ARTICLE

Long-term outcomes of anti-VEGF treatment of retinal vein occlusion

Kimberly L. Spooner[1] · Samantha Fraser-Bell [1,2,3] · Thomas Hong[1] · James G. Wong[1,2,4] · Andrew A. Chang[1,2]

Abstract

Background/objectives To analyze the long-term outcomes of eyes with retinal vein occlusion (RVO) 8 years after commencing treatment with anti-vascular endothelial growth factor (VEGF) agents.

Subjects/methods Retrospective, multicentre study of 221 eyes diagnosed with RVO, which were commenced on anti-VEGF therapy between 2009 and 2011. VA and CRT were recorded at baseline and at subsequent annual time points. The mean number of injections administered each year and the incidence of adverse events were recorded.

Results Of a total of 221 eyes which commenced treatment with anti-VEGF agents for RVO, 95 were diagnosed with BRVO and 126 with CRVO. 8-year data were available for 94 eyes (43%). The mean age of patients was 65.1 ± 12.0 years. Mean VA improved from baseline by 16.9 letters, (57.8–74.7 letters), ($P < 0.001$). For BRVO eyes, mean VA improved from 60.5 to 74.8 letters ($p < 0.001$) and for CRVO eyes from 52.0 to 66.4 letters ($p < 0.001$). In all RVO eyes, there was a reduction in mean CRT from 501.0 to 249.1 µm; in BRVO eyes from 472.4 to 284.7 µm and in CRVO eyes from 533.9 to 267.5 µm. In the 8th year after starting treatment, eyes with RVO were receiving a mean of four injections.

Conclusion Good long-term outcomes of VEGF inhibition for eyes with RVO were found in this study. Patients maintained a gain of 3-lines of vision 8-years after the commencing therapy. This encouraging result contrasts with long-term studies of patients with neovascular age-related macular degeneration, where initial gains are lost over time.

Introduction

Retinal vein occlusion (RVO) is the second most common cause of vision loss due to retinal vascular disease [1]. The prevalence of RVO is estimated at 0.5–2.0% for branch RVO (BRVO) and 0.1–0.2% for central RVO (CRVO) [2]. Untreated eyes with CRVO generally have a more reduced vision on presentation than eyes with BRVO, which declines significantly over time [2]. Although eyes with untreated BRVO have a better visual prognosis, it is uncommon for them to achieve a final vision of >20/40 [3].

With the advent of intravitreal anti-vascular endothelial growth factor (VEGF) agents, outcomes of eyes with RVO have improved significantly. The landmark randomized controlled trials (RCTs) reported improvements of 2–3 lines of vision for up to 2 years [4–6]. Although short to medium term efficacy is undisputed, there are few data on long-term outcomes.

Ranibizumab (Lucentis; Genentech, South San Francisco, CA., USA) was first approved for the treatment of macula deem following RVO by the FDA in June 2010. The FDA approved aflibercept (Eylea; Regeneron, Tarrytown, CA., USA) followed soon after in September 2012 for CRVO and October 2014 for BRVO. After completion of the Ranibizumab for the Treatment of Macular Oedema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety (CRUISE) and the Ranibizumab for the Treatment of Macular Oedema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) studies, eyes with RVO were able to continue to access ranibizumab in an open-label extension study called the HORIZON study and then enrolled in another open-label extension study called RETAIN [7, 8]. The RETAIN

✉ Andrew A. Chang
achang@sydneyretina.com.au

1   Sydney Retina Clinic, Sydney, NSW, Australia

2   Discipline of Ophthalmology, The University of Sydney, The Save Sight Institute, Sydney Medical School, Sydney, NSW, Australia

3   Retina Associates, Sydney, NSW, Australia

4   Strathfield Retina Clinic, Strathfield, NSW, Australia

study thus included patients who had completed BRAVO or CRUISE and had been followed-up in HORIZON. RETAIN reported outcomes of eyes with RVO managed with ranibizumab for a total of 4 years. Of the 789 patients enrolled in BRAVO and CRUISE, 4-year data were only available for 53 (7%) participants. From these 53, 42 (80%) patients had a final BCVA of 20/40 or better [8]. There are even fewer long-term data on eyes treated with aflibercept, which may, in part, be due to its later FDA approval [9–11]. Thus, there is a need for more long-term data on outcomes of treatment in eyes with RVO.

This retrospective, multicentre study examined outcomes of eyes with RVO that commenced treatment with anti-VEGF agents between 2009 and 2011 in routine clinical practice and followed for 8-years.

Methods

Design and setting

This was a multicentre, retrospective study of eyes that commenced intravitreal treatment with anti-VEGF agents for RVO between 2009 and 2011 and underwent treatment in routine clinical practice. Institutional approval was obtained from the University of Sydney and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all included patients.

Patients and data collection

The electronic pharmacy databases of three retinal tertiary practices were searched for patients diagnosed with RVO who commenced anti-VEGF agents between 2009 and 2011. Patients were included in the study if they were treatment-naive, had a minimum follow-up of 12-months, and received at least three anti-VEGF injections in the first year. Patients were treated with either bevacizumab (Avastin; Genentech Pharmaceuticals, San Francisco, CA), ranibizumab (Lucentis; Genentech Pharmaceuticals; San Francisco, CA), or aflibercept (Eylea; Regeneron Pharmaceuticals; Tarrytown, NY) at the discretion of the treating doctor. The treating physicians typically treated patients at this time with 3-monthly loading doses, then used an individualized treatment regimen, similar to treat-and-extend.

Eyes with loss of vision not related to RVO or which had received prior treatment with laser were excluded. The diagnosis of RVO was made clinically and confirmed by 7-field fundus fluorescein angiography (FA) in all cases, as that was the routine practice of the treating physicians. Ischemic type of CRVO was defined as a retinal non-perfusion area of ≥10-disc diameters, which could involve the periphery and/or macular. Macular ischemia was

defined as a foveal avascular zone (FAZ) of ≥1000 μm and broken capillary rings at the borders of the FAZ with distinct areas of capillary non-perfusion. It was routine for all patients to undergo visual acuity testing and spectral-domain OCT at each visit. Visual acuity was performed using a Snellen chart with the patient's regular correction, where available, and complemented with pin-hole correction. Values were converted to ETDRS letter score for statistical analysis.

Outcomes

The primary outcome measure was the mean change in VA from baseline to 8-years. Secondary outcome measures included the proportions of eyes with VA ≥ 70 letters (20/40 Snellen equivalent) and ≤35 letters (20/200) and the proportion of eyes that gained ≥15 letters and lost ≥15 letters at 8-years. Visual outcomes were also stratified by baseline VA: good vision (≥70 letters), moderate vision (36–69 letters), and poor vision (≤35 letters). The mean change in CRT during the 8 years and the number of injections were also assessed.

The 1-year follow-up visit was defined as the first visit in the 10–14- month window after the first anti-VEGF injection, and so forth for subsequent years. The 8-year cohort was defined as all eyes with follow-up data for more than 7 years and 10 months. We used the last observation carried forward for eyes without 8 years follow-up to reduce bias ($n = 221$). Eyes without 8 year follow-up tended to do worse than eyes with 8 years of follow-up. We have also separately presented the data of eyes ($n = 94$) with 8 year follow-up under a sub-heading.

Statistical Analyses

Visual acuity was measured using Snellen vision and converted to ETDRS vision for analyses [12]. Descriptive data included the mean, standard deviation, and percentages where appropriate. Correlations between continuous variables were analyzed using Pearson's correlation coefficient, and a t-test was used to analyze differences between groups. Due to the small sample size, nonparametric analysis using the Mann–Whitney rank-sum test was performed. Kaplan–Meier survival analysis was performed to examine the time of dropout by baseline visual acuity. Data were analyzed using SPSS for windows version 24 (IBM, Chicago, IL, USA). A P value of 0.05 was used to declare a statistically significant difference between groups.

Results

A total of 296 eyes of 296 patients diagnosed with RVO commenced anti-VEGF therapy between January 1, 2009,

and July 31, 2011. Of these, 30 eyes that did not receive at least three injections, and 45 eyes with prior laser treatment were excluded. The remaining 221 eyes from 221 patients were included in the study. Of these, 95 were graded as having BRVO and 126 as CRVO. At baseline, 33% ($n =$ 42) of CRVO eyes were classified as ischemic. Eight years

of treatment was completed by 44 BRVO (46%) eyes and 50 CRVO (40%) eyes.

Demographic characteristics

The group comprised 60% men and 40% women. The mean age at the initial treatment visit (baseline) was 66.0 ± 12.6 years. Table 1 gives an overview of baseline demographics.

Outcomes of all eyes with RVO

Before the commencement of anti-VEGF treatment, the mean VA of all RVO eyes was 55.3 ± 15.8 letters. After 1-year of anti-VEGF treatment, the mean VA was 63.5 ± 24.2 letters (Snellen equivalent, 20/50). These gains were maintained up to year eight, with a final mean vision of 69.9 ± 17.6 letters ($p < 0.001$, Snellen equivalent 20/40).

A similar proportion of eyes attained VA ≥ 70 letters (Snellen equivalent 20/40 vision or better) at baseline and at 8-years (22 vs. 60%) (Table 2). When including only eyes with 8-year data, the proportion was 40% at baseline, and 67% at 8-years. At baseline, VA was ≤35 letters (Snellen equivalent 20/200 or worse) in 15 of 221 eyes (7%), and after 8 years, 17 eyes (8%) had a final VA of 20/200 or worse.

Eight years after starting anti-VEGF, 115 of 221 eyes (52%) gained 15 letters or more from study baseline, 24 of 221 eyes (11%) had gained 5 to 14 letters, and 24 eyes (11%) had demonstrated a loss of vision (Table 2).

Table 1 Demographic and clinical characteristics of included patients.

	BRVO ($n = 95$)	CRVO ($n = 126$)	All eyes ($n = 221$)	p value
Age, years	66.1 ± 12.9	65.8 ± 12.4	66.0 ± 12.6	0.913
BCVA (ETDRS letters)	60.5 ± 14.3	52.0 ± 17.6	55.3 ± 15.8	0.003
CRT (µm)	472.4 ± 136.1	533.9 ± 209.9	505.6 ± 176.4	0.036
IOP (mmHg)	14.1 ± 3.9	13.8 ± 4.1	14.0 ± 4.0	0.764
Gender				0.434
Male	53 (56%)	79 (63%)	133 (60%)	
Female	42 (44%)	47 (37%)	88 (40%)	
Ischaemic type	20 (21%)	42 (33%)	62 (28%)	0.156
Hypertension	83 (87%)	101 (80%)	183 (83%)	0.396
Hypercholesterolemia	55 (58%)	76 (60%)	130 (59%)	0.465
Diabetes mellitus	8 (8%)	29 (23%)	35 (16%)	0.028
History of smoking	24 (25%)	33 (26%)	55 (25%)	0.250
Mean number of injections per year	3.7 ± 3.9	4.3 ± 3.3	4.1 ± 3.5	0.182
Mean Injection interval (weeks)	12.2 ± 3.2	16.1 ± 7.2	14.0 ± 5.2	0.226

P value is the comparison between the BRVO and CRVO group.

BCVA best corrected visual acuity, *BRVO* branch retinal vein occlusion, *CRT* central retinal thickness, *CRVO* central retinal vein occlusion, *ETDRS* early treatment of retinopathy study letter score, *IOP* intraocular pressure.

Table 2 Visual acuity characteristics of eyes with retinal vein occlusions.

	All eyes ($n = 221$)	BRVO ($n = 95$)	CRVO ($n = 126$)	Eyes with 8-years follow-up ($n = 94$)	Eyes lost to follow-up ($n = 127$)
Baseline					
BCVA (ETDRS Letters)	55.3 ± 15.8	60.5 ± 14.3	52.0 ± 17.6	57.8 ± 16.8	51.8 ± 15.3
Proportion VA ≥70 Letters (20/40)	49 (22%)	31 (33%)	18 (15%)	38 (40%)	32 (25%)
Proportion VA ≤35 Letters (20/200)	15 (7%)	5 (5%)	10 (8%)	9 (10%)	6 (5%)
CRT (µm)	505.6 ± 176.4	472.4 ± 136.1	533.9 ± 209.9	501.0 ± 191.2	512.2 ± 210.1
8-Years					
BCVA (ETDRS Letters)	69.9 ± 17.6[a]	74.8 ± 13.6[a]	66.4 ± 20.2*	74.7 ± 19.2	60.7 ± 16.5[a]
ETDRS Letters gained	14.3 ± 18.8[a]	14.3 ± 16.1[a]	14.4 ± 19.9*	16.9 ± 19.9	8.4 ± 14.8[a]
Proportion VA ≥70 Letters (20/40)	133 (60%)	72 (76%)	61 (48%)	63 (67%)	70 (55%)
Proportion VA ≤35 Letters (20/200)	17 (8%)	4 (4%)	13 (10%)	11 (12%)	6 (5%)
Proportion gaining ≥15 Letters	115 (52%)	53 (56%)	62 (49%)	50 (53%)	42 (33%)
Proportion losing ≤15 Letters	18 (8%)	2 (2%)	16 (13%)	7 (7%)	11 (9%)
CRT Change (µm)	-209.3 ± 215.7*	-187.7 ± 172.2	-246.8 ± 225.5	-251.9 ± 227.9	-175.4 ± 174.4[a]
Injection interval at final visit	13.9 ± 6.5[a]	11.8 ± 3.5	14.9 ± 4.2	11.7 ± 6.1	16.3 ± 9.2

BCVA best corrected visual acuity, *BRVO* branch retinal vein occlusion, *CRVO* central retinal vein occlusion, *ETDRS* Early Treatment of Diabetic Retinopathy Study Score, *VA* visual acuity.

[a]Last observation carried forward.

There was a reduction in mean CRT from 505.6 ± 176.4 μm to 296.3 ± 67.8 μm ($p < 0.001$) among all RVO eyes. At the final follow-up visit, 63% ($n = 139$) eyes had resolution of macular oedema.

Outcomes of eyes with branch retinal vein occlusion

At baseline, the mean VA of BRVO eyes was 60.5 ± 14.3 letters. After 1-year of anti-VEGF treatment, the mean VA had improved to 68.8 ± 21.6 letters ($p < 0.001$). These gains were maintained up to 8-years, with a mean VA change of 14.3 ± 16.1 letters in the BRVO group ($p < 0.001$).

Reduction in mean central retinal thickness (CRT) was significant in eyes with BRVO with mean baseline CRT being 472.4 ± 136.1 μm. CRT reducing significantly to 325.6 μm at year-1, which was maintained to year-8 (−187.7 μm, $p < 0.001$) (Fig. 1A), representing a mean reduction of 38% in retinal thickness.

Outcomes of eyes with CRVO

At baseline, the mean VA of CRVO eyes was 52.0 ± 17.6 letters. After 1-year of anti-VEGF treatment, the mean VA had improved to 64.1 ± 21.9 letters ($p < 0.001$). These gains were maintained up to year eight, with a mean improvement in VA of 14.4 ± 20.9 letters ($p < 0.001$).

Mean VA at 8 years improved significantly in eyes with non-ischemic CRVO and ischemic CRVO; however, the improvement was more significant in eyes with non-ischemic CRVO (MD: 4.6 letters, 95% CI: −15.1 to 3.2, $p = 0.002$).

Mean baseline CRT in eyes with CRVO was 533.9 ± 209.9 μm, which reduced significantly to 354.3 μm at year-1 ($p < 0.001$) and continued to decline after 8 years of treatment (267.5 μm, $p < 0.001$), (Fig. 1A). The mean reduction in CRT in eyes with non-ischaemic CRVO eyes was similar to that in eyes with ischaemic CRVO ($p = 0.07$) (Fig. 1A). The mean number of injections received by ischaemic and non-ischemic eyes was similar ($p = 0.85$) (Table 3).

Injection Frequency

During the follow-up, a total of 3873 anti-VEGF injections (58% bevacizumab, 25% ranibizumab, and 17% aflibercept) were administered over 8-years. The mean number of injections administered in the first year was 6.6 ± 2.9 at 7.7 weekly intervals and in the 8th year was 3.9 ± 3.7 injections at 13.1 weekly intervals. (Fig. 2)

Eyes with retinal vein occlusion and 8-year follow-up data

Of the 221 eyes that started anti-VEGF therapy, 94 (43%) were still receiving anti-VEGF treatment at the same centre
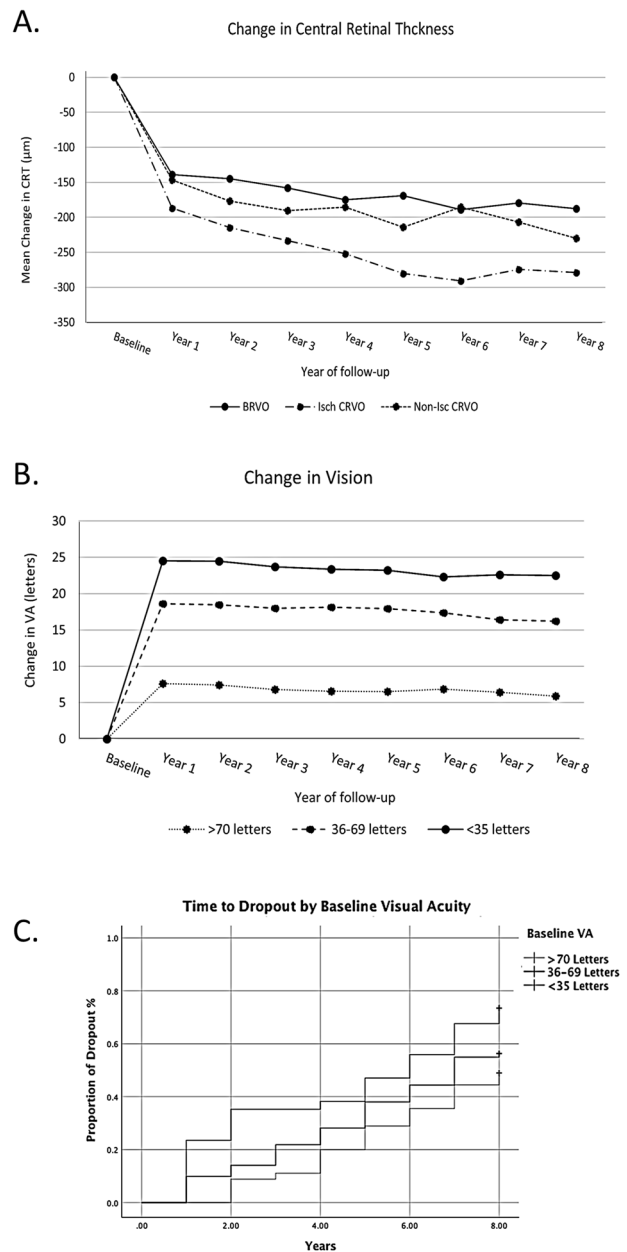

Fig. 1 Anatomical and functional changes of patients over 8-years of treatment. A Mean change in central retinal thickness among 221 eyes over 8-years of anti-VEGF therapy; **B** Mean change in visual acuity (VA) stratified by baseline VA (i) ≥70 letters; (ii) >35 to <70 letters; and (iii) ≤35 letters. (BRVO = branch retinal vein occlusion, Isch CRVO = ischemic central retinal vein occlusion. Non-Isch CRVO = non-ischemic central retinal vein occlusion, CRT = central retinal thickness); **C** Kaplan–Meier Survival Curve demonstrating proportion of dropout by baseline visual acuity.

8-years later. The age of patients with an 8-year follow-up was similar to those who were lost to follow-up (Table 2). Baseline vision was also similar, but those that were lost to follow-up improved vision by half the number of letters than those that remained (Table 2). Baseline CRT was similar numerically but statistically different for those that

Table 3 Baseline and final ocular features of eyes with central retinal vein occlusion receiving anti-vascular endothelial derived growth factor agents.

	Ischemic CRVO ($n = 42$)	Non-Ischemic CRVO ($n = 84$)	p value
Baseline BCVA (ETDRS letters)	45.9 ± 17.8	54.8 ± 14.3	0.061
BCVA change	9.3 ± 19.6	15.2 ± 21.8	0.002
Final BCVA	55.3 ± 19.2	70.2 ± 20.2	0.035
Baseline CRT (µm)	572.0 ± 191.2	472.4 ± 136.1	0.051
CRT Change	279.2 ± 170.9	230.2 ± 268.5	0.072
Final CRT	292.9 ± 78.9	242.1 ± 73.6	0.286
Total Injections	37.6 ± 26.4	34.5 ± 23.0	0.851

CRVO central retinal vein occlusion, *BCVA* best corrected visual acuity, *CRT* central retinal thickness as measured on spectral domain optical coherence tomography.
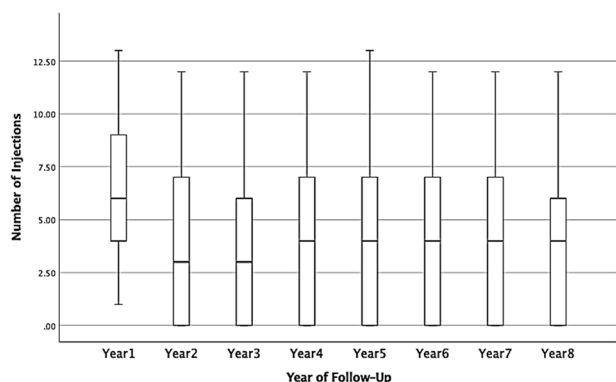
Fig. 2 Box plots showing median and IQR of injections administered per patient per year of 221 eyes over 8-years of anti-VEGF therapy.

continued treatment than those lost to follow-up (501 µm vs. those lost to follow-up at 572 µm, $p = 0.039$). The interval between injections was longer in those who were lost to follow-up before their last visit compared to the interval in those who continued treatment for 8 years.

At the final year of follow-up, 71 eyes (76%) were dry on OCT, with 35 of these eyes not requiring any treatment in the final year. Those that were dry on OCT and not requiring treatment had significantly better vision then those who were still being treated (MD: 11.5 letters, 95% CI: 1.5–21.4 letters, $p = 0.03$).

Outcomes by Baseline Visual Acuity

To study the baseline vision relationship with VA gain, we examined the outcomes after stratifying by baseline VA (Fig. 1B). The 94 eyes with data for at least 8-years were stratified into three groups relating to baseline vision: good vision, ≥70 letters (18 eyes); moderate vision >35 to <70 letters (58 eyes); and poor vision, ≤35 letters (9 eyes). The mean VA of eyes with good baseline vision was initially

74.5 ± 5.0 letters. These eyes gained 7.6 ± 6.1 letters at year-1, and maintained this gain to year-8, with a final VA of 80.1 ± 7.1 letters (Snellen equivalent 20/25). Similarly, the reduction in CRT of -152.8 ± 121.3 µm at 1-year was maintained to year-8. Of note, the eyes with good vision had the highest mean number of injections of 39.2 ± 29.3 over the duration of the study (on average, five injections per year).

The mean vision of eyes with moderate baseline VA (58 eyes) was 54.1 ± 8.4 letters and gained 18.5 ± 19.1 letters at year-1 ($p < 0.001$), and was maintained this gain to year-8, with a final VA of 71.2 ± 16.0 (Snellen equivalent 20/40) letters, an increase of 17.1 ± 18.2 letters ($p < 0.001$). Similarly, the reduction in CRT at 1-year was maintained for 8 years: a reduction of -253.4 ± 194.5 µm in retinal thickness at the final visit ($p < 0.001$), with a mean of 34.0 ± 25.1 injections administered.

The mean vision of eyes with poor baseline VA was 19.8 ± 14.2 letters and gained 24.5 ± 27.4 letters at year-1. This was maintained up to year-8, with a final vision of 43.3 ± 28.9 letters (Snellen equivalent 20/125⁻) ($p < 0.001$). These eyes also achieved the most significant mean reduction in CRT of -366.1 ± 334.9 µm from baseline ($p < 0.001$), with a mean of 35.6 ± 23.8 injections.

Outcomes of Eyes lost to follow-up

A total of 127 eyes (57%) that were subsequently lost to follow-up presented with a lower mean vision of 51.8 ± 15.3 letters vs. 57.8 ± 16.8 letters for those who had completed 8-years of follow-up (Table 2) (Fig. 1C). At the last visit, eyes lost to follow-up improved vision significantly less than eyes that continued to 8-years, $p = 0.03$ (Table 2). Mean CRT of eyes lost to follow-up decreased by -175.4 ± 174.4 µm at their final follow-up visit. Of those lost to follow-up, 39 patients had relocated (31%), 36 had died (28%), 42 (33%) had resolution of RVO (32 BRVO and 10 CRVO), and we have not been able to find out the reasons for loss to follow-up for the remaining 11 (9%).

Prognostic factors

Poorer baseline vision ($p < 0.01$) and younger age ($p = 0.04$, multiple linear regression final model) were associated with more significant improvement in VA at 8-years. The impact of baseline VA is illustrated in Fig. 1B. The eyes with the poorest baseline VA experienced the most significant gain in vision at the first follow-up visit, but their vision never caught up with eyes that started with higher VA.

Gender ($p = 0.43$), number of injections per year ($p = 0.86$), and baseline CRT ($p = 0.45$) were not associated with the change in VA.

Ocular adverse events

Two eyes diagnosed as ischemic CRVO at baseline developed rubeosis, one at 13-months after starting treatment and the other at 18-months. No eyes diagnosed with non-ischemic CRVO at baseline developed significant ischemia while receiving anti-VEGF treatment, although FFA was not routinely performed after baseline. Twenty-one eyes (10%) developed high IOP (>25 mmHg) within the first 12-months and were treated with ocular hypotensive drops. No eyes developed ocular hypertension after 12-months of treatment. Three eyes with BRVO and two with CRVO underwent cataract surgery during the 8-year follow-up period. No eyes developed endophthalmitis, inflammatory reactions, vitreous haemorrhage, retinal tear, or retinal detachment.

Discussion

Anti-VEGF therapy has revolutionized the outcomes of eyes with RVO. This study provides long-term evidence of the efficacy of anti-VEGF treatment for RVO in a clinical practice setting. A total of 296 eyes were identified, which commenced treatment between 2008 and 2011 to allow 8 years of follow-up data. In eyes with RVO and 8 years of follow-up ($n = 94$, 43%), mean vision improved by 18 letters at 1-year, and 16 letters at 8 years. This significant improvement of 14 letters in mean vision was seen in eyes with both BRVO and CRVO.

In comparison to neovascular age-related macular degeneration (nAMD), there are few long-term data on outcomes of eyes with RVO and no studies with which to compare our 8-year results [13, 14]. The initial gains at 1–2 years after starting treatment for nAMD are generally lost with vision returning to baseline or worse by 5–7 years [15–18]. In contrast, we have demonstrated significant vision gained 8 years of treatment with anti-VEGF. Previous extension studies of eyes with RVO receiving anti-VEGF treatment have found that vision gains obtained in the first 6-months in BRVO could be maintained for 4 years, but that many of the vision gains were lost in eyes with CRVO [8].

In the present study, 4% of patients lost three lines or more of vision at 8-years follow-up. There was a proportion of eyes that lost three lines of vision in the RETAIN study, but this was after 4-years (4.5%) and occurred solely in eyes with CRVO [8]. The extension studies, such as HORIZON and RETAIN, used a *pro re nata* regimen after fixed interval dosing during the pivotal trials. When eyes were switched to receive anti-VEGF by PRN, the number of injections per year decreased significantly, from 5.7 to 2.7 in BRVO and from 5.8 to 3.8 in CRVO, over the first 6-months of PRN treatment [7, 8]. In a real-world study by Chatziralli et al. (2018), which reported outcomes of eyes with RVO for at least 3 years,

vision gains were even lower than those in the RETAIN study which was attributed to the mean number of injections being almost half that seen in RETAIN (4.5 and 3.6 in the 2nd and 3rd year compared to 2.8 and 1.9 for CRVO and 2.6 and 2.0 in RETAIN vs. 1.3 and 0.9 in Chatziralli et al. for BRVO eyes) [13]. Eyes in our study were being treated using an individualized regimen, which mirrored an inject and extend regimen more closely. This may have led to better disease control with less fluctuation of macular oedema, which in the longer term may have led to less photoreceptor degradation.

Poorer baseline vision and younger age were associated with more significant improvement in vision at 8-years. However, the visual acuity in eyes with poor baseline VA, never caught up to eyes, which started with better vision. In contrast, the VA in one-fifth of eyes in this study was 20/40 or better at baseline, which may have limited the amount of vision improvement possible. These eyes would have been excluded in the majority of RCTs.

After 8-years 70% of BRVO and 30% of CRVO eyes achieved a vision of 20/40 or better, similar to the 80% of BRVO and 28% of CRVO eyes seen in the RETAIN study [8], and comparable to another RVO study by Chatziralli et al. where 76% of eyes with BRVO and 32% with CRVO achieved VA 20/40 or better [13].

We did not find an association between baseline CMT and vision outcomes in contrast to another study [13], where intraretinal fluid and increased retinal thickness were negative predicting factors for final visual acuity.

The prevalence of BRVO is much more common than CRVO (0.64% vs. 0.13%) [19]. However, there were more eyes with CRVO than BRVO in our study. We do not have available data on the number of all eyes diagnosed with BRVO that were not treated with anti-VEGF therapy. For instance, some of these eyes would have presented without macular oedema or resolved without treatment or received macular laser. It may be that eyes with CRVO were more likely to be treated with anti-VEGF agents since it represents a more severe disease with a worse natural history [3, 20]. In natural history studies, it has been reported that 30% of eyes which present as non-ischemic CRVO convert to ischemic CRVO within 3 months [3, 20]. No eyes in our study with non-ischemic CRVO converted to ischemic CRVO while receiving anti-VEGF therapy. However, a limitation of our study was that fundus FA was not routinely performed during follow-up, and therefore ischemic conversion might have remained undiagnosed clinically.

A limitation of this study is the high loss to follow-up rate which is a common issue in real-world clinical studies and long-term extension studies. The HORIZON and RETAIN trials reported 2- and 4-year outcomes of ranibizumab treatment in 86% and 7% of patients post BRAVO and CRUISE. Our 8-year retention rate compared favorably with these studies with data available from 43% of eyes. Eyes lost to

follow-up were more likely to have a significantly smaller improvement in VA and greater baseline CRT.

It is appropriate to consider eyes that are lost to follow-up in analyzing outcomes. Baseline CRT was statistically less for those that continued treatment compared to those lost to follow-up. Furthermore, the interval between injections was longer in those who were lost to follow-up before their last visit compared to the interval in those who continued treatment, which may have indicated poorer compliance before discontinuing.

Inherent in retrospective data from routine clinical practice is the lack of standardization of treatment regimens and heterogeneity in treatment patterns. Other limitations of this study include its small sample size, which limits subgroup analysis. Future studies with a more significant number of patients will be required to strengthen the statistical power allowing for subgroup analyses.

Conclusion

Patients receiving long-term anti-VEGF therapy for the treatment of macular oedema secondary to RVO in routine clinical practice gained a mean of 14 letters after 8 years of treatment, with 50% of eyes gaining over 15 letters (70% of BRVO eyes, 30% CRVO eyes). The mean gain in vision seen at 8-years is in contrast to eyes receiving treatment for nAMD [18], where much of the early gain is lost over time. This study has demonstrated that continuing long-term anti-VEGF therapy effectively improves and maintains visual and anatomic outcomes.

Summary

What was known before

- With the advent of intravitreal VEGF agents, outcomes of eyes with RVO have improved significantly. The landmark RCTs reported improvements of 2–3 lines of vision for up to 2 years. Although short to medium term efficacy is undisputed, there are few data on long-term outcomes.

What this study adds

- Patients receiving long-term anti-VEGF therapy for the treatment of macular oedema secondary to RVO in routine clinical practice gained a mean of 14 letters after 8 years of treatment, with 50% of eyes gaining over 15 letters. Continuing long-term anti-VEGF therapy effectively improves and maintains visual and anatomic outcomes.

Compliance with ethical standards

Conflict of interest SFB is a consultant Novartis, Allergan, Roche and Bayer. AAC is a consultant for Novartis, Allergan, Roche and Bayer. The following authors have no financial disclosures: KLS, TH, JGW.

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