Original Article

Long-term real-world outcomes in retinal vein occlusions: How close are we to the trials?

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Purpose: To assess and analyze the visual outcomes of patients with retinal vein occlusions in a real-world setting with a long-term follow-up of more than 5 years. **Methods:** Retrospective analysis of 56 patients having retinal vein occlusions from a tertiary eye center, with a mean follow-up of 7 years was performed. Primary outcome measures were mean change in best-corrected visual acuity (BCVA) from baseline at 6 months, 1 year, 2 years, 3 years, and final visit (≥5 years), proportion of patients having BCVA better than 20/40 and worse than 20/200, and mean number of injections. Secondary outcome measures were change in central macular thickness (CMT), development of subsequent retinal vein occlusion (RVO) in same eye or the other eye, and development of neovascular complications. **Results:** The mean change in letter score was + 11.84 in branch RVO (BRVO), +7.14 in non-ischemic central RVO (CRVO), and −9.5 in ischemic CRVO at 1 year, which changed to + 8.57, −5 and − 24, respectively, at the end of follow-up. CMT had improved from 506 ± 98.8 µm, 576.44 ± 149 µm, and 618 ± 178.27 µm, respectively, at baseline to 267 ± 94 µm, 345.20 ± 122.61 µm, and 265.50 ± 107.75 µm, respectively, in BRVO, non-ischemic, and ischemic hemi RVO (HRVO)/CRVO groups. The total mean number of injections given in BRVO, non-ischemic CRVO, and ischemic CRVO groups were 4.6, 6.6, and 4.1, respectively. None of the patients with BRVO developed neovascular glaucoma (NVG). Non-ischemic to ischemic HRVO/CRVO conversion was noted in 4/11 eyes at a mean duration of 12.6 months. NVG was noted in 7/9 eyes (77.8%) in initial ischemic CRVO/HRVO group and 3/4 (75%) converted eyes. **Conclusion:** Patients with BRVO have good visual outcomes with anti-VEGF, while in CRVO results may vary considerably owing to patient compliance and treatment burden on long-term follow-up in a real-world setting.

Key words: Anti-VEGF, long-term outcomes, neovascular complications, retinal vein occlusion, visual outcomes

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In the pre-anti-VEGF era, vein occlusions were mainly managed by laser photocoagulation. The Branch Retinal Vein Occlusion Study (BVOS) proved the beneficial effects of grid laser in macular edema in branch retinal vein occlusion (BRVO), while there was no treatment yet for macular edema in central retinal vein occlusion (CRVO) since the Central Retinal Vein Occlusion Study (CVOS) did not show any beneficial effects.[1,2]

With the advent of intravitreal anti-VEGFs and steroids, many trials have been conducted to assess their efficacy in macular edema. The SCORE and GENEVA trials assessed steroids, BRAVO and CRUISE assessed ranibizumab in BRVO and CRVO, respectively, which then extended to HORIZON and RETAIN to assess the long-term outcomes.[3-9] VIBRANT, GALILEO and COPERNICUS studies assessed Aflibercept in BRVO and CRVO, respectively.[10–12] MARVEL compared ranibizumab versus bevacizumab in BRVO and LEAVO compared aflibercept versus ranibizumab versus bevacizumab in CRVO.[13,14] While all these studies showed resolution of macular edema and achieved significant visual improvement, the question still remains whether these results can be replicated in a real-world? Are these benefits sustained at long-term? Can patients in real-world afford the treatment burden?

There are very few studies on long-term real-world outcomes in RVOs.[15–19] This study was performed to understand the visual outcomes of patients with vein occlusions in a real-world setting with a mean follow-up of 7 years.

Methods

This was a retrospective study conducted at a tertiary eye center on patients with retinal vein occlusion with a minimum of 5 years of completed follow-up. Approval was obtained from the institutional review board and the research adhered to the tenets of the Declaration of Helsinki.

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Of the 356 patients with vein occlusions and whose medical records were found from 2009 to 2021, 56 patients had completed > 5 years of follow-up. Patients who had less than 5 years of follow-up or with history of prior treatment or neovascular glaucoma (NVG) at presentation were excluded.

Patients' demographic data, best-corrected visual acuity (BCVA), pupillary reaction for relative afferent pupillary defect (RAPD) at presentation, medical history, changes in visual acuity, CMT on OCT, neovascular complications and treatment details including intravitreal injections, laser photocoagulation and vitrectomy were recorded. Patients with CRVO were classified into non-ischemic and ischemic CRVO (VA ≤20/200/ RAPD/fluorescein angiograph/ocular neovascularization). Number of out-patient hospital visits (excluding injection visits) in the first year, third years, and fifth year were also calculated. Insurance status was also additionally noted.

Primary outcome measures were mean change in BCVA from baseline at 6 months, 1 year, 2 years, 3 years, and final visit (≥5 years), proportion of patients having BCVA ≥20/40 and <20/200, and mean number of injections. Secondary outcome measures were change in CMT, resolution of edema (CMT <250 μm), development of subsequent RVO in same eye or the other eye, development of neovascular complications (Disc [NVD]/retina [NVE]/ iris [NVI]/glaucoma [NVG]), vitreous hemorrhage (VH) and tractional retinal detachment (TRD), and eyes converting from non-ischemic to ischemic CRVO.

Data was analyses using the Statistical Package for the Social Sciences (SPSS) software. For descriptive analysis, mean with standard deviation was calculated for numerical variables and percentage calculation was performed for categorical variables. Correlation analysis was performed using Wilcoxon Mann–Whitney *U* test and Spearman correlation. A *P* value of <0.05 was considered significant. Change in letter score over time was calculated using Friedman test (χ^2) as the data was non-parametric. Multiple regression analysis was used to evaluate the association between baseline characteristics and visual outcome.

Results

Demographics [Table 1]

Of the 56 patients included, 36 were male. We included 60 eyes of 56 patients. There were 40 eyes with BRVO, 3 with HRVO, and 17 with CRVO (11 non-ischemic HRVO/ CRVO and 9 ischemic HRVO/CRVO). The mean age at presentation was 63.25 years ± 12.59 and the median age was 65.5 years with interquartile range of 63–69 years. Of these, 26 were diabetic initially while 2 patients developed it later, 37 were hypertensive initially while 10 developed later and 9 had hyperhomocysteinemia. Seven eyes (11.6%) developed another vein occlusion in the same eye, while 10 patients (17.8%) developed bilateral RVO. Primary glaucoma was noted in 19 eyes (31.6%) at presentation and baseline high intraocular pressure (IOP) was noted in 35% of CRVO eyes. Of the 56 patients, 5 (9%) were insured, 2 (3.5%) were able to claim insurance for initial 3 injections and later exhausted the limit and so had paid out of pocket, while the majority, that is, 49 patients (87.5%) paid out of pocket. All of the patients in our study belong to the same city except for one patient.

Table 1: Demographic details

Demographics	BRVO (*n*=37; No. of patients)	CRVO/HRVO (*n*=19; No. of patients)
Age (mean±SD)	60.23±8.33	63.25±12.59
Gender (Male: Female)	21/16	15/4
Hypertension	22	15
Diabetes	14	12
Hyperhomocysteinemia	3	6
Bilateral involvement	7 (4 eyes excluded in study)*	3 (2 eyes excluded in study)**
Duration of symptoms (mean±SD)	33.50±39.66	31.75±36.85
Duration of follow-up (mean±SD)	84.97±22.97	88.45±24.72
Total mean number of injections received	4.65 (4.27)	5.50±3.90

*Due to other eye not completing 5-year follow-up or no macular edema.
**Due to no light perception at presentation

The mean duration of symptoms at presentation was 31.75 days ± 36.85 SD, which significantly correlated with baseline BCVA (*P* = 0.02), persistent CME at final visit (*P* = 0.004), and final visual acuity worse than 20/200 (*P* = 0.03). The total mean duration of follow-up was 88.72 ± 24.45 SD months. The mean total number of out-patient hospital visits in the first year were 7.5 and 11.1 in the first year, 21.8 and 26.5 in 3 years, and 33.2 and 37.3 in 5 years in the BRVO and HRVO/CRVO groups, respectively. Patients who had bilateral disease received higher number of anti-VEGF injections in the first year (*P* = 0.038), although this difference did not persist in the subsequent years. There was no statistically significant difference between the number of total injections taken by the insured group and those who paid out of pocket (Kruskal–Wallis test, *P* = 0.068).

Visual outcome [Table 2]

At 1 year, the change in letter score was + 11.84 in BRVO, +7.14 in non-ischemic CRVO, and − 9.5 in ischemic CRVO which changed to + 8.57, −5, and − 24 respectively, at the end of follow-up [Fig. 1]. The mean letter score was 55.17 at the baseline and increased to 63.75 at the final visit in the BRVO group with a statistically significant change, that is, $\chi^2 = 40.3$, *P* = 0.001 (Friedmann test). The mean letter score decreased from 64 ± 20.71 at the baseline to 59 ± 22 at the final visit in the non-ischemic CRVO/HRVO group and from 35.69 ± 21.03 to 12 ± 19.94 in ischemic HRVO/CRVO group with a statistically significant change, that is, $\chi^2 = 15.7$, *P* = 0.008.

In BRVO, with baseline BCVA ≥ 70 letters (20/40), proportion of eyes having final visual acuity ≥ 20/40 was 86.7%. In those with baseline < 70 letters, number of letters improved in 68%, remained stable in 20%, and decreased in 12%. Proportion of eyes gaining ≥ 15 letters was 42.5% at the end of final follow-up.

In the non-ischemic CRVO/HRVO group, 57% showed improvement in letter score from baseline. In the ischemic CRVO/HRVO group, 23% remained stable compared to baseline, 8% of patients noted improvement and 69% worsened. Proportion of eyes gaining ≥15 letters was 28.57% in the non-ischemic CRVO/HRVO and none in ischemic CRVO/HRVO at the end of follow-up.

Table 2: Mean change in visual acuity over the period of time and visual outcomes in BRVO, non-ischemic, and ischemic CRVO at final visit

Letter Score	BRVO (Mean±SD)	Non-ischemic CRVO/HRVO (Mean±SD)	Ischemic CRVO/HRVO
Baseline	55.17±22.03	64±20.71	35.69±21.03
6 months	70.92±14.52	68±20	28±20.61
1 year	68.68±18.15	71±16	27±23.99
2 years	66.80±18.83	64±16	16±21.06
3 years	65.25±18.91	61±17	14±19.46
Final visit (>5 years)	63.75±21.08	59±22	12±19.94
Change in Letter Score			
6 months	14.38±18.38	4.28±6.82	−8.75±19.52
1 year	11.84±18.26	7.14±13.82	−9.58±19.82
2 years	11.62±16.67	0±22.91	−19.61±25.88
3 years	10.07±18.27	−2.14±26.28	−21.30±24.40
Final visit (>5 years)	8.57±20.82	−5±28.86	−24±26.56
Final vision better than 20/40 (Yes)	22 (55.0%)	3 (33.33%)	0
Final vision worse than 20/200 (Yes)	3 (7.5%)	0	9 (75%)
Final vision improved	21 (52.5%)	4 (57.15%)	1 (7.7%)
Final vision remained same	11 (27.5%)	0	3 (23.07%)
Final vision worsened	7 (17.5%)	3 (42.85)	9 (69.23%)
Final gain of ≥15 letters	17 (42.5%)	2 (28.57%)	0

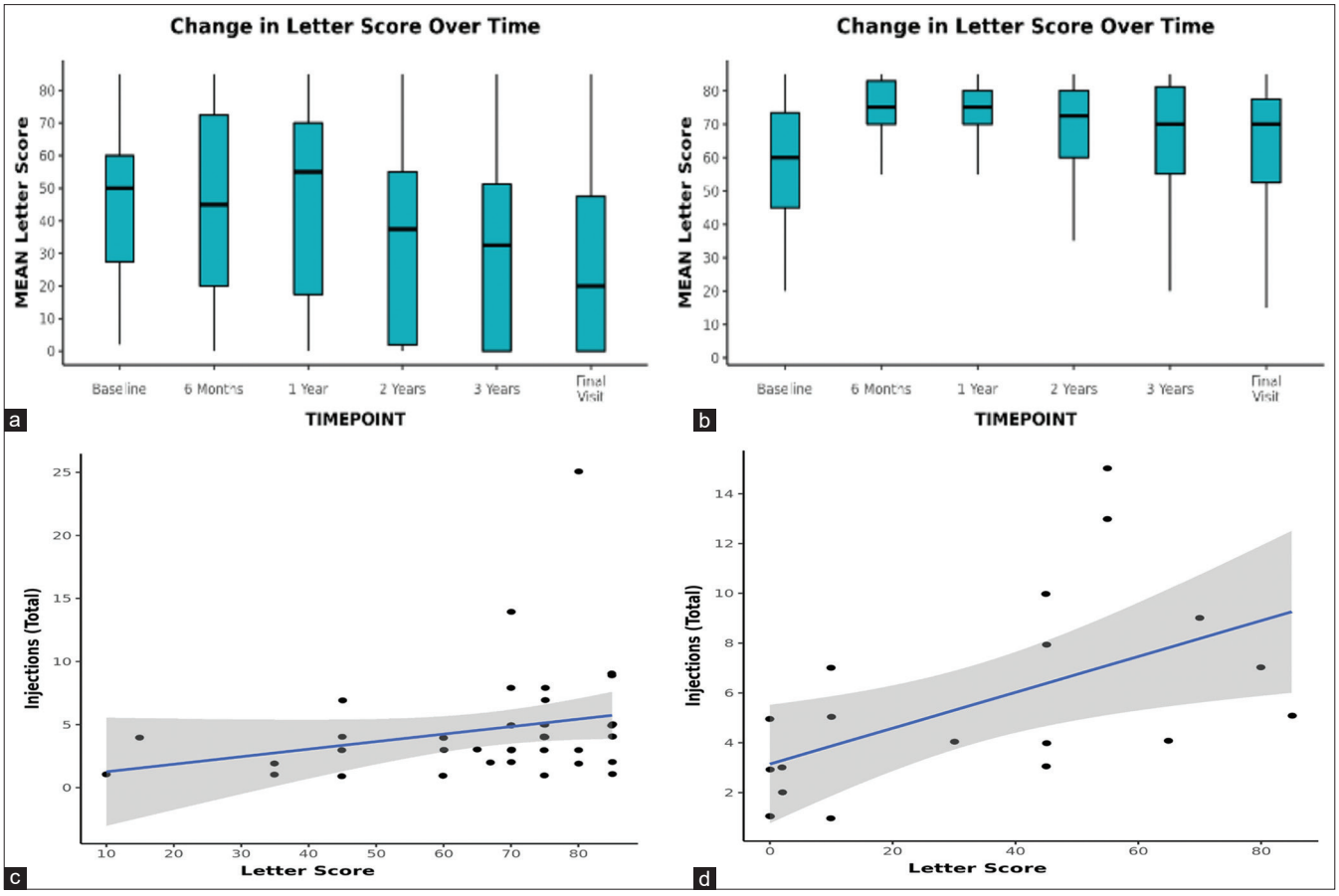

Figure 1: (a and b) Box-and-Whisker of distribution of letter score in BRVO (top left) and CRVO over different timepoints (top right). (c and d) Letter score with injection frequency in BRVO (bottom left) and CRVO (bottom right)

The total mean number of injections given in BRVO, non-ischemic CRVO and ischemic CRVO group were 4.6, 6.6, and 4.1, respectively. The number of injections given in the first year ($P = 0.022$) and total number ($P = 0.008$) of injections positively correlated with the final vision better than 20/200 in the CRVO/HRVO group. The median (IQR) number of injections in the first year was 2.5 (1.25–3.75) and 4 (3.25–4.75) in patients whose final visual acuity was worse than and better than 20/200 groups respectively.

There was no strong correlation between number of hospital visits and number of injections taken ($r = 0.59$). There was very weak negative correlation between age of the patient and total number of hospital visits ($r = -0.18$) and total number of injections ($r = \mu 0.19$). Also, there was no significant correlation between total number of hospital visits in five years and number of letters gained at final visit ($r = 0.08$).

Macular edema

The mean baseline CMT was 506 ± 98.8 µm, 576.44 ± 149 µm, and 618 ± 178.27 µm in BRVO, non-ischemic, and ischemic HRVO/CRVO, respectively, improving to 267 ± 94 µm, 345.20 ± 122.61 µm, and 265.50 ± 107.75 µm at the final visit, respectively.

At the final visit, 31/40 BRVO eyes (77.5%) had regressed macular edema (CMT <250 µm). In CRVO/HRVO, 9/20 eyes (45%) had regressed edema, while 11/20 eyes (55%) had persistent edema. Five eyes (8.3%) developed lamellar macular hole (LMH), five eyes had epiretinal membrane (ERM) (8.3%), and two eyes (3.3%) had retinal atrophy.

Neovascular complications

None of the patients with BRVO developed NVI, NVA, or NVG. NVE was seen in 15 eyes (37%), NVD in 4 eyes (10%) [Table 3], and VH in 4 eyes (10%). Non-ischemic to ischemic HRVO/CRVO conversion was noted in 4 eyes at a mean duration of 12.6 months. NVG was noted in 7/9 eyes (77.8%) in initial ischemic CRVO/HRVO group and 3/4 (75%) converted eyes. There was no significant difference between the groups who developed NVG (median number of injections = 3) from those who did not (median number of injections = 4) in terms of number of injections received in the first year ($P = 0.07$).

Vitrectomy was performed in 15 (25%) eyes. Indications for vitrectomy were non-resolving VH (3 eyes), VH with TRD (1 eye), subhyaloid hemorrhage (SHH) (1 eye), VMT with CME (2 eyes), and ERM with CME (8 eyes).

Discussion

A significant number of patients developed hypertension (18%) and diabetes (4%) after the onset of vein occlusion in our study. Thus, RVOs can be a harbinger of systemic disease. Delay in presentation and treatment in a real-world setting results in poorer outcomes.

While several trials[8–10] have shown an improvement of 14 to 17 letters after anti-VEGF injections in RVO, these results are not reflected in real-world studies.[15,17,18] Also, mean number of injections given in these studies are 7–9 in the first year which is difficult to achieve in the real world. In most developing nations, where medical expenses are most often out-of-pocket expenses, cost of treatment is rather unaffordable to many, reflecting in low injection rate. Number of injections advised varies from those received due to patient refusal. Patient compliance may vary depending on whether the patient is insured, whether they are able to afford travel expenses, consultation expenses, and injection/treatment expenses, and also on how far they need to travel to avail the treatment service. Our study included patients from all economic classes, a majority of them living nearby. Almost 87.5% were not insured and paid out of pocket, and another 3.5% exhausted their insurance after the initial treatment, while only 9% were covered under insurance, which may be a major reason for lesser number of injections in our study.

Very few real-world long-term studies have been published so far [Table 4].[15–19] Most of these studies have treated patients with three loading doses followed by PRN/TAE, while we followed PRN regimen. The total number of injections were significantly lesser in our study which may have resulted in reduced visual gains after the first year. This can be a major limitation in real-world, especially in developing nations. There was no difference in number of injections taken between the insured group and non-insured group.

BRVO

In a real-world study by Chatziralli *et al*.,[17] nearly 76% of BRVO patients had a final BCVA of ≥ 6/12, while it was 86% in our study. Spooner *et al*.[19] published 8 years of follow-up results with 56% gaining > 15 letters, while it was 42.5% in our study.

The mean number of injections received was 7.2 in BRAVO and a total of nearly 15 in RETAIN while it was 2.8 in the first year with a mean total of 5 injections during the 85 months of follow-up in our study.

CRVO

Most seminal trials, which showed nearly +14 letter improvement in CRVO patients, majorly included non-ischemic CRVO and injected nearly 7 to 9 injections in the first year with monthly injections for first 6 months.[7,8,11,20] RAVE included only ischemic CRVO eyes and injected anti-VEGF every month for first 9 months with subsequent loss of the initial visual acuity gains once the injections were withheld.[21]

Table 3: Long-term complications in BRVO, non-ischemic and ischemic CRVO

Complication	BRVO (*n*=40)	Non-ischemic CRVO (*n*=7, i.e., 11-4)	Ischemic CRVO (includes those converted from non-ischemic to ischemic RVO) [*n*=9+4=13]
Vitreous hemorrhage	4	1	8 (2 converted)
NVD	4	0	5 (3 converted)
NVE	15	0	3 (2 converted)
NVI/NVA	0	0	8 (3 converted)
NVG	0	0	10 (3 converted)
TRD	0	0	2

Table 4: Comparison of various long-term results of real-world studies

Authors	Duration	Treatment regimen	Mean number of injections	Number of letters gain
Spooner *et al*.[19] (Australia)	8-year results for BRVO and CRVO	3 initial monthly doses and then treat and extend	6.6 (first year) 34-37 (total)	14.3 (BRVO) 15.2 (Non-ischemic) 9.3 (Ischemic)
Chatziralli *et al*.[17] (Greece)	4-year results for BRVO and CRVO	3 initial monthly doses and then PRN	5.1 and 8.6 (CRVO - first year and total, respectively) 4.5 and 6.2 (BRVO - first year and total, respectively)	15.1 (BRVO) 6.9 (CRVO)
De Salles *et al*.[15] (Sweden)	3-year results for BRVO and CRVO	3 initial monthly doses and then PRN	4.9 and 21.7 (CRVO - first year and total. respectively) 4.7 and 17 (BRVO – first year and total, respectively)	9.8 (BRVO) 0.2 (CRVO)
Wecker *et al*.[18] (Germany)	5-year results for BRVO and CRVO	3 initial monthly doses and then PRN or TAE	6	0 letters at 5 years. Not differentiated between CRVO and BRVO letters gained at the end.
Our study (India)	7-year results for BRVO and CRVO	PRN from beginning	3.2 and 5.5 (CRVO - first year and total, respectively) 2.8 and 4.6 (BRVO - first year and total, respectively)	8.5 (BRVO) −5 (non-ischemic CRVO) −24 (ischemic CRVO)

A comparison of various real-world long-term studies and our study has been summarized in Table 4. De Salles *et al*.[15] found only +0.2 letter change at 5 years in CRVO. NVG was identified in 75% of CRVO eyes, which was very similar to our study (77%). Wecker *et al*.[18] found +4.2 letter gain in the first year while the gain was 0 by the end of five years in RVO. In our study, although BCVA improved by +6.2 letters in the first year, mean decline by −5 letters was noted at final visit. Possible explanations for these differences may be the baseline data (nearly 50% with ischemic CRVO in our study) and fewer injections. In our study, there were 3 patients in the CRVO/HRVO group who were initially advised anti-VEGF injections but delayed treatment for 4–6 months: this could have attributed to poor visual gains. Another 3 patients with poor baseline visual acuity progressed to NVG within 3 months, and thus did not take further anti-VEGF injections. Other reasons for fewer anti-VEGF injections were patients who underwent early vitrectomy and additional laser photocoagulation attributing to dry macula.

Hall *et al*.[22] found no visual gains in ischemic CRVO despite giving anti-VEGF for six months. In RAVE, 50% of patients developed neovascular complications, despite intensive anti-VEGF therapy. These studies concluded that anti-VEGF in ischemic CRVO can decrease macular edema but cannot prevent neovascular complications.[21,22]

Hayreh found that 70% of ischemic CRVO develop NVI, while it was 66% in our study.[23] Conversion of non-ischemic to ischemic CRVO in our study was 9% at 3 months and 27% at 2 years. No conversion was noted after 2 years. These rates are similar to earlier studies: 16% at 4 months, 25% at 1 year, and 34% at 3 years.[2,24] In our study, 35% of CRVO patients had high baseline IOP, which could also be another factor for poorer outcome as suggested by Hayreh.[24] Uncontrolled IOP is a known risk factor for progression toward vision loss.

In LUMINOUS study, mean letter gains in BRVO were better in patients who received 3 loading doses versus those who did not (14 vs 7 letters).[25] Also, visual gains were greater with greater treatment frequency which is also reflected in our study. Sub-optimal visual gain may be due to undertreatment in real-world setting.[26] Presently, there is insufficient evidence on efficacy and cost-effectiveness of anti-VEGF in ischemic CRVO.[27]

The strength of our study lies in the projection of real-world outcomes of patients with RVOs and one of the longest follow-up studies published so far (7 years mean duration). The outcomes of RVOs have been analyzed in a holistic approach, considering not only anatomical, functional outcomes, and neovascular complications over the long-term but also patient's geographical location to rule out distance as a confounding factor for bias and insurance status. Patients with RVO require an aggressive follow-up routine and frequent injections, both of which depend on compliance and affordability of the patient. To the best of our knowledge, this is the first such long-term study from any developing nation to analyze the role of anti-VEGFs in RVOs. Ang *et al*.[28] have emphasized the urgent need for consensus on efficacy and treatment burden due to anti-VEGF to strengthen the real-world evidence base.

There are several limitations to our study: retrospective nature; small sample size; and number of injections lesser compared to other studies.

Conclusion

Patients with BRVO have good visual gains with anti-VEGF in real-world setting. While treating non-ischemic CRVO, real-world outcomes may not reflect trials due to treatment burden on patients and compliance. Although there is initial improvement in vision, on long-term follow-up the results may not be persistent. In ischemic CRVO, patients may progress to neovascular complications despite aggressive anti-VEGF therapy.

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Conflicts of interest

There are no conflicts of interest.

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