ORIGINAL ARTICLE

The use of anti–vascular endothelial growth factor in the treatment of retinal vein occlusion: a paradigm shift in management

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Abstract

Aims: This study aimed, firstly, to investigate the efficacy of intravitreal anti–vascular endothelial growth factor injection on macular edema and other ocular complications of retinal vein occlusion in Hong Kong. Secondly, to compare the efficacy of bevacizumab and ranibizumab in the treatment of retinal vein occlusion. Lastly, to compare the results of this study with those in the literature and make recommendations on the treatment of retinal vein occlusion in the anti–vascular endothelial growth factor era.

Methods: This was a consecutive case series of all patients with retinal vein occlusion who were treated with intravitreal anti–vascular endothelial growth factor injection at Hong Kong Sanatorium Hospital from August 2009 to February 2012. Re-injection was given as needed according to the best-corrected visual acuity and optical coherence tomography.

Results: There were 24 eyes of 23 patients with central retinal vein occlusion and 26 eyes of 26 patients with branch retinal vein occlusion receiving anti–vascular endothelial growth factor therapy. For those with central retinal vein occlusion, the mean best-corrected visual acuity was 0.10 at baseline, 0.20 at 1 month postinjection ($p = 0.001$) and 0.52 at final follow-up ($p = 0.02$), at a mean follow-up of 12.1 months. Their mean central foveal thickness was reduced by more than 200 μm at both 1 month ($p = 0.001$) and final follow-up ($p = 0.015$). For those with branch retinal vein occlusion, the mean best-corrected visual acuity was 0.33 at baseline, 0.48 at 1-month postinjection ($p = 0.046$) and 0.55 at final follow-up ($p = 0.014$), at a mean follow-up of 11.5 months. Their mean central foveal thickness was reduced by more than 100 μm at both 1 month ($p = 0.003$) and final follow-up ($p = 0.007$). Neither neovascular nor injection-related complication was noted in all compliant patients. No significant difference in efficacy was found between ranibizumab and bevacizumab. The mean number of injections was 5.6 and 3.4 for those with central retinal vein occlusion and branch retinal vein occlusion, respectively.

Conclusion: Intravitreal anti–vascular endothelial growth factor injection given as needed is safe and effective in terms of visual outcome, reduction of macular edema, and prevention of complications. The injection regimen should be individualized based on clinical status, patient expectation, and financial affordability, with consideration of adjuvant treatment.

Key words: Macular edema; Retinal vein occlusion; Vascular endothelial growth factor A

Introduction

Retinal vein occlusion (RVO) is a major cause of sudden painless visual loss. In both central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), the area of non-perfusion or capillary dropout on fundus fluorescein angiogram (FFA) is critical for further classification into ischemic or non-ischemic types. The 2 main complications that lead to persistent visual loss in RVO are related to neovascularization (NV) and macular edema (ME).[1-3]

Apart from cardiovascular risk factor control, the traditional management of RVO involves the use of laser therapy. According to the Central Vein Occlusion Study, grid laser for ME does not improve visual acuity (VA).[4] While prophylactic pan-retinal photocoagulation (PRP) in ischemic CRVO reduces the chance of anterior segment NV, the likelihood of persistent NV or neovascular glaucoma is not decreased.[5] In the Branch Vein Occlusion Study, grid laser for ME with VA ≤ 20/40 improved the VA at least 2 lines from baseline,[6] and prophylactic PRP reduced the chance of NV and vitreous hemorrhage.[7] However, grid laser is not recommended as routine therapy to avoid overtreatment.

Corticosteroid is a potent anti-inflammatory agent that stabilizes the blood-retinal barrier. The efficacy of intravitreal steroid injection was demonstrated in the Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) study.[8] Despite the improvement in VA and ME, 20% to 35% of patients required anti-glaucomatous medication for the intraocular pressure (IOP) rise among the steroid responders, and 21 patients required surgery for cataract progression in 2 years.[8]

Since the discovery of vascular endothelial growth factor (VEGF) being the key molecular mediator for persistent visual loss in RVO,[9] the application of monoclonal antibodies to VEGF (e.g. bevacizumab, ranibizumab) has been extended to RVO. Several studies have shown the efficacy of anti-VEGF in the treatment of ME related to RVO, with both functional and anatomical improvement.[10-15] However, many of these studies employed a frequent and regular intravitreal injection regimen to maintain the effect of anti-VEGF, which is associated with considerable financial burden and potential risks of the procedure. No studies to date compared a regular with an as-needed (prn) regimen, in which intravitreal anti-VEGF injection was repeated as required. Moreover, many of the studies focused on ME, but not on other complications of RVO. Data on the efficacy of different anti-VEGF agents were also limited.

The aims of this study were multifold, as follows: (1) to investigate the efficacy of intravitreal anti-VEGF injection on ME and other ocular complications associated with RVO in Hong Kong; (2) to compare the efficacy of bevacizumab and ranibizumab in the treatment of RVO; and (3) to compare the results of this study with those in the literature and make recommendations for the treatment of RVO in the anti-VEGF era.

Methods

This was a consecutive case series of patients with RVO who received an intravitreal anti-VEGF injection regimen at a private ophthalmic institute in Hong Kong. All RVO patients who received intravitreal anti-VEGF injection at Hong Kong Sanatorium Hospital from August 2009 to February 2012 were included. Patients were identified from the ophthalmic procedure record from the ophthalmic clinics of the hospital. All clinical information was retrieved through the electronic patient records.

Following administration of the intravitreal anti-VEGF injection, patients were followed up at 1 to 2 weeks. Best-corrected visual acuity (BCVA) measurement, fundus examination, and optical coherence tomography (OCT) were done. For subsequent follow-up, OCT was offered on a monthly basis where appropriate. The need for repeating the anti-VEGF injection was reviewed every month as guided by BCVA and OCT (prn regimen). In general, anti-VEGF injection was repeated if there was a drop in BCVA of more than 2 lines on Snellen chart, an increase of >100 μm in central foveal thickness (CFT), or cystoid ME shown on OCT, subjective to the discretion of the treating ophthalmologist.

The outcomes of interest were BCVA, CFT on OCT, any complications of the disease (NV, vitreous hemorrhage, glaucoma), and any complications from the intravitreal injection (endophthalmitis, retinal detachment). The BCVA and CFT at baseline, 1 month after injection, and at the final follow-up were recorded. BCVA was measured on Snellen chart, but was converted to the logarithmic minimum angle of resolution (logMAR) scale for statistical analysis. Any adjuvant treatment was also noted.

The clinical outcomes for CRVO and BRVO were analyzed separately. A subgroup analysis was also carried out independently for bevacizumab and ranibizumab. The effect of significant capillary dropout on the clinical outcome of RVO following anti-VEGF injection was also investigated. RVO patients with significant capillary dropout (> 10 disc diameters for CRVO, > 5 disc diameters for BRVO) were identified and further studied.

Statistical analyses

Statistical analyses were done by paired samples 2-tailed *t* test when comparing any continuous variables (logMAR VA, CFT) of the same patient before and after injection, independent samples 2-tailed *t* test when comparing continuous variables of different patient groups, and Chi-square test (or Fisher's exact test, where appropriate) when comparing categorical outcomes (presence of complications).

Results

Demographic data

Table 1 shows the baseline characteristics and clinical outcomes of patients with CRVO and BRVO. For CRVO,

Table 1. Baseline characteristics of patients and outcomes of eyes with central retinal vein occlusion or branch retinal vein occlusion.

	CRVO (24 eyes in 23 patients)	BRVO (26 eyes in 26 patients)
Sex (%)		
Male	19 (79)	11 (42)
Female	5 (21)	15 (58)
Mean ± SD age at presentation (years)	60.6 ± 15.1	60.8 ± 15.4
Laterality (%)		
Right	11 (46)	11 (42)
Left	13 (54)	15 (58)
Ischemia (%)		
Ischemic	3 (13)	3 (12)
Non-ischemic	14 (58)	10 (38)
Unknown (unassessable or no FFA)	7 (29)	13 (50)
Mean ± SD follow-up duration (months)	12.1 ± 12.1	11.5 ± 11.8
Type of anti-VEGF (%)		
Bevacizumab	16 (67)	21 (81)
Ranibizumab	8 (33)	5 (19)
Mean ± SD No. of injections	5.6 ± 6.3	3.4 ± 3.7
Mean ± SD BCVA (logMAR)		
Baseline	0.99 ± 0.78	0.48 ± 0.40
1 Month	0.69 ± 0.77	0.32 ± 0.43
Final follow-up	0.28 ± 0.45	0.26 ± 0.44
Mean difference in BCVA (logMAR)		
Baseline to 1 month	0.30 (p = 0.001)	0.16 (p = 0.046)
Baseline to final follow-up	0.71 (p = 0.002)	0.22 (p = 0.014)
Mean ± SD CFT on OCT (μm)		
Baseline	529.42 ± 196.56	401.71 ± 175.86
1 Month	325.57 ± 178.25	277.38 ± 62.37
Final follow-up	308.00 ± 96.36	299.56 ± 93.82
Mean difference in CFT on OCT (μm)		
Baseline to 1 month	-203.85 (p = 0.001)	-124.33 (p = 0.003)
Baseline to final follow-up	-221.42 (p = 0.015)	-102.15 (p = 0.007)
Adjuvant treatment for ME (%)		
Subtenon triamcinolone	7 (29)	2 (8)
Macular laser	0	3 (12)
Intravitreal steroid implant	1 (4)	0
Ocular complications (%)		
Disease-related		
Neovascularization	2 (8)	1 (4)
Epiretinal membrane	1 (4)	0
Vitreomacular traction	1 (4)	0
Treatment-related	0	0

Abbreviations: CRVO = central retinal vein occlusion, BRVO = branch retinal vein occlusion, SD = standard deviation, FFA = fundus fluorescein angiogram, VEGF = vascular endothelial growth factor, BCVA = best-corrected visual acuity, logMAR = logarithmic minimum angle of resolution, CFT = central foveal thickness, OCT = optical coherence tomography, ME = macular edema.

24 eyes of 23 patients received anti-VEGF injection during the study period. One patient had sequential bilateral involvement of CRVO. Most of the patients (79%) were men. The mean age at presentation was 60.6 years (range, 25 to 92 years). Patients received intravitreal anti-VEGF injection on the day of diagnosis of RVO. The mean follow-up duration from diagnosis was 12.1 months (range, < 1 to 35 months). There was no predominance in the laterality of involvement. Most of the CRVOs were non-ischemic (n = 14, 58%), 3 (13%) were ischemic, and the perfusion status of the rest was unknown either due to unassessable FFA or FFA was not performed. The mean number of intravitreal anti-VEGF injections was 5.6 (range, 1 to 25). Seven (29%) patients received subtenon triamcinolone as an adjuvant treatment for recurrent ME: 5 received a single injection, 1 received 2 injections, and 1 received 3 injections as well as

an intravitreal steroid implant.

For BRVO, 26 eyes of 26 patients received anti-VEGF injection during the study period. All patients had unilateral involvement. Unlike CRVO, there was no gender predominance. The mean age at presentation was 60.8 years (range, 35 to 90 years). The mean follow-up duration was 11.5 months (range, < 1 to 35 months). There was no predominance in the laterality of involvement. Most of the BRVOs were non-ischemic (38%), only 3 (12%) were ischemic, and the perfusion status of the rest was unknown. The mean number of intravitreal anti-VEGF injections was 3.4 (range, 1 to 15). Five (19%) patients had adjuvant treatment for recurrent ME: 3 received macular laser following the conventional guideline, and 2 received subtenon triamcinolone injection once each.

Clinical outcomes for anti–vascular endothelial growth factor

For CRVO, the mean presenting BCVA was 0.10 (logMAR, 0.99). The BCVA improved to 0.20 (logMAR, 0.69; p = 0.001) 1 month after injection, and further improved to 0.52 (logMAR, 0.28; p = 0.02) at the final follow-up. Following intravitreal anti-VEGF injection for CRVO, improvement was also observed in CFT. At baseline, the mean CFT was 529.42 μm. At 1 month after injection, there was a reduction of 203.85 μm (p = 0.001). At the last follow-up, the mean final CFT was 308.00 μm, i.e. a reduction of 221.42 μm from baseline (p = 0.015).

For BRVO, the mean presenting BCVA was 0.33 (logMAR, 0.48). At 1 month after injection, the mean BCVA improved to 0.48 (logMAR, 0.32; p = 0.046). At the last follow-up, there was further improvement to 0.55 (logMAR, 0.26; p = 0.014). The mean baseline CFT was 401.71 μm. There was a significant reduction of 124.33 μm at 1 month after injection (p = 0.003). At the last follow-up, the mean final CFT was 299.56 μm for a reduction of 102.15 μm from baseline (p = 0.007).

Complications

Four CRVO patients had disease-related complications. One patient defaulted follow-up for 17 months and was found to have high IOP and NV. Another patient re-presented with vitreous hemorrhage after defaulting follow-up for 10 months. One patient had symptomatic epiretinal membrane, and another had cystoid ME due to vitreomacular traction. All of these patients were treated with pars plana vitrectomy. In the BRVO group, only 1 patient was found to have vitreous hemorrhage at presentation. No other disease-related complications were found during follow-up. No adverse effects of intravitreal anti-VEGF injection were noted in the 50 eyes of the 49 patients with RVO.

Outcomes for bevacizumab and ranibizumab

The baseline characteristics and clinical outcomes of patients receiving bevacizumab or ranibizumab for CRVO or BRVO are summarized in **Table 2** and **Table 3**, respectively.

Table 2. Baseline characteristics and outcomes of eyes with central retinal vein occlusion receiving bevacizumab and ranibizumab.

	Bevacizumab (n = 16)	Ranibizumab (n = 8)	p Value
Sex			
Male	12	7	0.63
Female	4	1	
Mean ± SD age at presentation (years)	60.3 ± 17.4	61.3 ± 9.7	0.89
Mean ± SD follow-up duration (months)	14.4 ± 12.4	7.5 ± 10.7	0.20
Ischemia			0.12
Ischemic	2	1	
Non-ischemic	8	7	
Unknown (unassessable or no FFA)	6	0	
Mean ± SD No. of injections	5.3 ± 6.2	6.3 ± 6.9	0.74
Mean ± SD BCVA (logMAR)			
Baseline	1.10 ± 0.83	0.79 ± 0.69	0.37
Final follow-up	0.17 ± 0.15	0.49 ± 0.72	0.11
Mean difference in BCVA (logMAR)			
Baseline to 1 month	0.29	0.32	0.85
Baseline to final follow-up	0.93	0.30	0.15
Mean ± SD CFT on OCT (μm)			
Baseline	565.54 ± 192.30	472.38 ± 202.45	0.31
Final follow-up	299.00 ± 96.64	335.00 ± 104.32	0.54
Mean difference in CFT on OCT (μm)			
Baseline to 1 month	-257.22	-192.00	0.62
Baseline to final follow-up	-266.54	-137.38	0.99

Abbreviations: SD = standard deviation, FFA = fundus fluorescein angiogram, BCVA = best-corrected visual acuity, logMAR = logarithmic minimum angle of resolution, CFT = central foveal thickness, OCT = optical coherence tomography.

Of the 24 eyes with CRVO, 16 (67%) received bevacizumab and 8 (33%) received ranibizumab. Patients from these 2 treatment groups were comparable in terms of baseline characteristics. No statistically significant differences were found between the 2 groups in age, follow-up duration, number of injections, baseline ischemic status, baseline BCVA, and baseline CFT on OCT ($p > 0.05$). At both 1 month after injection and final follow-up, there were also no statistically significant differences in the improvement in BCVA or CFT on OCT ($p > 0.05$).

Of the 26 eyes with BRVO, 21 (81%) received bevacizumab and 5 (19%) received ranibizumab. Although the ranibizumab group began with less favorable baseline BCVA and CFT, the differences in BCVA and CFT improvements were not statistically significant ($p > 0.05$).

Outcomes for ischemic retinal vein occlusion

The clinical outcomes for ischemic CRVO and BRVO are summarized in **Table 4** and **Table 5**, respectively. No statistical comparison of the ischemic and non-ischemic groups was performed due to the small sample size.

Among the 3 eyes with ischemic CRVO, the common characteristic was a poor presenting BCVA of < 0.1 on Snellen chart. Following the anti-VEGF regimen, all of the eyes showed anatomical improvement in CFT on OCT. Two of the 3 eyes had satisfactory final BCVA of 0.29 and 0.8. None of these eyes had disease-related complications.

Among the 3 eyes with ischemic BRVO, 2 presented with good BCVA of 0.67 on Snellen chart. Following the anti-VEGF regimen, this satisfactory BCVA was maintained. Apart from 1 eye with vitreous hemorrhage at presentation, there were no disease-related complications during the study period.

Discussion

This is one of the largest case series of RVO patients receiving an intravitreal anti-VEGF treatment regimen in the Hong Kong population. The study was based in a major private hospital providing both primary and tertiary ophthalmic care in the territory. In the private sector, repeated anti-VEGF injection is associated with less financial limitation than in the public sector. Patients also have a choice between the 2 types of anti-VEGF formulations available in Hong Kong, bevacizumab and ranibizumab.

For CRVO, patients had a poor presenting VA of 20/200. There was 1 line of VA improvement at 1 month after injection, and 3 lines of VA improvement from baseline at the last follow-up. For BRVO patients, the mean presenting VA was better at 20/60. Following an anti-VEGF injection, there were almost 2 lines of VA improvement from baseline at 1 month after injection, and the effect was sustained to the final follow-up with repeated anti-VEGF injections. The mean final BCVA on Snellen chart was above 20/40, which is compatible with independent activities of daily living.

Anatomical improvement following anti-VEGF injection was also significant. For CRVO, the mean baseline CFT was over 500 μm. More than 200 μm reduction in CFT was observed after injection. Although the mean baseline

Table 3. Baseline characteristics and outcomes of eyes with branch retinal vein occlusion receiving bevacizumab and ranibizumab.

	Bevacizumab (n = 21)	Ranibizumab (n = 5)	p Value
Sex			
Male	8	3	0.62
Female	13	2	
Mean ± SD age at presentation (years)	62.3 ± 15.6	54.8 ± 14.5	0.34
Mean ± SD follow-up duration (months)	13.0 ± 12.7	5.4 ± 2.9	0.02
Mean ± SD No. of injections	3.8 ± 4.0	2.0 ± 1.0	0.35
Mean ± SD BCVA (logMAR)			
Baseline	0.40 ± 0.24	0.79 ± 0.75	0.31
Final follow-up	0.15 ± 0.14	0.71 ± 0.87	0.22
Mean difference in BCVA (logMAR)			
Baseline to 1 month	0.18	0.06	0.22
Baseline to final follow-up	0.25	0.08	0.43
Mean ± SD CFT on OCT (μm)			
Baseline	390.33 ± 179.70	470.00 ± 163.18	0.48
Final follow-up	289.36 ± 87.65	335.25 ± 120.03	0.41
Mean difference in CFT on OCT (μm)			
Baseline to 1 month	-227.20	-118.00	0.43
Baseline to final follow-up	-100.97	-134.75	0.56

Abbreviations: SD = standard deviation, BCVA = best-corrected visual acuity, logMAR = logarithmic minimum angle of resolution, CFT = central foveal thickness, OCT = optical coherence tomography.

Table 4. Clinical outcomes of eyes with ischemic central retinal vein occlusion.			
	Patient 1	**Patient 2**	**Patient 3**
Type of anti-VEGF	Ranibizumab	Bevacizumab	Bevacizumab
No. of injections	10	10	2
BCVA (Snellen)			
Baseline	0.1	0.01	0.01
Final follow-up	0.8	0.29	0.01
CFT on OCT (μm)			
Baseline	599	354	661
Final follow-up	264	235	217
Difference in CFT (μm)			
Baseline to final follow-up	-335	-119	-444
Complications	Nil	Nil	Nil

Abbreviations: VEGF = vascular endothelial growth factor, BCVA = best-corrected visual acuity, CFT = central foveal thickness, OCT = optical coherence tomography.

Table 5. Clinical outcomes of eyes with ischemic branch retinal vein occlusion.			
	Patient 1	**Patient 2**	**Patient 3**
Type of anti-VEGF	Ranibizumab	Bevacizumab	Bevacizumab
No. of injections	2	2	6
BCVA (Snellen)			
Baseline	0.01	0.67	0.67
Final follow-up	0.07	0.67	1.00
CFT on OCT (μm)			
Baseline	NA	199	290
Final follow-up	NA	NA	284
Difference in CFT (μm)			
Baseline to final follow-up	NA	NA	-6
Complications	Nil	VH at presentation	Nil

Abbreviations: VEGF = vascular endothelial growth factor, BCVA = best-corrected visual acuity, CFT = central foveal thickness, OCT = optical coherence tomography, NA = not applicable, VH = vitreous hemorrhage.

CFT was better for BRVO (401.71 μm), a considerable CFT reduction of 100 μm was also noticed following anti-VEGF injection. For both CRVO and BRVO, the mean final CFT on OCT was maintained at the level of about 300 μm, provided that patients were compliant with follow-up and repeated intravitreal anti-VEGF injections.

Reviewing the functional and anatomical results together, the continued visual improvement following subsequent anti-VEGF injections for CRVO can be explained. The final BCVA showed further improvement over the presenting BCVA compared with that at 1 month postinjection. This is due to the more extensive venous stasis in CRVO than in BRVO, leading to more severe ME at presentation (CFT of 529.42 μm vs. 401.71 μm). The effect of ME on retinal dysfunction, as shown by delayed electroretinographic responses, was described by Greenstein et al.[16] The disrupted retinal circuitry may need time to recover owing to the more severe ME in CRVO.

The functional and anatomical results of anti-VEGF for the treatment of RVO were compared with international studies, and the results are summarized in **Table 6**.[10-15] Across the different studies, the improvement in VA following an anti-VEGF treatment regimen was generally consistent at the level of 3 lines from baseline. The visual outcome in this study, which involved a prn regimen of anti-VEGF injection based on the changes in BCVA and CFT, was comparable to that for the regular monthly injection regimens used in the multi-center randomized controlled studies, the CRUISE[10] study (Efficacy and safety of ranibizumab injection in patients with ME secondary to CRVO) and the BRAVO[11] study (Efficacy and safety of ranibizumab injection in patients with ME secondary to BRVO).

Significant improvement of ME was observed in the different studies. In the CRUISE[10] and BRAVO[11] trials, the best anatomical outcome was observed with monthly injection of ranibizumab 0.5 mg. The CFT demonstrated a continuous reduction throughout the first 6 months with the monthly injection regimen, leading to a mean CFT reduction of 452 μm and 345 μm at the end of the study period in patients with CRVO and BRVO, respectively.[10,11] The anatomical outcome of a monthly injection regimen was

Table 6. Comparison of major retinal vein occlusion studies in the literature.

	CRUISE*[10]	BRAVO*[11]	ROCC[12]	Rouvas et al[13]	Spaide et al[14]	Ehlers et al[15]
Type of RVO	CRVO	BRVO	CRVO	BRVO	CRVO	BRVO
Type of anti-VEGF	Ranibizumab	Ranibizumab	Ranibizumab	Ranibizumab	Ranibizumab	Bevacizumab
Study design	Multicenter RCT	Multicenter RCT	Multicenter RCT	Case series	Case series	Case series
No. of eyes	392	397	32	28	20	53
Duration of follow-up	6 Months	6 Months	6 Months	9 Months	12 Months	9 Months (mean)
Injection regimen	Monthly	Monthly	Monthly x 3 then prn	prn	Monthly x 3 then prn	prn
Change in visual acuity	+12.7 letters (0.3 mg) +14.9 letters (0.5 mg) +0.8 letters (sham)	+16.6 letters (0.3 mg) +18.3 letters (0.5 mg) +7.3 letters (sham)	+12 letters (0.5 mg) -1 letter (sham)	+14.3 letters	+18.5 letters	+8 letters
Change in CFT on OCT	-434 μm (0.3 mg) -452 μm (0.5 mg) -168 μm (sham)	-337 μm (0.3 mg) -345 μm (0.5 mg) -158 μm (sham)	-304 μm (0.5 mg) -151 μm (sham)	-140 μm	-388.6 μm	-136 μm

Abbreviations: CRUISE = Efficacy and safety of ranibizumab injection in patients with macular edema secondary to central retinal vein occlusion (CRVO), BRAVO = Efficacy and safety of ranibizumab injection in patients with macular edema secondary to branch retinal vein occlusion (BRVO), ROCC = Retinal vein OCClusion, RVO = retinal vein occlusion, VEGF = vascular endothelial growth factor, CFT = central foveal thickness, OCT = optical coherence tomography, RCT = randomized controlled trial, prn = as needed.

* For CRUISE and BRAVO trials, eyes were randomized to ranibizumab 0.3 mg, ranibizumab 0.5 mg, or sham injection. All other studies involved either ranibizumab 0.5 mg or bevacizumab 1.25 mg injection.

superior to that of the prn regimen in this case series.

To date, no consensus has been reached on the best anti-VEGF treatment regimen for RVO. While a better anatomical outcome was observed with the monthly injection regimen, the visual outcome of the prn regimen in this case series was non-inferior. However, the number of injections given in the prn regimen is less than that of a regular monthly regimen. In this case series, the mean number of injections was 5.6 in a mean follow-up period of 12.1 months for CRVO, and 3.4 in a mean follow-up period of 11.5 months for BRVO. Although the risk of intravitreal injection is small, each injection carries a potential risk of endophthalmitis, vitreous hemorrhage, or retinal detachment — each of which could potentially lead to irreversible visual loss.

In the case series by Risard et al,[17] patients with CRVO received 3 consecutive monthly injections of ranibizumab and were subsequently divided into 2 cohorts involving quarterly or monthly prn injections for the first year. In the second year, the 2 cohorts converged as 1 group, with the need for re-injection evaluated on a monthly basis. It was found that the initial visual gain and CFT reduction achieved by the first 3 consecutive anti-VEGF injections were subsequently lost in the group with quarterly prn injections, but returned upon switching back to a monthly prn regimen in the second year. Although a less frequent injection regimen limited the magnitude of visual gain, the underlying visual potential remained favorable as evidenced by the subsequent catch-up in visual improvement.

The prn regimen, in contrast to the regular regimen, offers flexibility tailored to the individual need and expectation of patients. Patients with high visual demand and less financial concern may be offered more frequent injections, while treatment for those with a limited budget may be aimed at maintaining a reasonable level of vision and preventing neovascular complications with less frequent injections. Nonetheless, the threshold beyond which the severity and duration of ME lead to irreversible visual damage is still uncertain. The level of VA or CFT that warrants a prompt re-injection remains to be determined.

The frequent need for re-injections is a major drawback for anti-VEGF treatment for RVO. In some patients, a combination approach involving anti-VEGF and other adjuvant treatments may be considered. Grid laser remains an effective treatment for ME associated with BRVO, and is a good treatment option for patients with financial concerns. The SCORE study[8] identified intravitreal steroid to be effective for treating ME in RVO, but with potential side-effects of IOP rise and cataract progression. However, it is possible to identify steroid responders through a challenge of topical steroid and avoid treating high-risk patients with this method. Cataract progression is less of a concern for older patients, especially those who are pseudophakic. Moreover, the need for re-injection of intravitreal steroid can be minimized with a sustained-release steroid implant, the efficacy of which was demonstrated in the GENEVA (Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA) study.[18] In this trial, most patients treated with a dexamethasone implant did not experience a substantial increase in IOP; at peak (day 60), less than 16% of all eyes had an increase in IOP to ≥25 mm Hg.[18] In patients in whom antero-posterior or tangential traction due to vitreomacular interactions or epiretinal membrane is a factor in ME, pars plana vitrectomy can also be considered. Therefore, OCT is useful not only in quantifying the degree of ME, but also in delineating the tractional forces experienced by the macular architecture.

In this study, no significant differences were found between bevacizumab and ranibizumab in the treatment of RVO in terms of VA or CRT improvement. However, no clinical conclusion could be drawn as the study was limited by the small sample size and lack of statistical power. Since the

visual outcome in this case series, in which most patients were treated with bevacizumab was comparable to that of many other studies in which ranibizumab was used, bevacizumab probably provides a non-inferior alternative to ranibizumab in the treatment of RVO.

In the past, CRVO, especially the ischemic type, was notoriously associated with neovascular complications, exemplified by '100-day glaucoma'. However, in this series, anti-VEGF was found to be effective in preventing neovascular complications during the course of the study. With anti-VEGF injections, most patients achieved satisfactory visual outcome, even in the presence of significant capillary dropout. The differentiation of RVO into ischemic or non-ischemic subtypes is probably less important for prognostic purpose. However, FFA still provides valuable information for patient counseling regarding the course of the disease. Patients with significant capillary dropout may be expected to require a more frequent and prolonged course of intravitreal anti-VEGF treatment. Moreover, the old idea of the limited efficacy of prophylactic PRP in ischemic CRVO is being challenged. With the potent angiogenic suppressant of anti-VEGF, persistent NV or neovascular glaucoma is rarely seen. Prophylactic PRP can therefore be considered for the ischemic subtype with considerable non-perfusion which in turn may lower the production of VEGF from ischemic retinal areas and reduce the need for anti-VEGF injections.

This study is limited by its retrospective nature. The timing of anti-VEGF re-injection may vary with the clinical judgment of individual ophthalmologists and patients' preferences. It is difficult to isolate the effect of adjuvant treatment from anti-VEGF injections on the final outcome in a case series. Nonetheless, this case series has shown that a favorable visual outcome can be achieved with a less-than-monthly prn regimen of anti-VEGF for patients with RVO. A prospective comparative study with well-defined clinical criteria and a schedule for retreatment are required to establish the efficacy of the prn regimen, but is realistically difficult in the private setting.

The application of anti-VEGF in RVO has caused a major paradigm shift in its management. Instead of reactive management of complications, the aim of treatment has changed to a proactive approach of maintaining a reasonable level of vision and minimizing the number of re-injections. As recurrent ME is common before reperfusion, the anti-VEGF injection regimen should be tailor-made according to a patient's clinical status, expectations, and financial status, with consideration of adjuvant treatment.

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