Long-term outcomes and predictive factors for patients with retinal vein occlusion treated in real-world clinical practice

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ABSTRACT

Purpose: To assess the long-term outcomes in the management of macular edema (ME) secondary to retinal vein occlusion (RVO).

Materials and methods: This study comprised 25 patients with branch RVO (BRVO) and 30 patients with central RVO (CRVO). Initial treatment consisted of monthly anti-VEGF injections for 6 months in BRVO and 6 to 12 months in CRVO. Subsequent treatment for patients who did not meet stability criteria was based on response to treatment.

Results: The mean follow-up time was 46 months. The mean number of injections per patient in the first year was 7.7 for BRVO and 9.2 for CRVO and decreased dramatically in the years thereafter. About 67% of the eyes received anti-VEGF agents only. At the final visit, for patients with BRVO and CRVO,respectively, central subfield thickness had decreased -167 and -280 µm, and visual acuity gain gain was 11.5 and 19.0 letters. ME had resolved in 84% of patients with BRVO and 67% of patients with CRVO. Older age (P<0.001),diabetes (P=0.01) and persistence of ME (P<0.001) limited the visual improvement in BRVO, and retinal ischemia (P<0.001) and severe disorganization of the retinal inner layers (P<0.001) after treatment limited the visual improvement in CRVO.

Conclusion: Initiating early intensive intervention with anti-VEGF during the early phase of ME can suppress recurrence in chronic phase. In the chronic phase, when the disease becomes resistant to anti-VEGF therapy, scatter laser photocoagulation may decrease the treatment burden in ischemic BRVO, and dexamethasone implant may improve cost-effectiveness in both BRVO and CRVO.

Keywords: Branch retinal vein occlusion, Central retinal vein occlusion, Dexamethasone intravitreal implant, Macular edema, Vascular endothelial growth factor.

INTRODUCTION

Atherosclerotic cardiovascular disease, highly prevalent in older people, is associated with retinal vein occlusion (RVO).[1] Thrombotic occlusion of the main retinal vein, "central RVO'' (CRVO), and thrombotic occlusion in a tributary of the main retinal vein ‘'branch RVO'' (BRVO), increase vascular resistance, reducing perfusion status of the retina.[2] Retinal ischemia further promotes expression of hypoxia-induced angiogenic factors, leading to vision-compromising complications such as macular edema (ME) and neovascularization.[2]

Reducing vascular permeability, vascular endothelial growth factor (VEGF) inhibitors are the current first-line treatment option and have become the standard of care in clinical practice. Clinical trials have evaluated intravitreal ranibizumab, aflibercept, and bevacizumab for optimal potential for functional and structural improvement.[1,3-7] Sustained-release intravitreal dexamethasone implants are important in treatment of cases with RVO, but mostly as a second preference.[1] Destructive scatter argon laser photocoagulation is a treatment of choice in the management of neovascular complications or in cases with widespread peripheral retinal ischemia, that need follow-up consistently over a long period before neovascularization occurs, when reliable monitoring is not feasible.[1]

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Despite the overwhelming early response, some functional achievements are subsequently lost due to persistent or recurrent ME, and retreatments are necessary in a significant subset of patients.[1,2,8-16] Information regarding the response to multiple different treatments and optimal retreatment intervals is lacking. Additionally, management requires to be tailored to involve maintenance and practicability.[1] Real-world evidence studies can provide information on treatment that helps to maintain initial gains and stabilizes the disease over a long period.[11] In this study we report in detail predictive factors, number and types of treatments, and changes in visual and anatomical results over time of patients treated for ME secondary RVO in a real-life clinical practice.

MATERIALS AND METHODS

This observational, retrospective single-center study was approved by the Institutional Review Board of Sisli Memorial Hospital. The study adhered to the tenets of the Declaration of Helsinki. All participants signed an informed consent before every treatment procedure. The clinical records of all patients treated with the diagnosis of RVO in Istanbul Retina Institute between June 2012 and October 2019 were retrospectively analyzed. Only treatment-naive patients with a minimum follow-up of 2 years were included. Patients were not eligible for the study if they had any other additional ocular disorder that could compromise their visual acuity (VA).

All patients provided a medical history and had complete ophthalmologic assessment at baseline and follow-up visits. The morphology of retinal layers and central subfield thickness (CST) were evaluated using optical coherence tomography (Spectralis, HRA+SD-OCT). Acquisition and analysis of OCT images and grading of disorganization of the retinal inner layers (DRIL) were carried out as previously described.[17,18] Fluorescein angiography using a wide-angle camera or 55-degree lens to determine the extent of nonperfusion or leakage was performed at baseline (or after a few injections if retinal hemorrhage precluded accurate assessment), during follow-up (at the physician's discretion), and before each treatment with laser photocoagulation.

Treatement was initiated as soon as possible after the diagnosis of ME. Both central macular edema and VA of less than 20/30 were regarded as therapeutic criteria. The initial treatment plan consisted of a schedule of monthly anti-VEGF injections for 6 months in BRVO and 6 to 12 months in CRVO. In patients who met stability criteria (achieved maximum stable VA, absence of subretinal fluid (SRF) or intraretinal fluid (IRF) involving the foveal center on SD-OCT) at the end of the protocol, monthly anti-VEGF therapy was discontinued and they were examined at least every 3 months. Patients with stable disease over 2 years were re-evaluated at 6-monthly intervals. Those who did not meet stability criteria continued to receive treatment. Participants with moderate persistent or recurrent disease activity after initial monthly therapy requiring less frequent treatment transitioned to anti-VEGF with treat-and-extend, as needed, or a bimonthly regimen at the discretion of the physician based on clinical features and treatment response. Patients with a poor or marginal response (severe persistent or recurrent IRF or SRF in the macula despite receiving anti-VEGF injections) switched to dexamethasone implant and/or, if the ischemic type of BRVO was present, scatter laser photocoagulation. Macular edema resolution was assessed as no IRF or SRF for at least 6 months after the last treatment.

For statistical analysis, we used SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Pearson's chi-square tests were used to compare categorical variables. Fisher's exact test was used to determine whether there were nonrandom associations between two categorical variables. Independent *t* tests were used to explore differences in means among continuous variables between groups. Repeated measures ANOVA tests were used to compare BCVA and CST values at later time points with baseline. Linear regression analyses compared final BCVA with baseline and final BCVA with predictive data. Potential baseline predictors for VA were: age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking, glaucoma, baseline VA, duration of RVO, ischemic type of RVO, CST, and the presence of subretinal fluid, hyperreflective foci, epiretinal membrane (ERM) and vitreomacular interface abnormalities. The impact of potential morphologic features on VA obtained by OCT at the last visit were analyzed separately, and included: presence of ME, DRIL, integrity changes in inner and outer photoreceptor segment (IS/OS) line and vitreomacular interface abnormalities.

RESULTS

Table 1 shows the baseline demographic and clinical characteristics. In 25 (45%), ME was secondary to BRVO (macular BRVO=8 and major BRVO=17), and in the remaining 30 (55%), ME was secondary to CRVO (CRVO=26 and hemi-RVO=4).

Background medical conditions included: hypertension in 33 (60%), diabetes mellitus in 11 (20%), hyperlipidemia

Table 1: *Main Baseline Demographic and Clinical Characteristics.*

Variable	Total Group	Branch Retinal Vein Occlusion	Central Retinal Vein Occlusion	*P*
	***n* = 55**	***n* = 25**	***n* = 30**	
Mean±SD age, yr (range)	61.8±14.0	58.4±12	64.7±14	0.09
	(37-90)	(41-87)	(37-90)	
Sex F/M, %	44/56	56/44	33/67	0.10
Duration of RVO ≤3 mo, n (%)	43 (78)	20 (80)	23 (77)	1.0
Time to initial treatment after onset of RVO ±SD, wk	6.9±7.9	6.0±6.8	7.6±8.7	0.45
Mean±SD IOP, mmHg	15.1±2.2	15.5	14.8	0.26
Ischemic RVO*, n (%)	23 (42)	11(44)	12(40)	1.0
Mean±SD follow-up, mo	45.8±20.3	47.1±20.0	44.7±20.7	0.67
Visual Acuity				
Snellen acuity (range)	20/120	20/80	20/180	**0.01**
	(20/32–20/2000)	(20/32–20/200)	(20/32–20/2000)	
VALS	46.0	56.5	37.0	**0.01**
VALS ≥ 70, n (%)	16 (29)	9 (36)	7 (23)	0.37
VALS ≤ 35, n (%)	20 (36)	5 (20)	15 (50)	**0.02**
Optical Coherence Tomography Features				
CST±SD, µm (range)	572±204	505±124	628±240	**0.02**
	(367-1119)	(367-826)	(368-1119)	
Subretinal fluid, n (%)	20 (36)	9 (36)	11 (37)	1.0
Hyperreflective foci, n (%)	31 (56)	9 (36)	22 (73)	**0.007**
Vitreoretinal adhesion, n (%)	13 (23)	9 (25)	4 (13)	0.06
Epiretinal membrane, n (%)	4 (7)	0 (0)	4 (13)	0.11

CST = Central subfield thickness, IOP = Intraocular pressure, n = Number, RVO = Retinal vein occlusion, SE = Snellen equivalent, SD = Standard deviation, VALS = Visual acuity letter score *Including nonischemic RVOs converted to ischemic in the course of the study. Bold values indicate statistical significance ($P<0.05$).

in 11 (20%), primary open angle glaucoma in 4 (7%), and history of smoking in 15 (27%). None of the the ocular and systemic risk factors were significantly different between the CRVO and BRVO groups.

Figure 1 describes BCVA and SRT change, and intravitreal injection distribution over time in patients with BRVO. Final VA of 20/40 or better was achieved in 64%, and only 16% of cases had final VA ≤20/200 (Table 2). The percentage of patients whose ME had resolved at the last visit was 84%. Of the BRVO eyes that completed the initial planned treatment regimen of 6-monthly anti-VEGF injections, 56% did not require further intravitreal injection treatment. The remaining 11 eyes (44%) underwent subsequent retreatments with intravitreal injections including anti-VEGF or dexamethasone implant. Of the patients in the BRVO group who needed further retreatments, 73% had the ischemic type of RVO.

Figure 2 describes BCVA and SRT change, and intravitreal injection distribution over time in patients with CRVO. Final VA of 20/40 or better was achieved in 57%, and 37% of cases had final VA ≤20/200 (Table 2). A significant number of cases, 30%, stabilized early after 6 monthly injections, obviating the need for further anti-VEGF treatment, and no subsequent treatments were given. Additionally, in about 37% of the participants who completed the planned protocol of 12 monthly anti-VEGF injections, further intravitreal injections were not given, although 33% underwent subsequent retreatments with intravitreal injections. Of the patients in the CRVO group who needed further retreatment, 80% had the ischemic type of RVO. The percentage of patients presenting with no edema for at least 6 months after the last injection was 67%.

About 67% of the eyes received anti-VEGF agents only. The remaining eyes underwent anti-VEGF plus dexamethasone

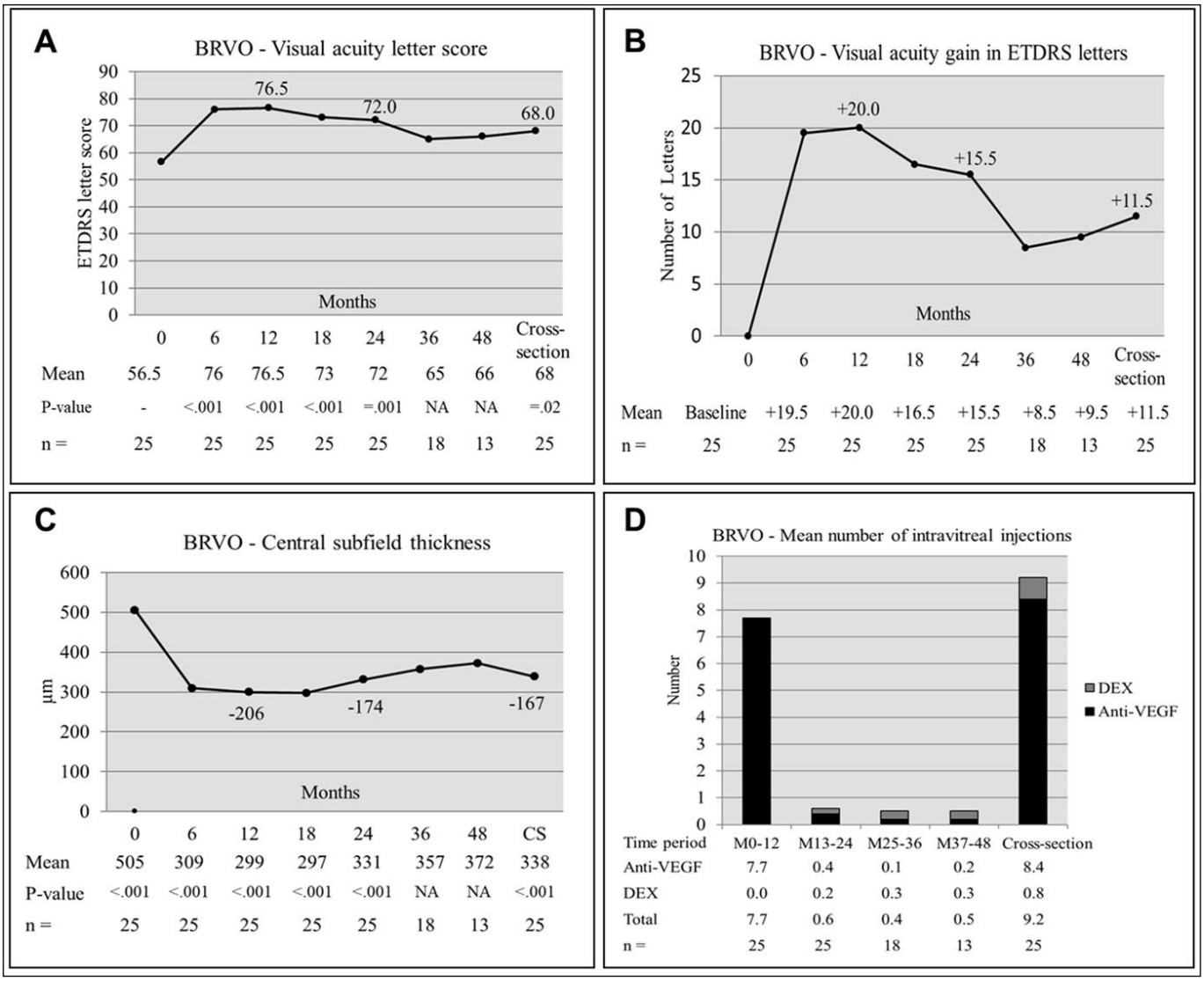

Figure 1: *Graphs representing visual and anatomical outcomes and number of intravitreal injections in patients with branch retinal vein occlusion (BRVO). P values of repeated measures ANOVA test comparing values at some time points with baseline values are also presented.* **A.** *Mean best corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score is plotted at 6-month (from 0 to 24 months) and 12-month intervals (from 24 to 48 months) from baseline.* **B.** *Visual acuity gain in ETDRS letters.* **C.** *Mean central subfield thickness plotted at 6-month (from 0 to 24 months) and 12-month intervals (from 24 to 48 months) and overall.* **D.** *Mean number of injections administered per 12-month interval.*

(13%), anti-VEGF plus laser photocoagulation (13%), or all three of the treatments (7%). Table 3 shows treatments received during the follow-up period. Eleven patients (20%), 6 with BRVO and 5 with CRVO, received scatter photocoagulation, and 5 eyes (83%) with BRVO and only one eye (20%) with CRVO had resolution of ME at the final visit.

During the follow-up period, IOP increased transiently in 3 of the 11 patients whose treatment included dexamethasone implant. Vitreous hemorrhage occurred in 2 eyes (6%), retinal hemorrhage in 1 eye (3%), and iris or angle neovascularization in 4 eyes (13%) in the CRVO group and these were managed successfully by scatter argon laser photocoagulation and topical antiglaucoma treatment. The presence of DRIL at the final visit was found in 28% (7/25) and 40% (12/30) of cases with BRVO and CRVO, respectively.

Predictive factors for final visual outcome

In linear regression analysis, the presence of subretinal fluid at baseline was associated with better final logMAR VA (coefficient = -0.3, 95% CI = -0.5 to -0.1, P=0.006), and increasing age (coefficient = 0.6, 95% CI = 0.1 to 0.3, P<0.001) and presence of diabetes mellitus (coefficient

Table 2: *Visual Acuity Letter Score Outcomes at Month 12, Month 24, and Last Follow-up Visit*						
Variables	**Branch Retinal Vein Occlusion**			**Central Retinal Vein Occlusion**		
	Month 12	Month 24	Last Visit (mean 47 mo)	Month 12	Month 24	Last Visit (mean 45 mo)
VALS ≥15 improvement from baseline, n (%)	15 (60)	12 (48)	11 (44)	20 (66)	21(70)	20 (66)
VALS ≥15 worsening from baseline, n (%)	0 (0)	1 (4)	4 (16)	1 (3)	2 (7)	2 (7)
VALS ≥70, n (%)	23 (92)*	18 (72)	16 (64)	16 (53)*	18 (60)	17 (57)
VALS ≤ 35, n (%)	0 (0)	1 (4)	4 (16)	8 (26)	10 (33)	11 (37)
**P*= 0.002 (Fisher's exact test) n = Number, VALS = Visual acuity letter score						

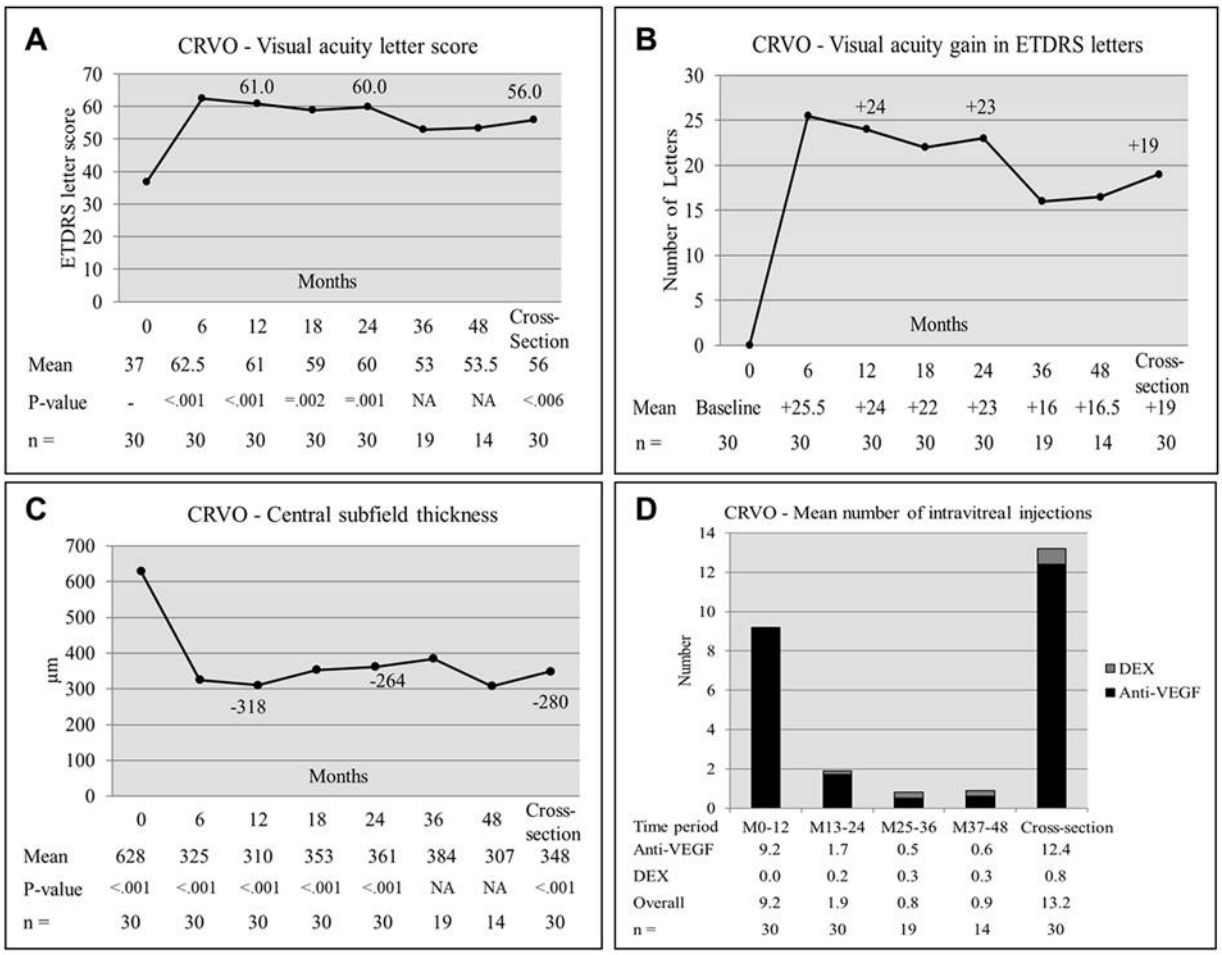

Figure 2: *Graphs representing visual and anatomical outcomes, and number of intravitreal injections in patients with central retinal vein occlusion (CRVO). P values of repeated measures ANOVA test comparing values at some time points with baseline values are also presented.* **A.** *Mean best corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score is plotted at 6-month (from 0 to 24 months) and 12-month intervals (from 24 to 48 months) from baseline.* **B.** *Visual acuity gain in ETDRS letters.* **C.** *Mean central subfield thickness plotted at 6-month (from 0 to 24 months) and 12-month intervals (from 24 to 48 months) and overall.* **D.** *Mean number of injections administered per 12-month interval.*

= 0.3, 95% CI = 0.1 to 0.5, *P*=0.01) were significantly associated with poorer final VA in the BRVO group. Additionally, the presence of ischemic-type RVO was significantly associated with poorer VA in the CRVO group (coefficient = 0.8, 95% CI = 0.7 to 1.2, *P*<0.001). When potential morphologic features obtained by OCT at the last visit were included in the analysis, the presence of ME and DRIL were associated with poorer VA in the BRVO group (coefficient = 0.5, 95% CI = 0.4 to 0.8, *P*<0.001) and the CRVO group, respectively (coefficient = 0.9, 95% CI = 0.9 to 1.4, *P*<0.001).

Table 3: *Number and Percentage of Types of Treatments Received During Follow-up*

Treatment	Branch Retinal Vein Occlusion		Central Retinal Vein Occlusion		Total Group	
	Eyes, n (%)	Treatments, n (range)	Eyes, n (%)	Treatments, n (range)	Eyes, n (%)	Treatments, n (range)
Monotherapy						
Anti-VEGF alone	16 (29)	7.7 (6–12)	21 (38)	12.9 (6–43)	37 (67)	10.7 (6–43)
Combination therapy						
Anti-VEGF (1) Argon Laser (2)	4 (7)	(1) 7.5 (6–12) (2) 1.3 (1–2)	3 (5)	(1) 11.6 (6–14) (2) 2.0 (1–3)	7 (13)	(1) 9.5 (6–14) (2) 1.6 (1–3)
Anti-VEGF (1) DEX (2)	3 (5)	(1) 10.6 (6–14) (2) 3.7 (1–7)	4 (7)	(1) 11.0 (6–14) (2) 2.5 (1–6)	7 (13)	(1) 10.8 (6–14) (2) 3.0 (1–7)
Anti-VEGF (1) Argon Laser (2) DEX (3)	2 (4)	(1) 11 (10–12) (2) 2 (2) (3) 4 (3–5)	2 (4)	(1) 12 (12) (2) 2 (1–3) (3) 5 (1–9)	4 (7)	(1) 11.5 (10–12) (2) 2 (1–3) (3) 9.0 (1–9)

Anti-VEGF = Anti-vascular endothelial growth factor, DEX = Dexamethasone implant, RVO = Retinal vein occlusion

DISCUSSION

Our results indicate that early intensive treatment with anti-VEGF during the first year, which has been reported in multicenter trials, is feasible even in real-world settings and subsequent treatment might be individualized on the basis of treatment response, and patients would require fewer injections. Most of the improvement in the visual acuity letter score (VALS) and CST was achieved during the first 6–12 months, when treatment was performed monthly. The early improvement was preserved to some extent during months 12 to 24, when patients withdraw from the monthly treatment protocol, and decreased during months 36 to 48, when in a subset of cases functional achievements were lost due to bouts of recurrent ME, and a significant number of good responders with resolution of ME were lost to follow-up.

It has been proposed that RVOs may be compensated over time by recanalization and collateral vessel development, and good outcomes could be provided if ME and nonperfusion are managed by VEGF inhibition during the acute phase of the disease.[2] Real-life studies with reinjection criteria based on the presence of ME have shown that ME secondary to RVO is a chronic condition necessitating continuing, probably monthly, monitoring and periodical retreatments.[16] In general, the decision of whether or not to treat is based on the presence or absence of ME; however, it is often influenced by patient compliance and the waiting list.[16] The physicians should take into account the social status and compliance challenges as much as the available research evidence and cost-effectiveness of the treatment applied.[19]

Real-world evidence and clinical trial data on long-term outcomes in RVO patients is limited.[9,11-16,20] Rezar et al. reported mean 5 years follow-up results of 28 patients managed with anti-VEGF agents for ME secondary to BRVO. One of the major conclusions of this study was that early treatment is associated with better recovery of vision.[11] The RETAIN study included patients previously treated with intravitreal ranibizumab who completed the BRAVO or CRUISE studies and were followed in HORIZON.[9] The mean number of injections per year in BRVO and CRVO groups, respectively, was 7.3 and 8.1 in year 1, 2.6 and 4.5 in year 2, 2.1 and 3.6 in year 3, and 2.0 and 3.3 in year 4. Resolution of ME occurred in 50% of participants with BRVO and 44% of participants with CRVO who entered the RETAIN study. It should be noted that the results of RETAIN may not be fully representative of the original cohort, because data were available for only 11% of the initial BRAVO and CRUISE participants at 4 years [9]. Spooner et al. reported 5-year results of patients treated with anti-VEGF agents for ME secondary to RVO (31 BRVO and 37 CRVO/hemi-RVO).[20] The average number of injections performed during the first year in the BRVO and CRVO groups were 6.9 and 7.3, respectively. Subsequent years showed no variance in frequency of anti-VEGF treatment in both groups, with a mean of 5.5 per year. Anti-VEGF treatment was successfully discontinued in the first 2 years in approximately 15% of the eyes with no recurrence of ME, and approximately 65% of the eyes had resolution ME at 5 years. One of the major findings of this research was that the number of anti-VEGF treatments did not reduce from 2 to 5 years.[20] Lower rates of ME resolution after 1 year of anti-VEGF therapy in comparison to our study may be related the lower number

(range, 1–13) of anti-VEGF injections given to some of the patients during the acute phase of the disease.

In comparison to patients whose ME resolved with anti-VEGF injections alone, those whose ME did not resolve were older (71 vs 58 years old for CRVO and 66 vs 57 years old for BRVO). Sophie and al. reported that in ranibizumab-treated participants with CRVO, those whose disease resolved with injections alone tended to be younger, and it was suggested that there could be two different patient populations with CRVO.[21] Both increasing age and presence of diabetes mellitus were found to be negative predictors for the final VA results in patients with BRVO in our research. This was in line with Chatzırallı et al. and Yiu et al., who also reported that increasing age is negative predictor for the final VA results in patients with RVO.[13,22] Proinflammatory mediators and metabolic alterations in Müller glial cells rather than alterations in endothelial cells could play a role in the changes of retinal capillary basement membrane during diabetes and aging, leading to retinal ischemia and exudation.[23]

The presence of ischemic RVO and severe DRIL at the final visit were found to be negative predictors for the final visual outcome in patients with CRVO in our study population. This was in line with Berry et al. who reported that DRIL extent in patients with CRVO correlated with worse VA after treatment.[24] It has been proposed that the severity of DRIL pre- and post-treatment represents an OCT finding that could serve as a biomarker for patients with ME associated with RVO.[17] The underlying pathophysiology of DRIL and its influence on VA has not yet been completely clarified. Retinal cell loss within the inner retinal layers, leading to disruption of neural transmission from photoreceptors to the retinal ganglion cells has been suggested as a possible explanation.[25] The DRIL probably represents compromise of the inner retinal circulation in RVO, and an OCT parameter such as DRIL would correlate with BCVA more significantly than the parameters of the outer neurosensory layer.[26]

Regarding the ischemic type of RVO as a predictive factor for the final visual outcome, it has been reported that ischemic eyes with RVO have a larger final foveal avascular zone and worse functional outcome.[13,14] At the same time, worsening of retinal ischemia seems to be more common in cases with unresolved ME. Probably, progression of retinal nonperfusion also contributes to inability to achieve stabilization.[21] In terms of progression of retinal ischemia and its association with poorer outcomes, it has been proposed that scatter photocoagulation may reduce VEGF levels and promote resolution of ME in RVO.[11,21] Adding scatter laser photocoagulation to intravitreal injections led to edema resolution in 83% (5/6) and 20% (1/5) of patients with ischemic BRVO and CRVO, respectively. Laser treatment applied in the affected retinal areas of patients with ME secondary to BRVO has been proven to be effective in providing improvement of VA; however, in view of the availability of anti-VEGF therapy, laser treatment should be considered as a second-line intervention.[1,11] On the other hand, scatter laser photocoagulation is the standard of care for the treatment of neovascular complications associated with CRVO; however as has been previously reported, adding laser photocoagulation to peripheral areas of nonperfusion provides little obvious benefit in chronic ME and does not result in either reduced reinjection frequency or improved VA.[1,26]

Anti-VEGF treatment initiated early after the onset of RVO results in higher efficiency because VEGF plays predominant role in the early period.[27] Monthly anti-VEGF treatment significantly decreases VEGF levels, leading to improvement of retinal hypoxia. It has been proposed that the aggressive inhibition of VEGF prevents worsening of retinal nonperfusion and promotes reperfusion.[28,29] On the other hand, Nicholson et al. suggested that early anti-VEGF treatment does not completely protect against worsening of retinal nonperfusion in CRVO.[30,31] Although ME improves after anti-VEGF treatment, repeated recurrence and resistance of ME is an important problem in many RVO patients. Interestingly, in one-third of the cases with ME secondary to RVO, the intravitreal VEGF levels may fall within the accepted normal limits. It seems that there could be some particular pathophysiological mechanisms contributing to ME, and this could be the explanation why some individuals show limited response to anti-VEGF treatment alone.[1]

In the chronic phase of RVO, expression of inflammatory cytokines other than VEGF increases, and pathophysiological events become more complicated.[27] Corticosteroids inhibit the metabolic pathways of VEGF and, in addition, are the most potent anti-inflammatories available. It is obvious that corticosteroids are important agents for treating ME secondary to RVO, but usually as a second choice.[1] Switching to sustained-release corticosteroid in nonresponders who have been treated with anti-VEGF agents for a minimum of 1 year is reasonable. Retreatment benefits of intravitreally-administered dexamethasone implants are substantially sustained for 4–6 months, and 2–3 injections per year may be necessary.

The present study has several potential limitations. The sample size was small and there was no control group. A significant number of patients exited early. Patients achieving early stabilization were more likely to be lost to follow-up, and the study may have been underpowered to assess some of the long-term variables. The present treatment strategies in the management of RVO may not represent the most appropriate alternative in current clinical practice worldwide.

In conclusion, this study summarize the long-term outcomes, providing a valuable opportunity to elucidate and discuss the management of ME secondary to RVO in real-life settings. Long-term follow-up data showed that prompt and strict monthly anti-VEGF treatment alone in the first year provide ME resolution and maintain VA improvement. The mean number of injections per patient decreased dramatically during the following years. Subsequent treatment may be individualized on the basis of treatment response. If patients with chronic ME and retinal nonperfusion secondary to BRVO require injections during long-term management in a real-world setting, segmental laser photocoagulation may control ischemia and may allow treatment to be reduced or even stopped. In the chronic phase of RVO, the disease becomes resistant to anti-VEGF therapy and retreatment as needed with dexamethasone implant would necessitate approximately 2–3 injections per year.

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