 95% confidence limits and a glaucoma hemifield test result within normal limits); 3) Normal optic disc (defined as a round or slightly oval structure measuring 1.5 mm horizontally and 1.75 mm vertically with a cup-shaped depression [the physiologic cup] located slightly temporal to its geometric center and a neuroretinal rim with a relatively uniform width and a color that ranged from orange to pink); the size of the cup-to-disc ratio was judged taking into account the optic disc diameter; 4) Open anterior chamber angle without mesodermal tissue or neovascularization; 5) No history of attacks of intermittent angle-closure glaucoma; 6) No anamnestic information or obvious signs of systemic or local causes of increased IOP, such as ocular trauma, use of steroids or pigment dispersion; 7) Clear ocular media; 8) Normal retinal nerve fiber layer (RNFL) without localized or diffuse defects.

### The concept of primary open angle glaucoma (POAG) associated with unilateral central/ hemicentral RVO (investigation of the contralateral uninvolved eye) [24]

1) Structural and/ or functional glaucomatous lesion; structural lesion includes acquired characteristic progressive optic neuropathy (cupping/ saucerization of the optic disc, diffuse or localized thinning of the neuroretinal rim area, and/ or retinal nerve fiber layer changes with diffuse or localized defects); functional damage encompasses characteristic reproducible changes in the visual field (retinal nerve fiber bundle defects [paracentral defects]), corresponding to optic disc lesions; 2) IOP within statistically normal limits (10–21 mmHg) (normal pressure glaucoma) or with increased values ( $> 21$  mmHg) (high-pressure glaucoma); 3) Open anterior chamber angle (not occludable, no neovascularization, no goniodysgenesis); 4) No obvious evidence of an ocular or systemic possible cause of IOP increase (pseudoexfoliation, ocular trauma, pigment dispersion, use of steroids); 5) No ocular fundus or neurologic lesion other than the glaucomatous cupping that could explain the visual field defect; 6) Clear ocular media.

### **The concept of normal and pathological gonioscopic aspects in patients with unilateral central/ hemicentral RVO [25]**

A) Normal (not occludable) anterior chamber angle (> 20 grade): the posterior third of the trabecular meshwork (usually pigmented) is visible for more than 180 degrees, on static gonioscopy with the eye in the primary position. This configuration involves both eyes.

B) Narrow drainage angle ( $\leq 20$  grade): non-visibility of the posterior trabecular meshwork for  $\geq 180$  degrees of the angle circumference on non-indentation gonioscopy with the eye in the primary position. It has two variants, namely, moderately narrow angle (angular width 15-20°) and extremely narrow angle ( $\leq 10^\circ$ ). This configuration involves both eyes.

C) Primary angle closure suspect (PACS), namely an eye in which appositional contacts between the peripheral iris and the posterior trabecular meshwork are considered possible/probable: a) narrow drainage angle, IOP below 22 mmHg, no peripheral anterior synechiae (PAS) in the angle, and without glaucomatous optic neuropathy (GON); b) absence of the ocular pathology, that can induce PAS formation (uveitis, neovascularization, trauma, surgery).

D) Primary angle closure (PAC): 1) narrow drainage angle; 2) eyes in which narrow angles or shallow anterior chambers were thought to be secondary to the other ocular conditions, such as, lens abnormalities, chronic uveitis, trauma, rubeosis iridis or retinopathy of prematurity, were excluded; 3) optic disc and visual field definitely considered as non-glaucomatous; 4) the presence of at least one of the following features indicating that the trabecular obstruction by the peripheral iris occurred: a) PAS; b) IOP > 21 mmHg; c) excessive pigment deposition on the trabecular meshwork surface, especially superior; d) ischemic sequelae of acutely raised IOP (distortion of the radially oriented iris musculature, iris stromal atrophy, dilated nonresponsive pupil, focal necrosis of lens epithelium causing glaukomfleken); e) Clear history of clinical signs or symptoms such as headaches, congestion, blurred or halo vision, corneal edema or a mid-dilated pupil, consistent with sudden IOP rise; f) evidence of a surgical peripheral iridotomy; g) dark room provocation

test giving a rise in IOP of  $\geq 8$  mmHg from baseline.

E) Primary angle closure glaucoma (PACG): a) presence of PAC; b) consistent visual morbidity; c) typical GON characterized by irreversible structural and/ or functional glaucomatous lesion, indistinguishable from the primary open angle glaucoma; structural glaucomatous damage includes acquired characteristic progressive optic neuropathy (e.g. optic disc cupping; narrowing the area of neuroretinal rim; localized "notch"; disc hemorrhages; newly appeared asymmetry in the cup/ disc ratio  $\geq 0.2$  between both eyes; change in the cup/ disc ratio > 0.2) that could be documented alongside the follow-up, and/ or changes of the RNFL (diffuse or localized defects); functional glaucomatous damage comprises reproducible characteristic changes of the visual field (retinal nerve fiber bundle defects) corresponding to the optic disc lesion; d) atypical GON occurs after an acute symptomatic episode of angle closure and presents with a pale but flat optic disc, suggesting an anterior ischemic optic neuropathy.

### **The concept of fractal analysis in connection with the segmentation methods for retinal images**

The fractal concept offers a new dimension for the analysis of the structure-function relationship of retinal microvasculature [14,23].

### **The activities required to evaluate the efficacy of the treatment**

#### **The evaluation of the BCVA score**

This examination is carried out by using the visual acuity charts from the Early Treatment Diabetic Retinopathy Study (ETDRS). These charts have 14 rows of five letters, each corresponding to visual acuities from 20/ 10 to 20/ 200 when viewed at a distance of 4 meters. When 20 or more letters were read correctly at 4 meters (corresponding to a visual acuity of 20/ 100 or better), the visual acuity score was the number read correctly plus 30 (the total number of letters on the top six lines of the chart, which were used at a 1-meter distance for testing low

visual acuity). When fewer than 20 letters were read correctly at 4 meters, only the number of letters read correctly at 1 meter of the 30 letters on the top 6 lines was added to the 4-meter total to obtain the visual acuity score. A perfect visual acuity score was 100, corresponding to a visual acuity of 20/ 10. The visual angle doubled (e.g., 20/ 20 to 20/ 40, 20/ 100 to 20/ 200) with each decrement of 15 letters (the equivalent of three lines on these charts). A visual acuity score of five letters corresponded to a visual acuity of 5/ 200. If no letters could be read correctly at 1 meter, the presence or absence of a light perception had to be recorded. A four-meter testing distance with this chart yields the following Snellen equivalent lines: 20/ 10, 20/ 12.5, 20/ 16, 20/ 20, 20/ 25, 20/ 31.5, 20/ 40, 20/ 50, 20/ 63, 20/ 80, 20/ 100, 20/ 125, 20/ 160, and 20/ 200. At 1 meter, the following additional Snellen equivalent lines of visual acuity could be measured: 20/ 250, 20/ 315, 20/ 400, 20/ 500, 20/ 630, and 20/ 800. Every three lines represent a doubling of the visual angle.

### **The visual field determination**

The Goldmann perimeter with three object sizes and intensities (i.e., I2e, I4e, and V4e) is used in all cases. To prevent artifacts, an appropriate refraction is used while plotting the visual fields: (1) for central 30 grade visual fields, a manifest refraction with appropriate presbyopia correction; and (2) for visual fields peripheral to the central 30 grades, only manifest refraction for I2e and no corrective lens for I4e and V4e (unless the eye had high myopia or hyperopia, i.e., of 10 diopters or more). In cases of suspected concomitant ocular hypertension or primary glaucoma, the Humphrey Field Analyzer static achromatic automatic perimetry 30-2 test with Standard Swedish Interactive Thresholding Algorithm strategy is used. Reliability criteria included false-positive < 15%, false negative < 33%, and fixation loss < 20%.

### **The ocular fundus assessment**

Ocular fundus is thoroughly evaluated by direct and indirect ophthalmoscopy and, if needed, by using a contact lens. Ocular fundus findings of the central/ hemicentral RVO include: dotted and flame-shaped intraretinal hemorrhages (which are demonstrated in all

four retinal quadrants in cases of CRVO, and are usually found in only 2 quadrants in cases of hemicentral RVO, although intraretinal hemorrhages may involve 1/ 3-2/ 3 of the retina in hemicentral RVO), engorgement and tortuosity of the venous system, papilloretinal edema, telangiectatic capillary bed, cotton wool spots, and angiographic evidence of prolongation retinal circulation times. The two forms of venous occlusion (CRVO and hemicentral RVO), are evaluated together, because they are pathogenetically similar. In cases of CRVO, the only existing central retinal vein trunk within the optic nerve is involved, whereas patients with hemicentral RVO have two central retinal vein trunks as a congenital anomaly, and develop an occlusion in only one of them. Fundus photography is useful for documenting the severity of the retinal findings, the presence of new vessels elsewhere in the retina, the extent of intravitreal hemorrhages, and the new vessels on or near the optic disc, the response to treatment, and the need for additional treatment at future visits.

### **The fluorescein angiography**

Even if the importance of fluorescein angiography (FA) as an invasive procedure has declined in daily clinical practice, it is indispensable in assessing the dynamics of retinal capillaropathy, which is present immediately after the onset of occlusion, involving the entire retina including the macular region. FA assessments are focused on the disc and macula during early examination times, on the middle retinal periphery of each quadrant during the intermediate phases, and again on the disc and macula during late stages (> 5 minutes after fluorescein injection); iris images are obtained during the recirculation phase. Retinal capillary nonperfusion is angiographically measured on standard photographic fields, with a retinal area equal to the optic disc diameter used as a template [12]. Eyes with at least 10 disc areas of retinal capillary nonperfusion and/ or intraocular neovascularization are classified as having retinal ischemia. The FA is helpful in diagnosing RVOs and differentiating the ischemic RVOs from nonischemic RVOs. The diagnosis of RVOs is confirmed by an increase in the length of the retinal vessel transit time, with a transit time of 5 seconds or more being considered as

delayed. FA also provides information on the status of the retinal capillary bed including any presence of hyperpermeability or nonperfusion. Associated features in FA include late leakage in the macular area and late staining on the main posterior veins. ME, a common consequence of RVOs, is generally presented as hyperfluorescence in radially orientated cystoid cavities forming a “petaloid pattern”, which resembles typical cystoid ME. The FA based assessment of the degree of capillary nonperfusion is an important part in the evaluation of RVOs. Nonperfusion of the peripheral retina characterizes ischemic RVOs and is an important risk factor for the eventual neovascularization development. Macular nonperfusion is correlated with a poor visual prognosis, which may hinder visual acuity gain despite further treatments of ME. Wide-field FA is used to evaluate peripheral nonperfusion, yet current data on the benefits of this technique are inconclusive. Recently, OCT angiography (OCTA) has been used to successfully delineate vessels within the retina, choroid and the vasculature associated with the optic nerve. These non-contact imaging systems detect phase variations or changes in reflectivity to detect vascular flow, with the added benefit of concurrently obtaining OCT scans of the surrounding tissue. This allows a rapid, non-invasive evaluation of the ocular pathologies with their associated vessels, exemplified by OCTA assessment of choroidal neovascularization with the evaluation of the surrounding choroidal and retinal layers simultaneously. In particular, split-spectrum amplitude-decorrelation angiography improves the signal-to-noise ratio of flow detection and has been shown to be useful in visualizing the microvasculature networks within the eye.

#### **The optical coherence tomography**

Optical coherence tomography (OCT) is used to assess the morphology and thickness of the macula, optic disc, and RNFL. OCT examination is largely used at present to detect macular architectural changes and to quantify macular thickness. Typical macular changes in RVOs are presence of intraretinal cystoid spaces (multiple or confluent) responsible for an increased macular thickness. Associated findings are vitreous macular adherence, epiretinal membranes, subretinal fibrosis, lamellar macular

hole, intraretinal exudates, and retinal hemorrhages. OCT could also provide prognostic indicators for patients with RVOs. Visual acuity is not only related to the presence of ME, but also closely associated with the integrity of the foveal photoreceptor layer. Eyes showing loss or disturbance of the inner segment/ outer segment junction line on the OCT images tend to have a poorer visual prognosis than those with preserved inner segment/ outer segment line. OCT also provides data on the location of the accumulated fluid, such as location within retinal layers or location in the subretinal space. Additional information, such as the presence and integrity of the outer limiting membrane, inner segment/ outer segment junction of photoreceptors is crucial as well.

#### **The gonioscopic examination**

Gonioscopy is considered the current reference-standard examination, whose purpose is to visualize the anterior chamber angle as completely as possible. It enables the identification of the iridotrabecular contact and is the only examination method that is able to differentiate between appositional and synechial angle closure. However, gonioscopy has some drawbacks, namely implying the contact with the ocular globe, the need for highly trained examiners, as well as the use of a slit-lamp, and its results may be affected by light and/ or inadvertent indentation. Closure of the anterior chamber angle in CRVO may appear as a primary (in predisposed eyes) or secondary event; the latter case is caused either by neovascularization of the angle or by a marked anterior displacement of the lens-iris diaphragm due to an abnormal accumulation of blood or edema fluid in the posterior segment of the eye, a non-rubeotic state which has some similarities with malignant glaucoma.

#### **The intraocular pressure measurement**

IOP is determined by using the Goldmann applanotometer and is adjusted according to the corneal thickness.

#### **The systemic evaluations**

Apart from a routine medical evaluation (namely, for systemic arterial hypertension, diabetes, and dyslipidemia), an extensive check-up for systemic disorders is unnecessary in most

patients with central/ hemicentral RVOs. Given that hematological risk factors for spontaneous systemic venous thrombosis are only sporadically present in patients with retinal vein occlusions, not all the patients with retinal vein occlusions need to be subjected to exhaustive hematological investigations (namely, determination of plasma homocysteine, Leiden mutation of V factor, C and S protein deficiencies, activated protein C resistance, and antithrombin and antiphospholipid antibodies). Such tests are necessary only when clearly indicated. All the participants will provide a written informed consent.

### **The injection scheme for intravitreal bevacizumab therapy [18]**

Initially, the treatment for acute central/ hemicentral RVO patients consists of 4 consecutive intravitreal bevacizumab injections administered off-label at a dose of 2.5 mg per injection, with each injection spaced at approximately 45 days apart. Thereafter, intravitreal bevacizumab injection therapy is flexible, and subsequent injections will be administered during scheduled visits whenever a visual acuity loss of  $\geq 5$  ETDRS letters occurs, the FT increases above the cutoff ( $252 \mu\text{m}$ ) for the upper level of normal FT, i.e., the average FT measurements in the healthy eye ( $212 \pm 20 \mu\text{m}$ ) plus 2 standard deviations, and/ or iris/ angle neovascularization appears (regardless of the IOP level). Panretinal photocoagulation will be performed as soon as the intraocular neovascularization is diagnosed, unless it subsides after 2 consecutive intravitreal bevacizumab injections administered at 30 days apart and topically given steroids and cycloplegics. In cases of elevated IOP, a topical fixed combination of timolol and dorzolamide (FCTD; Cosopt, Merck & CO., Inc., Whitehouse Station, NJ) is added. Surgery is advised, unless IOP normalizes in response to these treatments, after an additional intravitreal bevacizumab injection.

Considering our currently acquired experience [3,4,6,7,18,20] with intravitreal injections of 2.5 mg (0.1 ml) bevacizumab (instead of 1.25 mg [0.05 ml] bevacizumab, which represents the standard dose given worldwide), we believe that after an initial aggressive treatment with 4 consecutive

injections administered off-label at approximately 45 days apart, the therapy may be continued with subsequent dosing given pro re nata (PRN) until the stabilization of the best corrected visual acuity score. No adverse effects or ocular toxicity, including clinically evident sterile or infectious endophthalmitis, IOP increase, retinal ruptures, retinal detachment, and systemic thromboembolic events were encountered during our clinical practice [18].

## **Conclusions**

Central/ hemicentral RVO has to be considered an ophthalmic emergency [9,18,19]. The highlighting of the ocular conditions most frequently associated with central/ hemicentral RVOs (OH, POAG, PACS, PAC, and PACG) is mandatory. Therapy with anti-VEGF agents has to be promptly applied as soon as possible after RVO onset. The sooner the treatment is started after the RVO onset, the sooner the patient is likely to have gains in visual and FT [9,10,16,18,20,26]. Every delay of therapy adversely influences the delayed deterioration of visual functions, which are difficult to restore even with subsequent treatment. Regardless of the anti-VEGF agents used (bevacizumab/ranibizumab/aflibercept) [8,17,21,26], and of the treatment approaches chosen (treat-and-extend/ PRN algorithm) [19,21], the efficacy of therapy depends primarily on the precociousness of the therapy after RVO diagnosis [15,27].

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The authors have no proprietary or commercial interest in any of the materials discussed in this article; they declare no conflict of interest. The authors have nothing to disclose: NONE.

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