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REVIEW ARTICLE

Use of Anti-VEGF Drugs in Retinal Vein Occlusions

Manuel AP Vilela[1,*]

[1]*Medical School, Federal University of Health Sciences of Porto Alegre, Brazil and Ophthalmological Service, Cardiology Institute, University Foundation of Cardiology, Porto Alegre, Brazil*

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Abstract: Retinal vein occlusion (RVO) is one of the most prevalent causes of visual loss in the Western World. Its pathogenesis is still not completely known. Chronic macular edema and ischemia compromise the functional and anatomical status of the retina. Antivascular endothelial growth factor (anti-VEGF) injections have demonstrated better results than other previous options, including observation or laser therapy. This narrative review aims to analyze the current aspects related to these drugs.

Keywords: Retinal vein occlusion, branch retinal vein occlusion, central retinal vein occlusion, anti-VEGF, ranibizumab, aflibercept, bevacizumab.

1. INTRODUCTION

RVO affects around 16 million people worldwide. It is the second most common retinal vascular disease after diabetic retinopathy. Overall RVO prevalence is estimated as being 5.2 per 1000 inhabitants (95% confidence interval [95%CI], 4.40-5.99), while branch retinal vein occlusion (BRVO) prevalence is 4.42 per 1000 (95% CI, 3.65-5.19) and central retinal vein occlusion (CRVO) prevalence is lower, at 0.80 per 1000 (95% CI, 0.61-0.99) [1-3].

Systemic arterial hypertension and atherosclerosis are among the main risk factors ; with different significance are diabetes (more associated with CRVO), hyperlipidemia, smoking, and obesity. In younger patients, thrombophilic disorders (such as hyperhomocysteinemia, anticardiolipin antibodies, lupus anticoagulant, factor V Leiden, antithrombin deficiency, protein S and S deficiency, prothrombin gene mutations), oral contraceptive use, high viscosity and inflammatory conditions could be associated. Glaucoma used to be a local factor related to RVO [3-5].

If the site of occlusion is on the central retinal vein, it will produce the classical clinical picture described in 1878 as CRVO [6]. Its pathogenesis is still not completely known, but vein compression and thrombus formation are the accepted mechanisms. The closer the occlusion is to the lamina cribrosa, the worse the prognosis will be. This distance of the thrombus from the lamina cribrosa can explain differences between the number of collateral vessels for drainage [7-10].

Local or diffuse elevated intravenous and capillary pressure causes endothelial damage and abnormal permeability with extravasation of serous fluid and blood. This raises the interstitial pressure and causes more capillary occlusion and ischemia. An elevated level of local cytokines is upregulated. Abnormal levels of cytokines such as vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), interleukin-8 (IL-8) induce disruption of endothelial zonula occludens, fragmentation, fenestrations, and degeneration of the endothelium basement membrane and neovascularization. VEGF was officially discovered in 1983 by Senger's group in Boston, but its existence had been suspected since the 1800s and encompasses 5 major subtypes: A, B, C, D, and Placental Growth Factor (PLGF). VEGF is, however, necessary for the neuron preservation in the very early phases. This physiological response should be considered when the treatment is recommended [11-14].

2. CLASSIFICATION

A paramount point is related to the clinical importance of characterizing the true status of retinal perfusion. Isolated fundoscopy enables diagnosis, but it is insufficient for defining the precise status. RVO classification enables us to know much about case management and prognosis. It is an essential step. The most used methods describe (1) the site of occlusion and (2) perfusion status.

When retinal venous branches are involved, there could be two possibilities. It can be in a major branch (the superior temporal is the most frequent) or in a tiny branch around the macula. Pathologic arterio-venous crossing with localized compression, endothelium lesion, and turbulent flow are the main potential causes. When patients have a two-trunked central retinal vein, sometimes one trunk can be impaired and retinal manifestations will be hemispheric (HRVO). The chronic effects of high venous pressure could be complementary for the recurrence of macular edema (and/or worsening arterial inflow and thus increasing hypoxia) [8, 15].

*Address correspondence to this author at the Medical School, Federal University of Health Sciences of Porto Alegre, Brazil and Ophthalmological Service, Cardiology Institute, University Foundation of Cardiology, Porto Alegre, Brazil; Tel: 55-51-33953602; E-mail: mapvilela@gmail.com

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Another possibility for retinal vein occlusion classification is related to perfusion status. All forms can be ischemic or non-ischemic. So we can have ischemic (i) or non-ischemic (ni) CRVO, BRVO, and HRVO. Intravenous fluorescein angiography (IVFA) has been used to analyze the extent of nonperfused retinal capillaries, thus enabling us to recognize perfusion status. This is based on the number of nonperfusion zones (NPZ). However, the precise number of these zones is not uniform and there is a lack of consensus on this subject [15, 16]. The use of these perfusion criteria can predict different case management approaches and outcomes. We can define a broad option for case management, ranging from simple observation to complex therapeutic decisions.

iCRVO has greater risk of developing abnormal neovascularization than ni-OVCR at the anterior segments (iris, 57.7% x 3.0%; angle, 47.4% x 2.0%) and neovascular glaucoma (33.3% *vs* 1.0%). Otherwise, in the case of iBRVO, neovessels at the retina are more common than in iCRVO and occur in almost a quarter of patients. The ischemic patterns that IVFA could reveal occur in around 2/3 cases with BRVO and in 1/3 cases with CRVO. It is very important to consider that in cases with ni-CRVO (2/3 of cases), there is a significant chance of becoming ischemic over time (9-34%) [13, 15].

IVFA is not useful in up to 50% of cases in the acute phase (2-3 initial months). This is because hemorrhages prevent precise analysis of NPZ. Hayreh SS *et al.* [16]. proposed that other parameters offer more precise information. Thus the level of visual acuity, pupil reactions, the visual fields (VF) and electroretinogram (ERG) (isolated or in combination) have more sensitivity and specificity to recognize the ischemic forms and the best therapeutic responses.

Other technologies, such as optical coherence tomography (OCT), are helping not only with case management but also with predicting prognosis. If we recognize modifications in specific zones such as the ellipsoid zone (EZ), photoreceptors (PR), external limiting membrane (ELM) or in the presence of disorganization of retinal inner layers (DRIL), there will be a strong relation to final best correct visual acuity (BCVA), number of injections and this will be correlated with the extent of ischemia and size of macular nonperfusion in IVFA and ultra-wide fundus fluorescein angiography (UWFFA) [17-20].

The new retinal cameras in UWFFA provide us with almost 80% of retinal circulation for analysis. If the NPZ index in CRVO is greater than 35%, then the ischemic form is well established. Optical coherence tomography angiography (OCT-A) also offers new information. It can define which capillary layer is more affected (usually the deepest), vascular density, and the status of the foveal avascular zone (FAZ). Vascular density can be seen on a large and unique scale [21-24].

The purpose of this study is to review the use of anti-VEGF drugs in RVO.

3. ANTI-VEGF DRUGS

3.1. General Considerations

It is of fundamental importance to know about the natural history of RVO, otherwise, misinterpretation about the therapeutic effects of different options can result. Data from different studies have shown that after a maximum period of follow-up, a lot of patients had resolved the occurrence of edema, but in most of the final best correct visual acuity (BCVA) did not change very much and the ischemic forms had the worst functional results [13, 15, 16, 25]. In each kind of RVO, the reason for this is the ischemic or/and edematous impairment of the macula. Edema is the basic treatable reason for the loss of visual acuity (VA). However, we cannot expect the same results with these drugs for cases with iRVO since cell deaths are the main cause of functional loss [13, 21-29].

RVO had been treated only with observation, or laser photocoagulation or vitrectomy until the initiation of the off-label use of Bevacizumab (2008) and/or the emergence of intravitreal corticosteroids trials [3, 12, 24-29]. There are currently different drugs in use to block VEGF in RVO. There are some basic molecular and affinity differences between these drugs [30].

Bevacizumab (Avastin®, Genentech, South San Francisco, CA, USA) is a 149 kDa recombinant monoclonal humanized full-length immunoglobulin G1 antibody derived from the same mouse monoclonal antibody, that binds all forms of VEGF-A and blocks its binding to endothelial receptors. It was approved in 2004 for the treatment of colorectal cancer, non-small cell lung cancer, metastatic renal cancer, glioblastoma, and metastatic HER2 negative breast cancer. Intravitreal Bevacizumab (IVB) has been used in an off-label way as an efficient and cheaper alternative [30].

Ranibizumab (Lucentis®, Genentech Inc., South Francisco, CA, USA) is a 48 kDa recombinant humanized monoclonal immunoglobulin G1 Fab fragment that binds to the receptors of all biological isoforms of VEGF-A and blocks the binding of VEGF-A to VEGFR1 and VEGFR2 receptors on endothelial cells. Ranibizumab has 100 times more affinity for VEGF than Bevacizumab [30].

Aflibercept (Eylea®, VEGF Trap-Eye, Regeneron Pharmaceuticals, Tarrytown, NY, USA) is a 115 kDa recombinant fusion protein with portions of VEGF receptor 1 and 2 bound by a fragment crystallizable (FC) portion with binding receptors for all isoforms of VEGF-A (greater affinity than Ranibizumab and Bevacizumab), VEGF-B, and placental growth factor (PIGF) [30]. Ziv-aflibercept (IVZ) is the same molecule and differs only in the osmolarity of its solution [31, 32]. Ranibizumab and Aflibercept are approved by the US Food and Drug Administration for RVO.

Conbercept (Lumitin®, Chengdu Kanghong Biotechnology) is a 143k Da humanized, soluble, VEGF receptor (VEGFR) protein comprising extracellular domain-2 of VEGFR-1, and domains-3 and -4 of VEGFR2. All of them are connected by an Fc region of human immunoglobulin G. It binds to VEGF-A, VEGF-B, VEGF-C, and PIGF with high affinity. It was approved by the Chinese Food and Drug Administration in 2013 [33, 34].

3.2. General Results

There is a plethora of randomized clinical trials supporting anti-VEGF effectiveness in RVO. Studies, sample sizes, follow-up periods, and outcomes are included in the TABLE. In

the vast majority, the functional and anatomical gains are significantly better when compared to the other options [35-76]. BRAVO [35] (multicenter, randomized, sham injection-controlled study), CRUISE [37] (multicenter, randomized, sham injection controlled study), HORIZON [38] (24-month, multicenter, single-arm study with patients recruited from BRAVO and CRUISE), BRIGHTER [39] (phase IIIb, open-label, randomized, active-controlled, 3-arm, multicenter study), RELATE [40] (randomized, double-masked, controlled study), BLOSSOM [41] (12-month, phase III, double-masked, randomized, sham-controlled, two-arm, multicenter study) trials have demonstrated the relevant difference when intravitreous Ranibizumab (IVR) was adopted for RVO (Table **1**).

Intravitreous Aflibercept (IVA) in the COPERNICUS [42, 43] (2-year, phase 3, randomized, double-masked clinical trial conducted in different countries), GALILEO [36, 44] (18-month, phase III, multicenter, randomized, double-masked clinical study conducted in Europe), VIBRANT [45, 46] (double-masked, phase III, randomized, controlled study), SCORE2 [47, 48] (multicenter, noninferiority randomized controlled trial), and LEAVO [49] (prospective, 3-arm, double-masked, randomized, noninferiority trial) studies also showed similar better outcomes.

Bevacizumab has been evaluated in multiple studies, most of them retrospective or with small and uncontrolled séries [59, 60, 67, 73, 75]. In the trials like SCORE2 [47] (randomized clinical trial), MARVEL [50] (prospective, randomized, clinical trial), Lip *et al*. [51], ECHO [52] (multicenter, retrospective, open-label chart review study), Lotfy *et al.* [53] (prospective, comparative, randomized, interventional study) IVB showed equivalent results of IVR or IVA.

Intravitreous Conbercept (IVC) is well-tolerated, with the same incidence of adverse effects and similar visual and anatomical results in RVO. Larger sample sizes and longer follow-ups are necessary to validate the drug [33, 34, 54].

Comparative studies have demonstrated the very close results with all these anti-VEGF options for CRVO, HRVO or BRVO. The results of IVR, IVA or IVB were basically remarkable [35-74]. Compared to the sham groups and natural history, the outcomes with all kinds of anti-VEGF inhibitors are impressive. [12, 25, 48] In general, the gains in visual acuity (VA) (number of letters, changes in the best-correct visual acuity logMAR tables, percentages of patients with more than 15 letters conquered) and in the reduction of macular thickness are much higher and significant. (TABLE) Recent analyses found similar visual gain, equal reduction in macular thickness and noninferiority with the comparison between Aflibercept *vs* Ranibizumab *vs* Bevacizumab in RVO [47-50, 53, 54, 62, 63, 66, 67, 69, 77-80]. The integrated results show that Aflibercept can be used with a reduced number of injections, even after the first one [87]. It is possible to observe some differences with continuous use *versus pro re nata* (PRN) or treat-and-extend (TAE) regimens and some variation related to crossover patients [80, 88].

Even after years of continuous injections, around half of the patients with RVO still have unresolved edema [55, 56]. The results of the most important studies showed the same trend and limitation. They were quite similar after 2 or 6 months or after 1 or 2 years [82-87].

A lot of controversies and limitations are involved. None of the anti-VEGFs inhibitors are effective for all RVO patients. Injections must be started early for better VA gains (crossovers patients showed a reduced gain) [47, 51, 52]. Anti-VEGF can reduce macular thickness with late injections, but does not offer the same functional gain. Additional evidence showed that in real life, inferior results are observed [96-100]. The need for periodical retreatments and a large number of injections is almost a rule. The adherence is not easy and missing an injection could interfere with the result. Health-care provision of these drugs and retinal exams in the real-life is a concern in most countries [101, 102]. It is possible to use continuous injection (or injections for 1-6 months) until the macula is dry and after that, adopt PRN or TAE models [92, 93]. In the control visits, VA and OCT are mandatory for follow-up decisions [93-97].

It is necessary to be cautious regarding these comparisons and efficacy analyses. They are imprecise because of high heterogeneity and this could be explained by the differences in the time of diagnosis, duration of macular edema, size of the studies, the use of additional therapies, different kinds of controls, severity of occlusion is either not clear or not the same (ischemic and nonischemic in unequal proportions), inclusion of crossovers, length of follow-up, distinct re-treatment parameters, dissimilar regimen used (PRN, continuous, TAE), and the particular conditions of a trial *versus* real life. Patients with advanced glaucoma, recent intraocular surgery, diabetes mellitus, and age-related macular degeneration were excluded from most of the trials [81, 82, 85].

A very complex subject related to these drugs is their cost-effectiveness. These costs are quite different, considering the annual use of Bevacizumab. USA Health Insurance Companies spent around 13 billion dollars a year. Switching to a cheaper medication for just one year means a reduction of 3 billion dollars. In the end, each letter gain costs around U$ 1100. In the case of persistent edema, other options or associations must be used. We have to consider similar results, the same risks, quality of life and other reasons, like reimbursement, that influenced the decisions [101, 102].

Switches between different intravitreal anti-VEGF drugs have been used after 3 - 6 consecutive injections with insufficient effect, persistent and/or recurrent edema. There is evidence that switching or combined therapy could provide improved functional and anatomical outcomes in RVO [103-109]. The use of intravitreal dexamethasone (Ozurdex®, Allergan, Inc., Irvine, CA, USA) could be an option for managing suboptimal anti-VEGF responders as naive patients [110-112]. Simultaneous administration of anti-VEGF and dexamethasone should be considered in patients with naïve RVO and/or persistent or recurrent macular edema. There are few studies with encouraging results about this alternative option. They have shown benefits with a reduced number of injections, longer intertreatment intervals, and sustained response when it is adopted [113-117]. Suprachoroidal triamcinolone acetonide plus IVA showed an increase in VA and improved OCT compared with IVA alone at three months. This option reduced the need for additional anti-VEGF injections [118].

Table 1. Studies on the results of treatments using anti-VEGF.

Author/Study	Intervention	Follow-up (Months)	Level	Number of Patients	-	-	Outcomes	-	-
-	-	-	-	-	**Baseline letters**	**Final letters**	**Letters gain +**	**sham/control/comparative**	Macular Thickness (μm)
BRVO	-	-	-	-	-	-	-	-	-
RETAIN [55]	**(IVR 0.5 mg)**	48	I	34	54	74	20.1	> 15 ETDRS letters 61.8% BRVO	-200
HORIZON-BRVO [38]	**(IVR 0.3/0.5 mg)**	24	II	304	57	72	14.9	-	-370
-	**(Sham/0.5 mg IVR**	-	II	304	55	71	9.4	-	-418
-	**(IVR 0.5/0.5mg)**		II	304	53	71	16.2	-	-412
BRIGHTER [39]	**(Laser)**	24	I	92	56	66	11.6	-	-197.5
-	(IVR 0.5 mg)	-	I	183	-	-	17.3	-	-224.7
-	(IVR0.5 mg/Laser)	-	I	180	-	-	15.5	-	-248.9
BLOSSOM [41]	(Sham/IVR 0.5 mg)	12	II	89	57	71	7.7	-	-269.7
-	(IVR 0.5 mg)	-	II	177	-	-	14.0	>15-letter: 55.6% IVR x 38.7 Sham/IVR	-280
VIBRANT [45, 46]	**(IVA La-ser/IVA 2 mg)**	12	I	183	57	70	12.2	-	-
-	**(IVA 2mg)**	-	I	183	58	76	17.1 IVA 12.2 la-ser/IVA	>15-letter: 57.1% IVA, 41.1% IVA+laser	-283 IVT -249 la-ser/IVA
Lip *et al*, 2015 [51]	**(IVB 1.25 mg)**	12	II	56	-	-	-	+3 lines: 24%	-76
Pichi *et al*, 2019 [58]	**(IVA 2 mg x IVR 0.5 mg)**	12	II	70	-	-	-	0.2 logMAR (both; NS)	-294 IVA x 276 IVR
Tan *et al*, 2014 [59]	**IVR 0.5 mg x sham) Laser both**	12	II	36	-	-	12.5 IVR -1.6 Sham	-	-376 μIVR -175.6 Sham (P=0.02)

(Table 1) contd….

Author/Study	Intervention	Follow-up (Months)	Level	Number of Patients	-	-	Outcomes	-	-
Parodi *et al*, 2015 [60]	**(IVB 1.25 mg x STL)**	12	II	35	-	-	-	+15 letters: 58% (IVB) x 0% (laser)	-213 IVB x unchanged laser
Higashyana *et al*, 2010 [61]	**IVB 1.25 mg x TA)**	12	I	43	-	-	16.5 IVB 11.0 IVT	-	-304 IVT -262 IVB
Sun *et al*, 2017 [33]	**(IVC 0.5 mg)**	9	II	30	-	-	17.8	-	-289.9 µ
RELATE [40]	**(IVR 0.5 mg)**	6	II	42	54	66	12.1	(NS)	-203 IVR 0.5mg -292 IVR 2mg (p=0.19)
-	**(IVR 2.0 mg)**	-	II	-	48	64	14.6	-	-
BRAVO [35]	**(IVR 0.3 mg)**	6	I	397	55	71	16.4	-	-
-	**(IVR 0.5 mg)**	-	I	397	54	74	18.3	-	-
-	**(Sham/IVR 0.5 mg)**	-	I	397	54	67	12.1	>15 ETDRS letters: 55.2% IVR 0.3 mg, 61.1% IVR 0.5 mg, 28.8% Sham (P<0.0001)	337 IVR 0.3 mg, -345 IVR 0.5 mg, -158 Sham (P<0.0001)
Terashima *et al*, 2019 [65]	**(IVR 0.5 mg x IVR+ STL)**	6	II	46	58.4	73.4	17.1 IVR 15.0 IVR/STL NS	>20/40: 90.9% IVR x 79.2% IVR/STL (NS)	-341 IVR -296 IVR/STL
Li *et al*, 2017 [34]	**(IVC 0.5 mg)**	6	II	18	-	-	-	0.67 => 0.28 logMAR IVC	-262
-	(IVR 0.5 mg)	-	-	17	-	-	-	0.51=>0.24 logMAR IVR (p=0.76)	-203 (p=0.2)
Son *et al*, 2017 [62]	**(IVR 0.5 mg x IVB 1.25 mg)**	6	II	80	-	-	-	0.55 =>0.24 logMAR (IVR) 0.58=>0.29 logMAR (IVB) (NS)	-236 (IVR) -219 (IVB) (NS)
Cekic *et al*, 2010 [66]	**IVB 1.25 mg x IVT)**	6	II	31	-	-	24 IVB 7 IVT	-	-190 IVTA x -132 IVB
Kaldirim *et al*, 2018 [67]	**(IVR 0.5 mg)**	6	II	22	-	-	-	0.59 =>0.24 logMAR	-195
-	IVA 2.0 mg	-	-	20	-	-	-	0.57=>0.19 logMAR	-201

(Table 1) contd….

Author/Study	Intervention	Follow-up (Months)	Level	Number of Patients	-	-	Outcomes	-	-
-	IVD	-	-	20	-	-	-	0.59=>0.33 logMAR (p=0.004)	-163 (p=0.001)
MARVEL [50]	**(IVR 0.5mg)**	6	II	75	53	73	18.1	-	-165
-	**(IVB 1,25 mg)**	-	-	-	56	72	15.6(NS)	-	-185 (NS)
COMRADE B [57]	**(IVR 0.5 mg)**	6	II	126	-	-	17.3	-	-230.6
-	IVD	-	-	118	-	-	9.2	-	-112.3
CRVO	-	-	-	-	-	-	-	-	-
RETAIN [55]	**(IVR 0.5 mg)**	48	I	32	50	64	14.0	> 15 ETDRS letters: 53.1% CRVO	-419.2
NEWTON [56]	**(IVB/R…IVA 2.0 mg)**	24	II	20	-	-	8	-	-158
LEAVO [49]	**(IVR 0.5 mg)**	24	I	155	-	-	12.5 R	-	-405
-	IVA 2.0 mg	-	-	154	-	-	18.7	-	-378
-	IVB 1.25 mg	-	-	154	-	-	9.8	-	-334 (NS)
HORIZON-CRVO [38]	**(IVR 0.5/0.5mg)**	24	II	304	48	61	16.2 IVR 0.5 mg	+14.9 IVR 0.3/0.5, 9.4 sham/IVR 0.5 mg	-412 IVR 0.5/0.5 mg,
-	**(IVR 0.3/0.5 mg)**	24	-	-	47	56	14.9	-	-370
-	**(Sham/IVR 0.5 mg)**	24	-	-	-	-	9.4	-	-418
CRYSTAL [68]	**(IVR 0.5 mg)**	24	-	333	53	65	12.1	-	-335
-	**(Sham/IVR 0.5 mg)**	24	II	-	50	57	15.6	-	-
COPERNICUS [42, 43]	**(IVA 2 mg)**	24	I	189	51	64	13.0	>15 ETDRS letters: 49.1% IVA x 23.3% Sham +IVA (P<0.001)	- 390 IVA x 343 Sham + IVA (P<0.36)
-	**(Sham/IVA 2 mg)**	24	-	-	-	-	15.0	-	-
GALILEO [36, 44]	**(IVA 2 mg)**	18	I	177	54	70	13.6	-	-

(Table 1) contd….

Author/Study	Intervention	Follow-up (Months)	Level	Number of Patients	-	-	Outcomes	-	-
-	**(Sham)**	18	I	-	-	54	3.8	> 15 ETDRS letters: 57.3% IVA x 29.4% Sham (P<0.001)	-389 IVA x 306.4 Sham (P<0.11) (sham received IVA from the 52 week)
Casselholm De Salles *et al*, 2018 [69]	**IVA 2 mg x IVR 0.5 mg)**	18	II	45	-	-	22.4 IVA 20 IVR (NS)	> 15-letter 67.4% whole cohort	-550.4 IVA x -551.8 IVR (NS)
CRUISE [37]	**(IVR 0.5 mg)**	12	I	392	46	62	13.9	-	-
-	**(IVR 0.3 mg)**	12	I	392	47	62	13.9	>15 ETDRS letters: 50.8% IVR 0.5 mg, 47.0% IVR 0.3 mg, 33.1 % Sham + IVR 0.5 mg (P<0.001)	-452 IVR 0.3 mg, -462.1 IVR 0.5 mg, 427.2 Sham+IVR 0.5 mg
-	**(Sham/IVR 0.5 mg)**	12	I	393	49	57	7.3	-	-
Epstein *et al.*, 2012 [70]	**(IVB 1.25 mg)**	12	-	-	45	61	16.1	>15-letter: 60% IVB x 33% sham/IVB	-435 IVB x -404 sham/IVB (NS)
SCORE-CRVO [47]	**(observation)**	12	I	271	52	40	-12.1	>15-letter:64.1% IVA x 61.3% IVB	-
-	**(IVA 2 mg)**	12	I	293	50	69	19.0	-	-
-	**(IVB 1.25 mg)**	12	I	293	50.5	69.5	18.9	-	-
Lip *et al*, 2015 [51]	**(IVB 1.25 mg)**	12	II	100	-	-	-	+3 lines:30%	-171
COMRADE C [72]	**(IVR 0.5 MG X IVD)**	12	II	61	-	-	18.9	-	-376 (IVR) x -168 (IVD)
Lotfy *et al*, 2018 [53]	**(IVA 2.0 mg)**	12	II	39	-	-	-	0.8 => 0.3 logMAR (NS)	-216
-	(IVR 0.5 mg)	-	-	40	-	-	-	0.7=>0.3 logMAR (NS)	-196
Sun *et al*, 2017 [33]	**(IVC 0.5 mg)**	9	II	30	-	-	14.2	-	-420

(Table 1) contd….

Author/Study	Intervention	Follow-up (Months)	Level	Number of Patients	-	-	Outcomes	-	-
DIng *et al*, 2011 [73]	**(IVB 1.25 mg x IVT 4 mg)**	9	II	32	-	-	-	0.32 logMAR IVT x 0.38 logMAR IVB (NS)	no CMT differences
RELATE [40]	**(IVR 0.5 mg)**	6	I	39	47	62	15.5	-	-253
-	**(IVR 2.0 mg)**	-	-	-	46	62	15.8	(p=0.94)	-396 (9=0.03)
ROCC [74]	**(IVR 0.5 mg)**	6	I	32	-	-	12.0	Sham: -1.0 (letter gain)	- 304 IVR x 151 Sham
Gado *et al*, 2014 [75]	**(IVB 1.25 mg x IVD 0.7 mg)**	6	II	60	-	-	-	+0.2 logMAR (both)	No differ-ence
Ramezani *et al*, 2014 [76]	**(IVB 1.25 mg x IVT 4.0 mg)**	6	II	86	-	-	-	0.41 logMAR IVB x 0.6 logMARIVT	Higher CMT re-duction IVB than IVT
Saishin *et al*, 2017 [77]	**(IVR 0.5 mg/IVA 2 mg)**	6	II	26	-	-	-	0.31logMAR IVR x 0.20 logMAR IVA (NS)	-374 IVR x -465 IVA (NS)

Level I: well-conducted and designed randomized clinical trials; Level II: lower-quality randomized, well-designed case-control, and cohort studies; Level III: lower-quality cohort and case-control studies and case series. (IVT)= intravitreous triamcinolone; (IVD)= intravitreous dexamethasone; (NS) non-significant difference; (CMT= central macular thickness.

The laser association (conventional or subthreshold) needs better evidence, especially related to the existence of protocols and functional advantages, except in severe cases with neovascularization of the retina or iris in which isolated photocoagulation or photocoagulation associated with anti-VEGF results in the best choice [26, 27, 39, 40, 45, 46, 50, 59, 60, 65, 103-106]. The elimination of residual foci of ischemia with the use of the laser is still debatable and eventually adopted in individualized management. The aim is to reduce the intraocular levels of VEGF associated with chronic macula edema or neovascular foci with fewer associated injections [40, 109].

Severe complications related to anti-VEGF are very rare. But there are local and systemic potential side effects that must be discussed with patients. These include ocular pain (10-20%), conjunctival hemorrhage (20-30%), transient or sustained (8.9%) increase of intraocular pressure, accidental cataract, endophthalmitis (0.001%), vitreous hemorrhage (2-10%), retinal detachment, severe systemic complications (stroke or myocardial infarction, 0.02%) [119-122].

CONCLUSION AND AUTHOR'S INSIGHT ON THE TOPIC

Anti-VEGF inhibition is currently the first-line therapy for macular edema in all forms of RVO. Baseline BCVA influences on functional improvement. Early treatment and regular follow-up are mandatory to achieve good results. Real-life results are not so good. A lot of patients still show unresolved edema even after a prolonged period of injections. Combined therapy or switches could be an option for persistent macular edema.

LIST OF ABBREVIATIONS

anti-VEGF = Antivascular endothelial growth factor
BCVA = Best correct visual acuity
BRVO = Branch retinal vein occlusion
CRVO = Central retinal vein occlusion
DRIL = Disorganization of retinal inner layers
ELM = External limiting membrane
ERG = Electroretinogram
EZ = Ellipsoid zone
FAZ = Foveal avascular zone
HRVO = Hemispheric retinal vein occlusion
iBRVO = Ischemic branch retinal vein occlusion
IC = Confidence Interval
iCRVO = Ischemic central retinal vein occlusion
IL-6 = Interleukin-6
IL-8 = Interleukin-8
IVFA = Intravenous fluorescein angiography
ni-OVCR = Non-ischemic central retinal vein occlusion
NPZ = Nonperfusion zones
OCT = Optical coherence tomography
OCT-A = Optical coherence tomography angiography

PLGF = Placental Growth Factor
PR = Photoreceptors
PRN = Pro re nata
RVO = Retinal vein occlusion
TAE = Treat-and-extent
UWFFA = Ultra-wide fundus fluorescein angiography
VA = Visual acuity
VF = Visual Fields

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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