Ophthalmic Research

Research Article

Ophthalmic Res
DOI: 10.1159/000530294

Received: November 30, 2022
Accepted: March 10, 2023
Published online: April ▪▪▪, 2023

Real-World Outcomes of Ranibizumab Treatment in French Patients with Visual Impairment due to Macular Edema Secondary to Retinal Vein Occlusion: 24-Month Results from the BOREAL-RVO Study

Agnès Glacet-Bernard[a] Jean-François Girmens[b] Laurent Kodjikian[c] Cécile Delcourt[d] Franck Fajnkuchen[e,f] Catherine Creuzot-Garcher[g] Nathalie San Nicolas[h] Pascale Massin[i]

[a]Department of Ophthalmology/Paris-Est Créteil University (UPEC, Paris XII University)/Intercommunal Hospital Center and Henri Mondor Hospital, Créteil, France; [b]Department of Ophthalmology, INSERM-DGOS CIC 1423, Centre Hospitalier National d'Ophtalmologie (CHNO) des Quinze-Vingts, Paris, France; [c]Ophthalmology, Hopital de la Croix Rousse, Lyon University, UMR CNRS MATEIS 5510, Lyon, France; [d]Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team LEHA, UMR 1219, F-33000, Bordeaux, France; [e]Ophthalmology, Hôpital Avicenne, Bobigny, France; [f]Centre d'Imagerie et Laser, Paris, France; [g]Department of Ophthalmology, Dijon University Hospital, Dijon, France; [h]Novartis Pharma SAS, Rueil-Malmaison, France; [i]Ophthalmic Centre of Breteuil, Paris, France

Keywords
Retinal vein occlusion · Central retinal vein occlusion · Branch retinal vein occlusion · Ranibizumab · Real life

Abstract
Introduction: Information about real-world ranibizumab use is needed to optimize treatment of macular edema secondary to retinal vein occlusion (RVO). The BOREAL-RVO study assessed treatment use, effectiveness, and safety of 24-month treatment with ranibizumab 0.5 mg in patients with visual impairment due to macular edema secondary to RVO in a real-world setting. ***Methods:*** This was a multicenter, post-authorization, observational study in France, including patients starting ranibizumab for RVO. Primary endpoint was mean change from baseline in best-corrected visual acuity (BCVA) at month 6. Secondary endpoints were mean changes from baseline in BCVA at month 24 and central retinal thickness (CRT) at months 6 and 24, and treatment use in real-world setting. ***Results:*** 226 branch RVO (BRVO) and 196 central RVO (CRVO) patients were enrolled; 71.7% and 70.9% completed the 24-month follow-up, respectively. In BRVO, mean (SD) baseline BCVA was 55.2 (18.7) letters, with gains of 14.3 (13.7), 14.1 (16.5), 13.0 (17.5), and 11.4 (20.1) letters at months 3, 6, 12, and 24, respectively. In CRVO, mean (SD) baseline BCVA was 40.4 (25.6) letters, with gains of 16.0 (21.2), 9.5 (25.4), 9.2 (27.7), and 8.3 (23.8) letters at months 3, 6, 12, and 24, respectively. At month 24, 52% of BRVO and 41% of CRVO patients had gains of 15 or more letters. In BRVO, mean (SD) CRT values at baseline and months 3, 6, 12, and 24 were 550 (175), 315 (104), 343 (122), 335 (137), and 340 (105) μm. In CRVO, mean (SD) CRT values

karger@karger.com
www.karger.com/ore

Correspondence to:
Nathalie San Nicolas, nathalie.san_nicolas@novartis.com

at baseline and months 3, 6, 12, and 24 were 643 (217), 327 (152), 400 (203), 379 (175), and 348 (161) µm. On average, BRVO patients had 3.8 injections for 6.9 visits by month 6, and 7.2 injections for 19.7 visits by month 24. CRVO patients had 2.7 injections for 4.2 visits by month 6 and 7.1 injections for 21.1 visits by month 24. Factors predictive of better BCVA gain at month 6 were age under 60 at baseline, lower baseline BCVA and BCVA gain at month 3. There were no new safety findings. ***Conclusion:*** Major improvements in BCVA and CRT were observed at month 3 after the induction phase and then were sustained up to month 24, with a slight decrease, probably due to under-treatment. This study demonstrated ranibizumab to be a safe and effective treatment for BRVO and CRVO in the real-world setting, although more regular or proactive treatment could further improve outcomes.

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy and can lead to poor visual outcomes [1]. The most common type is branch RVO (BRVO), followed by central RVO (CRVO) and hemi-occlusion of the central retinal vein (HRVO) [1, 2]. BRVO and CRVO global prevalence in 2015 was estimated at 0.64% and 0.13%, respectively [3]. The main risk factors for any RVO include older age, hypertension, glaucoma, history of heart attack or stroke, hyperlipidemia, and obstructive sleep apnea [3–5].

Ranibizumab is a humanized monoclonal anti-vascular endothelial growth factor (anti-VEGF) antibody fragment that inhibits the effects of VEGF on neovascularization, angiogenesis, and vascular permeability. Ranibizumab was approved in Europe in 2011 for treating visual impairment due to macular edema (ME) secondary to RVO [6], based on data from the phase 3 randomized clinical trials (RCTs) CRUISE and BRAVO [7, 8].

However, results from RCTs may not reflect effectiveness in the real-world setting, where real-life practices may differ from the strictly controlled conditions of the RCTs. Post-authorization studies provide important information about how medicines are used in routine clinical practice and how effective they are. This study was mandated by the French Transparency Commission during the approval of ranibizumab reimbursement for RVO and diabetic ME, with the aim of providing data on the effectiveness, safety, and follow-up in a real-life setting. Here, we report the results from the BOREAL-RVO real-world observational study that evaluated the change in best-corrected visual acuity (BCVA) up to 24 months in patient starting treatment with ranibizumab for decreased vision due to ME secondary to RVO.

Methods

Study Design

This prospective multicenter observational study was conducted to assess real-world use and effectiveness of ranibizumab in patients with ME secondary to (1) CRVO and (2) BRVO/HRVO (called the BRVO group hereafter, for ease of reading). By decision of the Scientific Committee and similar to BRAVO [8], HRVO patients were included in the BRVO group as the treatment of ME for both entities is similar and may include grid laser photocoagulation. The study was conducted in France between December 2013 and April 2015, following approval from the French agencies for data protection (CNIL) and health research data management (CCTIRS). This study was conducted in accordance with the tenets of the Declaration of Helsinki. Participating patients were informed about the study and signed informed consent forms.

Selection of Investigators

One thousand six hundred sixty-six French retina specialists from both private practice and public hospitals were invited to participate, with the expectation that 150 would accept and that 120 would enroll patients. Each participating ophthalmologist had 16 months to enroll a maximum of 16 patients each.

Inclusion/Exclusion Criteria

Eligible patients were consenting patients starting ranibizumab treatment for visual impairment due to CRVO, HRVO, or BRVO, regardless of the level of initial visual acuity. Exclusion criteria were minimal, to achieve a study population representative of the larger patient population in France. Patients unwilling to participate, or who were already participating in another trial, were excluded.

Treatment

Patients were treated with intravitreal injection of ranibizumab 0.5 mg, according to prescribing information. Following ranibizumab initiation, patients were re-treated as needed according to the ophthalmologist's decisions based on anatomic and functional criteria.

Data Collection

Data were collected from patients' medical records at baseline and at months 3, 6, 9, 12, 18, and 24. Data were also collected via telephone interviews at baseline and at months 12 and 24. Detailed information was collected at baseline regarding patient characteristics, medical history, prior and concomitant medications.

Ophthalmologists measured patient BCVA according to their standard practice. BCVA data provided using the Snellen or Monoyer scales were converted to the Early Treatment Diabetic Retinopathy Study (ETDRS) scale using standard conversion tables. Central retinal thickness (CRT) was measured using optical coherence tomography on central ETDRS subfield. Adverse events

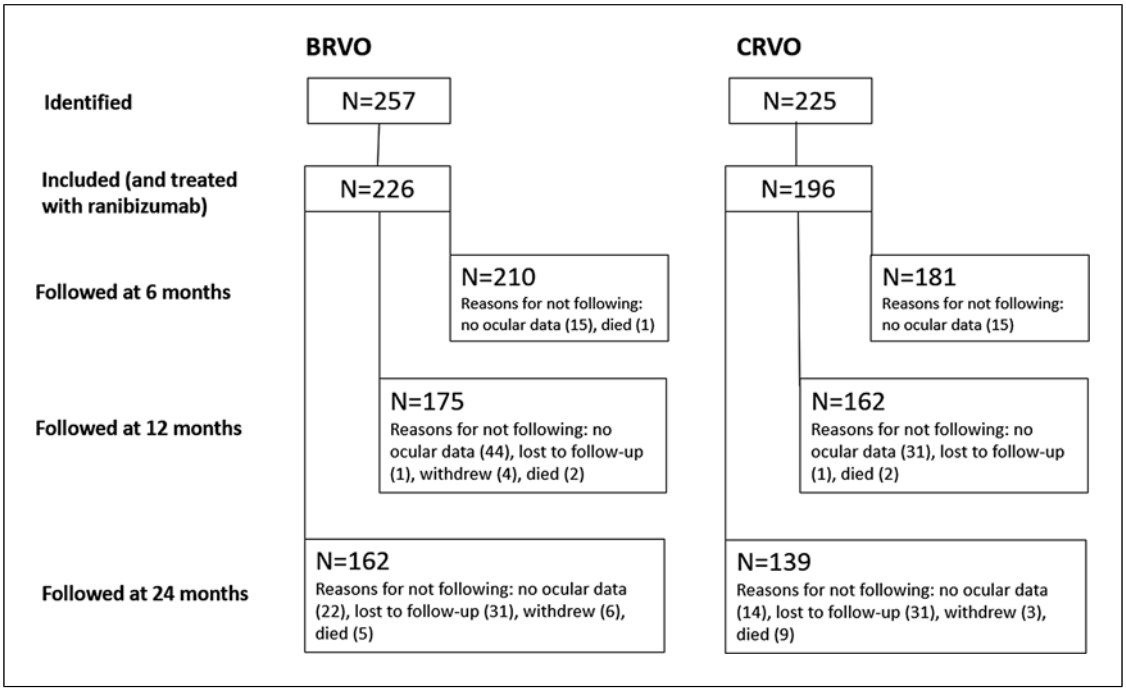

Fig. 1. Flowchart of patients in study. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

(AEs) were recorded at each visit. Fluorescein angiography was performed according to the ophthalmologist's routine practice, and ischemic RVO was defined as the presence of retinal nonperfusion of 10-disk areas or more.

Patients were monitored and treated according to the ophthalmologist's routine practice. Investigating ophthalmologists re-treated patients at their discretion and could switch treatment.

Statistical Analysis

The primary outcome measure was the change from baseline in BCVA at month 6 according to the ETDRS scale. Analyses were performed using SAS software version 9.3.

Based on previous RCTs evaluating ranibizumab in ME secondary to RVO [7, 8], a sample size of 285 patients allowed a relative precision of 10% relative to the average BCVA. Assuming potential attrition of 10%, it was planned to recruit 320 BRVO patients and 320 CRVO patients.

Quantitative variables were described using mean, standard deviation (SD), median, and extreme values, as well as 2-sided 95% confidence intervals. Qualitative variables were described as absolute frequency and percentage. Subgroup analyses were performed according to various baseline disease characteristics and demographics. Safety was assessed at month 24 for all patients who received at least one ranibizumab injection.

A multivariate analysis was used to identify potential predictive factors of BCVA improvement at months 6 and 24 in a generalized linear model and included patients followed and with BCVA measurements at these timepoints. Explanatory variables included baseline demographic and disease characteristics as well as treatment modalities and response. Variables that were significant in a univariate analysis (at the 20% threshold) were included in the multivariate analysis.

Results

Of the 1,666 ophthalmologists invited to participate in the study, 236 (14.2%) accepted, 82 (4.9%) included at least 1 BRVO patient, and 79 (4.7%) included at least 1 CRVO patient. The most common reason for nonparticipation of ophthalmologists was lack of time (59.4%).

Patients and Baseline Characteristics

Overall, 226 patients were enrolled into the BRVO cohort (176 with BRVO, 50 with HRVO) and 196 patients were enrolled into the CRVO cohort. Follow-up at month 24 was recorded for 71.7% of BRVO patients and 70.9% of CRVO patients (Fig. 1). Patient baseline characteristics were similar in each cohort (Table 1).

Treatment Exposure

Over the 24-month study period, patients were regularly examined, with a mean (SD) number of visits of 19.7 (7.8) and 21.1 (8.4) in the BRVO and CRVO cohorts, respectively. The mean (SD) number of intravitreal

Table 1. Baseline characteristics

	BRVO (*N* = 226)	CRVO (*N* = 196)
Male	110 (48.7)	101 (51.5)
Age, mean (SD), years	70.9 (11.1)	70.4 (14.3)
Bilateral RVO	8 (3.5)	5 (2.6)
Time since first RVO symptoms in the studied eye, median [min; max], months	1.0 [0.0; 101.0])	0.8 [0.0; 57.6]
Treatment-naïve in the studied eye patients	205 (90.7)	181 (92.3)
Previous ocular treatments in the studied eye for vision loss due to RVO (% of the eyes previously treated)	22 (9.7)	17 (8.7)
Laser	11 (50)	0 (0.0)
Bevacizumab	2 (9.1)	2 (11.8)
Dexamethasone implant	13 (59.1)	15 (88.2)
Aflibercept	0	0
Triamcinolone	1 (4.5)	1 (5.9)
Ranibizumab	0 (0.0)	0 (0.0)
BCVA (in ETDRS letters) in the studied eye		
Mean (SD)	55.2 (18.7)	40.4 (25.6)
Median [min; max]	59.0 [1.0; 83.0]	44.0 (0.0; 80.0)
BCVA category (in ETDRS letters) in the studied eye		
<20 letters	11 (4.9)	42 (21.4)
20–58 letters	80 (35.4)	82 (41.8)
59–69 letters	69 (30.5)	41 (20.9)
≥70 letters	66 (29.2)	31 (15.8)
CRT in the studied eye, mean (SD), μm	549.9 (175.2)	643.5 (217.3)
Ocular comorbidities		
At least 1 ocular comorbidity	127 (56.2)	127 (64.8)
Cataract (unoperated)	61 (27.0)	58 (29.6)
Glaucoma or ocular hypertension	48 (21.2)	49 (25.0)
Complications		
Rubeosis iridis	1 (0.4)	8 (4.1)
Ischemia	74 (32.7)	75 (38.3)
Concomitant non-ocular disease		
Arterial hypertension	101 (57.4)	113 (57.7)
Diabetes	23 (13.1)	31 (15.8)
History of cardiovascular disease (myocardial infarction, arrhythmia, etc.)	29 (16.5)	38 (19.4)
Migraine	6 (3.4)	10 (5.1)
History of stroke	114 (64.8)	5 (2.6)
Hypercholesterolemia	41 (23.3)	56 (28.6)
Concomitant anti-hypertension treatment		
None	102 (45.1)	84 (42.9)
1	60 (26.5)	40 (20.4)
2	38 (16.8)	45 (23.0)
3 or more	16 (7.1)	20 (10.2)

Values are patients *n* (%) unless otherwise indicated. Percentages were calculated for patients with available data for each variable. BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion; ETDRS, Early Treatment of Diabetic Retinopathy Study; RVO, retinal vein occlusion; SD, standard deviation.

injections over the same period was 7.2 (4.3) and 7.1 (4.4) in the BRVO and CRVO cohorts, respectively (Table 2), with approximately half the injections administered in the first 6 months.

Ranibizumab treatment starts with an induction phase of one injection per month for 3 months. Administration of 3 injections in the first 3 months was reported for 79.9% of BRVO patients and 76.4% of CRVO patients.

Up to month 24, treatment interruptions in the studied eye were noted for 85.8% of BRVO patients and 85.6% of CRVO patients. Interruption, defined as the absence of

Table 2. Frequency of ophthalmologist visits and anti-VEGF injections

	BRVO (*N* = 226*)	CRVO (*N* = 196*)
By month 3		
N	224	195
Visits, mean (SD)	4.0 (1.2)	4.2 (1.3)
Injections, mean (SD)	2.8 (0.6)	2.7 (0.7)
By month 6		
N	210	181
Visits, mean (SD)	6.9 (2.2)	7.3 (2.3)
Injections, mean (SD)	3.8 (1.2)	3.6 (1.2)
By month 12		
N	175	162
Visits, mean (SD)	12.3 (4.0)	12.6 (4.6)
Injections, mean (SD)	5.5 (2.3)	5.1 (2.4)
By month 24		
N	162	139
Visits, mean (SD)	19.7 (7.8)	21.1 (8.4)
Injections, mean (SD)	7.2 (4.3)	7.1 (4.4)

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; SD, standard deviation; VEGF, vascular endothelial growth factor. *Data are presented for the population of patients with available data at each timepoint.

treatment at one of the visits after the induction phase, was usually temporary. It was mostly due to clinical improvement (achievement of maximum BCVA, ME resolution, or ME regression; 72.6% and 79.1% in the BRVO and CRVO cohorts, respectively). The interruption was attributed to other reasons (no BCVA improvement, edema recurrence, persistent ME or AE) for 15.2% and 26.7% of BRVO and CRVO patients, respectively, who had interruptions.

Patients who required only 3 injections during the first 3 months and who did not switch or require additional injections due to favorable functional or anatomical outcomes are described as the "happy few," representing 12.2% of CRVO patients and 13.6% of BRVO patients. Of the 162 BRVO patients followed at month 24, 30.2% switched treatment from ranibizumab: 15.4% switched to dexamethasone implant, 13.6% to aflibercept, and 1.2% to triamcinolone (Fig. 2). Two patients (1.2%) switched back to ranibizumab after previously switching to another treatment. Of the 139 CRVO patients followed at month 24, 37.4% switched treatment from ranibizumab: 20.9% to aflibercept, 12.2% to dexamethasone implant, and 4.3% to bevacizumab. None of these patients switched back to ranibizumab.

Visual Acuity

In both cohorts, BCVA significantly improved from baseline at all follow-up times as early as month 3 and was sustained until month 24. Rapid BCVA gains from baseline were observed at month 3 (14.3 [13.7] and 16.0 [21.2] letters in BRVO and CRVO patients, respectively). The change from baseline then stabilized over time by month 6 (14.1 [16.5] and 9.5 [25.4] letters, respectively) with gains maintained up to month 24 (11.4 [20.1] and 8.3 [23.8] letters, respectively) (Fig. 3; online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000530294).

Gains from baseline to month 6 of at least 15 letters were noted for 94 (50.3%) BRVO patients and 67 (42.7%) CRVO patients (online suppl. Table 2). Gains in BCVA were maintained up to month 24 in both indications (Fig. 3).

At month 6, there was a trend toward better BCVA outcomes for CRVO patients who completed the induction phase (3 monthly injections in the first 3 months, n = 121), who gained 10.6 [95% CI: 5.8; 15.3] letters, compared to 5.8 [95% CI: −1.5; 13.0] letters for those who did not (n = 34). At month 24, CRVO patients who had more than 3 intravitreal injections of ranibizumab at M6 since inclusion were more likely to experience a gain of at least 5 ETDRS letters than patients who had less than 3 injections (p = 0.0064). At month 6, BCVA gains were similar for BRVO patients who completed induction (14.0 [95% CI: 11.3; 16.6] letters; n = 144) and those who did not (13.8 [95% CI: 7.9; 19.7] letters; n = 36).

In univariate analysis, factors predictive of lower BCVA gains at month 6 for BRVO were CRT of less than 500 μm at baseline (p = 0.0006), absence of retinal non-perfusion at baseline (p = 0.0118), diabetes (p = 0.0060), hypertension (p = 0.0101), and longer duration of symptoms (p = 0.0372). For CRVO, factors associated with loss of at least 5 ETDRS letters at 24 months from inclusion were the presence of retinal non-perfusion at baseline (p = 0.0157). Other factors were not correlated with the final visual prognosis, such as gender and associated systemic treatments.

Multivariate analysis identified several factors predictive of better BCVA change from baseline to month 6 and month 24 for BRVO and CRVO, respectively (online suppl. Tables 3, 4). Factors predictive of higher BCVA gains at month 6 for both BRVO and CRVO were younger age at baseline (p = 0.0270 and p = 0.0012, respectively), lower baseline BCVA (p < 0.0001 and p = 0.0244, respectively), and higher BCVA gain at month 3 (p = 0.0018 and p < 0.0001, respectively). Factors predictive of higher BCVA gains at month 24 for BRVO were

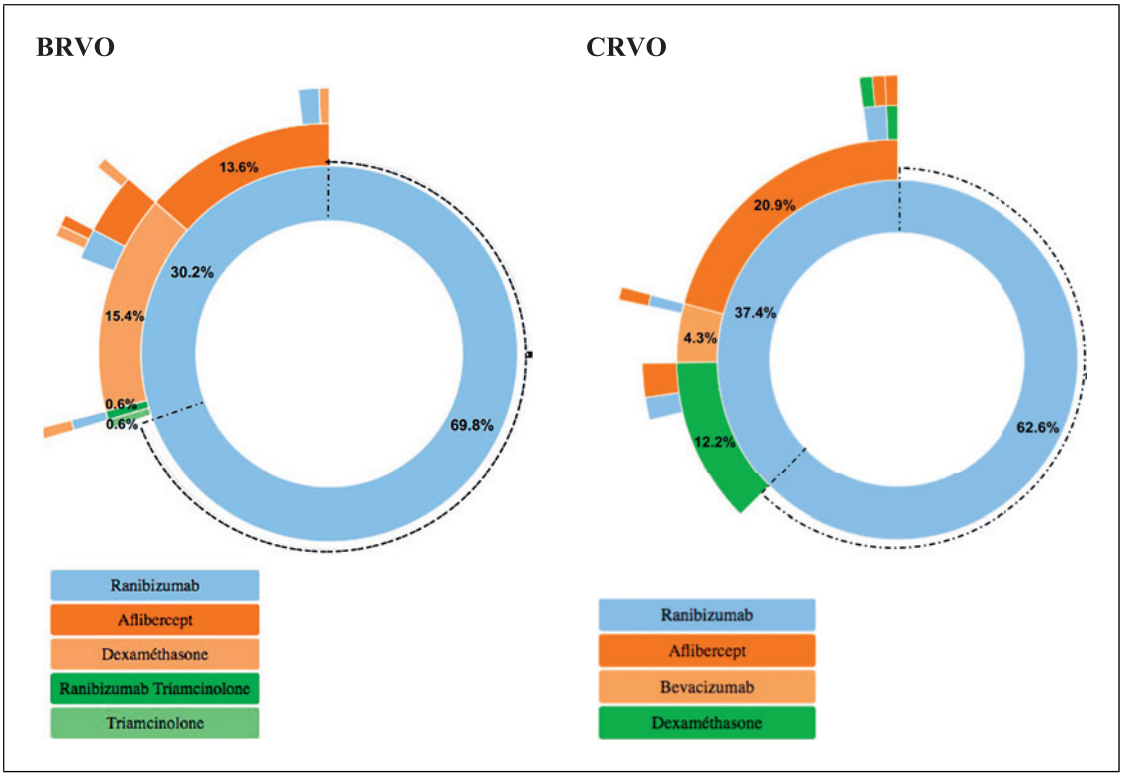

Fig. 2. Treatment switch during study period. This chart describes how patients who initiated anti-VEGF therapy with ranibizumab (in the innermost ring) switched to other anti-VEGF treatments (shown in the outer rings, reading from the inside toward the outside). Each color represents a different anti-VEGF treatment. For example, 30.2% of BRVO patients switched treatment from ranibizumab: 15.4% to dexamethasone implant and 13.6% to aflibercept.

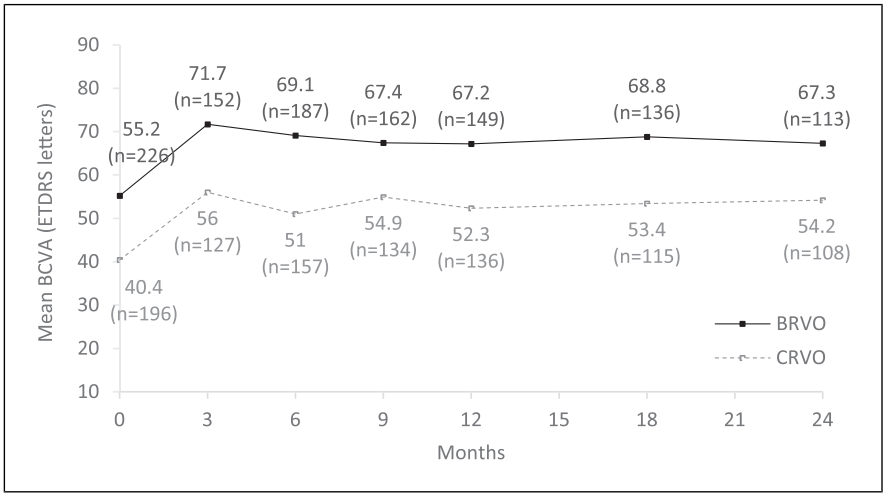

Fig. 3. Change in BCVA. BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ETDRS, Early Treatment of Diabetic Retinopathy Study; *n*, number of patients with available data at each timepoint.

CRT of more than 500 µm at baseline ($p = 0.0160$) and higher BCVA gain at month 3 ($p < 0.0001$). Factors predictive of higher BCVA gains at month 24 for CRVO were age below 70 years old at baseline ($p = 0.0005$), higher BCVA gain at month 3 ($p = 0.0018$), and no switch at M6 ($p = 0.0061$).

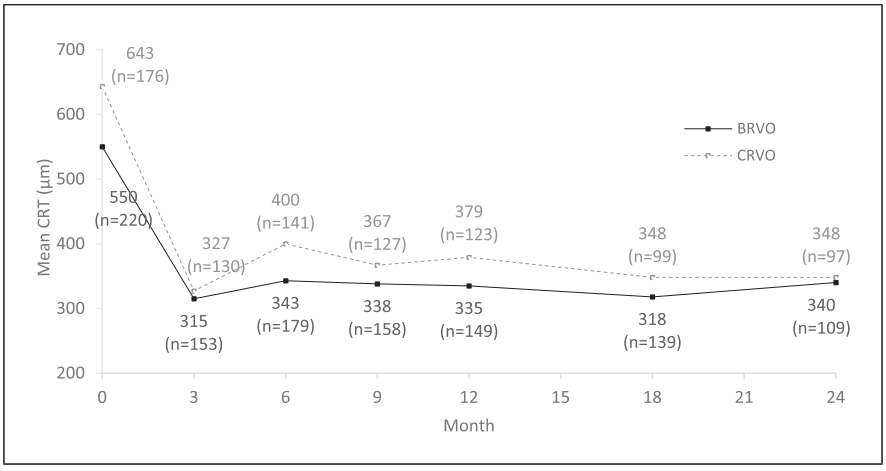

Fig. 4. Change in CRT. BRVO, branch retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion; *n*, number of patients with available data at each timepoint.

Central Retinal Thickness

The pattern of changes in CRT mirrors those of BCVA. CRT improved from baseline to month 3 in both BRVO and CRVO, with improvements maintained up to month 24 (Fig. 4; online suppl. Table 1). The mean (SD) improvement observed after 3 months of follow-up was −232 (167) µm and −330 (252) µm in the BRVO and CRVO groups, respectively, followed by stabilization in subsequent months. By month 24, CRT had reduced by a mean (SD) of −211 (210) µm and −305 (236) µm, respectively.

Other Measures

The rate of retinal non-perfusion and ophthalmologic comorbidities rose slightly during follow-up in both BRVO and CRVO patients (Table 3). At month 24, respectively, 36.4% and 34.5% of BRVO/HRVO and CRVO patients had peripheral retinal non-perfusion, 0.6% and 9.4% had rubeosis iridis, and 30.2% and 31.7% had glaucoma or ocular hypertension (Table 3). At month 24 of follow-up, 49 CRVO patients (35.3%) had received panretinal photocoagulation (PRP) laser treatment at least once, with an average of 3.8 (±2.4) PRP laser treatments since inclusion. At 24 months of follow-up, 21 BRVO patients (13.0%) had received macular laser treatment at least once, with an average of 1.4 (±0.7) macular laser treatments. Moreover, 29.6% of the BRVO patients (48 patients) had received at least once PRP laser treatment, with an average of 1.8 (±1.1) treatments by PRP laser since inclusion injection.

Safety

Approximately half BRVO and CRVO patients had at least one AE during the 24-month study. The most common category of AE was ocular disorders (online suppl. Table 5). Five BRVO patients had 8 severe AEs possibly related to ranibizumab: macular ischemia, retinal ischemia, transient blindness, increased intraocular pressure, myocardial ischemia, lymphoma aggravation, cerebral infarction, and hypertension. Two CRVO patients had 2 severe AEs possibly related to ranibizumab: transient ischemic attack and retinal ischemia. There were no fatal AEs related to ranibizumab. One BRVO patient experienced endophthalmitis, not related to ranibizumab at month 18. No new safety findings were identified, and results were in line with the well-characterized safety profile of ranibizumab.

Discussion

This 24-month prospective multicenter observational study assessed real-world use and effectiveness of ranibizumab in patients with ME secondary to BRVO (and HRVO) and CRVO. Improvements in BCVA and CRT were observed at month 3 and persisted up to month 24 in both cohorts.

The BOREAL-RVO study was designed to include a real-life cohort of patients, representative of the wider RVO patient population. As such, the current study population had lower baseline VA for CRVO patients (40.4 [25.6] letters) compared to patients in the pivotal RCT CRUISE (48.1 [14.6] letters) [7]. For BRVO patients, baseline BCVA was similar in the current study (55.2 [18.7] letters) and in BRAVO (53 [12.5] letters) [8]. One possible explanation is that the current study included patient with ischemia, whereas they were excluded from the RCTs.

The inclusion of ischemic CRVO patients can explain why BCVA gains at month 3 in CRVO patients were higher in the current study versus month 3 BCVA

Table 3. Other ocular findings during follow-up

	BRVO			CRVO		
	baseline, *n* = 226	month 6, *n* = 210	M24, *n* = 162	baseline, *n* = 196	month 6, *n* = 181	M24, *n* = 139
Bilateral RVO, *n* (%)	8 (3.5)	8 (3.8)	9 (5.6)	5 (2.6)	7 (3.9)	6 (4.3)
Rubeosis iridis, *n* (%)	1 (0.4)	1 (0.5)	1 (0.6)	8 (4.1)	13 (7.2)	13 (9.4)
Ischemia, *n* (%)	74 (32.7)	84 (40.0)	79 (48.8)	75 (38.3)	84 (46.4)	74 (53.2)
Peripheral only	59 (26.1)	62 (29.5)	59 (36.4)	52 (26.5)	55 (30.4)	48 (34.5)
Macular and peripheral	9 (4.0)	13 (6.2)	13 (8.0)	20 (10.2)	25 (13.8)	23 (16.5)
Macular only	6 (2.7)	9 (4.3)	7 (4.3)	3 (1.5)	4 (2.2)	3 (2.2)
At least 1 ophthalmology comorbidity, *n* (%)	127 (56.2)	127 (60.5)	123 (75.9)	127 (64.8)	128 (70.7)	109 (78.4)
Cataract (unoperated)	61 (27.0)	54 (25.7)	48 (29.6)	58 (29.6)	57 (31.5)	43 (30.9)
Glaucoma and ocular hypertension	48 (21.2)	46 (21.9)	49 (30.2)	49 (25.0)	54 (29.8)	44 (31.7)
Pseudophakia	48 (21.2)	48 (22.9)	50 (30.9)	40 (20.4)	36 (19.9)	42 (30.2)
Intraocular pressure, mean (SD), mm Hg	15.3 (3.7)	15.4 (3.7)	15.8 (5.8)	15.8 (4.4)	16.2 (4.3)	15.8 (3.5)

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; RVO, retinal vein occlusion; SD, standard deviation.

gains in CRUISE [7]. These patients have a higher potential of BCVA gains, before encountering the "ceiling effect" seen elsewhere [9]. Indeed, mean (SD) baseline BCVA was higher in CRUISE (48.1 [14.6]) than for CRVO patients in the current study (40.4 [25.6] letters). The RAVE study also included ischemic CRVO patients, showing that lower baseline BCVA in such patients yielded notable BCVA gains (21.1 letters at month 9) [10].

In the current study, ranibizumab treatment started with an induction period of three-monthly injections. Induction was completed for 79.9% of BRVO patients and 76.4% of CRVO patients. BCVA gains at month 6 were numerically higher – although not statistically significant – for CRVO patients who completed the induction phase. However, patients who received more than 3 injections in the first 6 months had more gains >5 ETDRS letters at 24 months ($p = 0.0064$). These results are in line with the large prospective LUMINOUS study, showing that an adequate loading dose led to numerically higher BCVA outcomes in both BRVO and CRVO patients at year 1 – although these were not statistically significant [11, 12].

Up to month 3, a similar pattern in improvements and gains in BCVA was noted in the current study versus the RCTs BRAVO and CRUISE [7, 8]. In the RCTs, BCVA gains continued to rise after month 3, as patients were still being treated (6 monthly injections within the first 6 months), to reach a maximal BCVA at month 6. This was not the case in the real-world BOREAL-RVO study.

After M3, the BCVA gains in the current study were lower than the gains observed in RCTs for BRVO and CRVO [7, 8], in line with the lower number of ranibizumab injections. In BRVO, the mean (SD) BCVA gain at month 6 was 14.1 letters in the current study (for an average of 3.8 injections) compared to the BCVA gains at month 6 in the BRAVO (18.3 letters for 6 injections) [8] and BRIGHTER (14.8 letters) RCTs [13]. Guidelines recommend that subsequent monthly injections must be continued until BCVA stability is reached [14], but they were not published at the time of the BOREAL-RVO study. Similarly, the BCVA gain at month 24 of 11.4 letters in the current study was lower than the 17.5 letter gain reported in HORIZON, the 12-month extension of BRAVO. Indeed, BRVO patients had fewer injections over 24 months in the current study (7.2 injections) than in HORIZON, where patients in the 0.5 mg ranibizumab group had an average of 10.5 injections over 24 months [15].

In CRVO, the mean BCVA gains at months 6, 12, and 24 were 9.5, 9.2, and 8.3 letters, respectively, in the current study. These gains were lower than those reported in the RCTs CRUISE at month 6 (14.9 letters) [7], CRYSTAL at month 12 (12.3 letters) and month 24 (12.1 letters) [9], and HORIZON at month 24 (12.0 letters) [15]. Again, the weaker gains in the current study were probably due to the lower number of injections over 24 months (7.1 injections) than in HORIZON (12.3 injections) or CRYSTAL (13.1 injections).

These real-life results on the use of ranibizumab in France mirror the outcomes observed in Germany. The

OCEAN study included 744 patients with RVO between 2011 and 2015 and followed them up for 2 years. BCVA improved rapidly within the first 3 months, up to 10.7 letter gain at 12 months and 11.8 letter gain at 24 months after a median of 4 (5) injections over 12 (24) months [16]. At the same time in Portugal, a retrospective, observational study including 200 patients treated with either ranibizumab or bevacizumab showed that median BCVA improved in both treatment groups in CRVO and BRVO patients at 6 months (−0.27 logMAR and −0.10 logMAR, respectively) and 12 months (−0.26 logMAR and −0.10 logMAR, respectively) compared to baseline ($p < 0.001$). The median number of injections was 3 during the first 6 months and 1 from 6 to 12 months [17]. The 5-year worldwide LUMINOUS BRVO Study showed at year 1 a mean VA gain equal to 11.9 letters from baseline with a mean of 5 ranibizumab injections in the 189 treatment-naïve BRVO patients. VA gains were higher in patients who received 6–9 injections (13.6 letters) than in those who received 2–5 injections (11.7 letters), or 1 injection (3.6 letters) [11]. In the LUMINOUS CRVO Study at 1 year, 144 treatment-naïve patients had a mean VA gain from baseline of 10.8 letters, with a mean of 5.4 ranibizumab injections [12]. LUMINOUS also underscored that outcomes vary across countries and are greatly affected by factors, such as treatment costs, reimbursement policies, ease of access to medicines, and suboptimal treatment due to less strict follow-up measures in certain countries [11, 12].

In the current study, BRVO patients had an average of 19.7 visits and 7.2 injections by month 24, while CRVO patients had an average of 21.1 visits and 7.1 injections. This suggests that patients were adequately monitored but undertreated. Under-treatment has been observed in other real-world studies of ranibizumab in RVO, in other countries, at the same period [11, 12, 16–21]. It is highly likely that patients were treated under a pro re nata (PRN) regimen. In Switzerland, a retrospective case series of 76 RVO patients with consecutive recruitment within two different periods (PRN 2009–2012, and treat and extend [T&E] 2012–2016) showed that T&E provided a better morphological outcome using more injections than PRN (9.6 and 4.2 at M12, respectively [$p < 0.001$]) [22]. At the time of the current study (between December 2013 and April 2015), the T&E regimen was not routinely used in RVO in France and became widespread only later on [23–25]. But as soon as 2010, in the USA, a retrospective, interventional study including 60 CRVO eyes receiving T&E ranibizumab or bevacizumab showed that high VA gains were achieved at M12 (+12.8 ETDRS letters) with 8.1 injections (and visits) [26]. In 2016, in the UK, a retrospective analysis of 44 patients newly diagnosed with CRVO receiving T&E aflibercept showed that high VA gains were achieved at M12 (+15.1 letters) with a mean number of injections (and visits) of 8 [27].

Of the patients still followed at month 24, 85.8% of BRVO patients and 85.6% of CRVO patients experienced an interruption of ranibizumab treatment, mainly due to achievement of maximum BCVA and ME resolution or regression. Considering the low proportion of "happy few" patients who completed induction without subsequent switch or additional injections due to favorable functional or anatomical outcomes (13.6% of BRVO patients and 12.2% of CRVO patients), treatment interruptions were indeed transient, and most patients usually warrant ongoing monitoring as they will need to be treated again.

By month 24, a third of patients had switched to other intravitreal treatments, mainly to aflibercept or dexamethasone implant. A few patients switched back to ranibizumab. The reasons for treatment switch were not collected. A small number of retrospective studies and small case series have investigated switching [28], as well as a small prospective trial which found that some patients unresponsive to one anti-VEGF treatment can benefit from switching to another [29].

In the current study, the proportion of patients with retinal ischemia, rubeosis iridis, and other ophthalmologic comorbidities rose slightly from baseline throughout the study. Patients should continue to be monitored with fluorescein angiography to look for peripheral retinal non-perfusion particularly when the treatment is stopped.

Lower baseline BCVA was predictive of higher BCVA gains at month 6 for both BRVO and CRVO, which has already been demonstrated in previous studies [9, 10]. Early BCVA gains by month 3 were predictive of better gains at month 6, and younger age at baseline was also predictive of better outcomes. In general, younger patients with less severe disease and in general good health had better improvements in BCVA. This supports findings from previous studies [4, 30–33]. As early as 1996, in 120 CRVO patients prospectively analyzed, older age, male gender, and the number of associated risk factors (systemic vascular risk factors and glaucoma) were found to be correlated with a poor visual outcome and with the development of retinal ischemia, as well as baseline visual acuity, initial extent of retinal non-perfusion, and rheologic

parameters (hematocrit, fibrinogen, and erythrocyte aggregation) [4]. As in our study, in the post hoc analysis of the prospective SHORE study, the only factors independently correlated with BCVA gain were younger age ($p < 0.0001$) and worse baseline BCVA ($p < 0.0001$) [32]. Several negative predictive factors for visual outcome based on optical coherence tomography imaging were not assessed in the BOREAL-RVO study, but were found in later studies, such as the disruption of the external limiting membrane and ellipsoid zone [33].

There were no new safety findings in this study. Surprisingly, many ocular AEs previously reported with ranibizumab in RCTs and in other indications were not reported in this study. Therefore, these safety results should be interpreted with caution since AEs may be underreported.

A strength of the current BOREAL-RVO study is that patients were included from a range of ophthalmologists throughout France, including private and public hospital ophthalmologists. While this yielded a cohort which we believe to be representative of the wider population, several limitations could be associated with this approach. In accordance with the real-life observational study design, a range of scales were used to measure BCVA (Monoyer, Snellen, and ETDRS). This could have led to loss of sensitivity. Among other limitations is the fact that a different pool of patients attended each visit (see Fig. 1) and the low patient sample with complete data, meaning these results should be interpreted with caution. Finally, the BOREAL-RVO study was performed in France, and it is not known whether these results can be extrapolated to other countries, especially because many other countries do not enjoy fully reimbursed healthcare.

Conclusion

This BOREAL-RVO study showed that ranibizumab treatment in the real-life setting led to a rapid and considerable improvement in BCVA and CRT at month 3, mirroring clinical trials. After month 3, because of under-treatment and despite regular follow-up, the outcomes were not maximized. This result was in favor of a change in RVO management practices in France toward a more proactive regimen (T&E). No new safety findings were identified in this 24-month study. In conclusion, the BOREAL-RVO study demonstrated ranibizumab to be a safe and effective treatment for BRVO and CRVO in the real-world setting.

Acknowledgments

The authors thank all the study investigators who conducted the study. Medical writing assistance was funded by Novartis and was provided by Dr. Fiona Dunlevy and Matrix Consultants.

Statement of Ethics

The study was conducted in France between December 2013 and April 2015 in accordance with the Declaration of Helsinki and complied with the relevant guidelines for human studies. Ethical approval was not required, according to French regulations for observational studies. The study was approved by the French agencies for data protection (CNIL) and health research data management (CCTIRS). Participating patients were informed about the study and signed informed consent forms.

Conflict of Interest Statement

Dr. Agnès Glacet-Bernard has received consultancy fees from Novartis and Bayer. Dr. Jean-François Girmens has received consultancy fees from AbbVie (Allergan), Bayer, and Novartis and has stock ownership at Tilak Healthcare. Pr. Laurent Kodjikian has received consultancy fees from AbbVie, Alimera, Bayer, Horus, Novartis, and Roche. Dr. Cécile Delcourt has received consultancy fees from Allergan, Chauvin Bausch + Lomb, Novartis, and Théa Pharma, and has received speaker fees from Apellis. Dr. Franck Fajnkuchen has received consultancy fees from Allergan, Bayer, Horus, and Novartis. Pr. Catherine Creuzot-Garcher has received consultancy fees from AbbVie, Bausch + Lomb, Bayer, Horus, Novartis, and Roche. Pr. Pascale Massin has received consultancy fees from Novartis. Nathalie San Nicolas is an employee of Novartis Pharma.

Funding Sources

This study was funded and sponsored by Novartis. The sponsor was involved in the collection and analysis of study data, and in preparation, revision, and approval of the present manuscript.

Author Contributions

Dr. Agnès Glacet-Bernard, Dr. Jean-François Girmens, Dr. Laurent Kodjikian, Dr. Cécile Delcourt, Dr. Franck Fajnkuchen, Pr. Catherine Creuzot-Garcher, and Pr. Pascale Massin were involved in the planning, conduct, analysis, reporting of the study, and revision of the manuscript. Dr. Agnès Glacet-Bernard and Nathalie San Nicolas wrote the manuscript with input of all other authors.

Data Availability Statement

The datasets from the BOREAL-RVO study are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

References

1 Glacet-Bernard A. Œdème maculaire des occlusions veineuses. In: Massin P, Creuzot-Garcher C, editors. Oedèmes maculaires rapport SFO 2016. Elsevier Masson, Rapport de la Société Française d'ophtalmologie; 2016.
2 Channa R, Smith M, Campochiaro PA. Treatment of macular edema due to retinal vein occlusions. Clin Ophthalmol. 2011;5:705–13.
3 Song P, Xu Y, Zha M, Zhang Y, Rudan I. Global epidemiology of retinal vein occlusion: a systematic review and meta-analysis of prevalence, incidence, and risk factors. J Glob Health. 2019 Jun;9(1):010427.
4 Glacet-Bernard A, Coscas G, Chabanel A, Zourdani A, Lelong F, Samama MM. Prognostic factors for retinal vein occlusion: prospective study of 175 cases. Ophthalmology. 1996 Apr;103(4):551–60.
5 Glacet-Bernard A, Leroux les Jardins G, Lasry S, Coscas G, Soubrane G, Souied E, et al. Obstructive sleep apnea among patients with retinal vein occlusion. Arch Ophthalmol. 2010 Dec;128(12):1533–8.
6 European Medicines Agency. Summary of opinion (post authorisation) for Lucentis (ranibizumab). In: Committee for medicinal products for human use (CHMP), editor. 2011.
7 Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010 Jun;117(6):1124–33.e1.
8 Campochiaro PA, Heier JS, Feiner L, Gray S, Saroj N, Rundle AC, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010 Jun;117(6):1102–12.e1.
9 Larsen M, Waldstein SM, Priglinger S, Hykin P, Barnes E, Gekkieva M, et al. Sustained benefits from ranibizumab for central retinal vein occlusion with macular edema: 24-month results of the CRYSTAL study. Ophthalmol Retina. 2018 Feb;2(2):134–42.
10 Brown DM, Wykoff CC, Wong TP, Mariani AF, Croft DE, Schuetzle KL, et al. Ranibizumab in preproliferative (ischemic) central retinal vein occlusion: the rubeosis anti-VEGF (RAVE) trial. Retina. 2014 Sep;34(9):1728–35.
11 Pearce I, Clemens A, Brent MH, Lu L, Gallego-Pinazo R, Minnella AM, et al. Real-world outcomes with ranibizumab in branch retinal vein occlusion: the prospective, global, LUMINOUS study. PLoS One. 2020;15(6):e0234739.
12 Lotery A, Clemens A, Tuli R, Xu X, Shimura M, Nardi M, et al. Effectiveness and safety of ranibizumab in patients with central retinal vein occlusion: results from the real-world, global, LUMINOUS study. Eye. 2021 Jul 29.
13 Tadayoni R, Waldstein SM, Boscia F, Gerding H, Gekkieva M, Barnes E, et al. Sustained benefits of ranibizumab with or without laser in branch retinal vein occlusion: 24-month results of the BRIGHTER study. Ophthalmology. 2017 Dec;124(12):1778–87.
14 Schmidt-Erfurth U, Garcia-Arumi J, Gerendas BS, Midena E, Sivaprasad S, Tadayoni R, et al. Guidelines for the management of retinal vein occlusion by the European society of retina specialists (EURETINA). Ophthalmologica. 2019;242(3):123–62.
15 Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG, et al. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. Ophthalmology. 2012 Apr;119(4):802–9.
16 Callizo J, Ziemssen F, Bertelmann T, Feltgen N, Vögeler J, Koch M, et al. Real-world data: ranibizumab treatment for retinal vein occlusion in the OCEAN study. Clin Ophthalmol. 2019;13:2167–79.
17 Vaz-Pereira S, Marques IP, Matias J, Mira F, Ribeiro L, Flores R. Real-world outcomes of anti-VEGF treatment for retinal vein occlusion in Portugal. Eur J Ophthalmol. 2017 Nov 8;27(6):756–61.
18 Lip PL, Cikatricis P, Sarmad A, Damato EM, Chavan R, Mitra A, et al. Efficacy and timing of adjunctive therapy in the anti-VEGF treatment regimen for macular oedema in retinal vein occlusion: 12-month real-world result. Eye. 2018 Mar;32(3):537–45.
19 Gale R, Gill C, Pikoula M, Lee AY, Hanson RLW, Denaxas S, et al. Multicentre study of 4,626 patients assesses the effectiveness, safety and burden of two categories of treatments for central retinal vein occlusion: intravitreal anti-vascular endothelial growth factor injections and intravitreal Ozurdex injections. Br J Ophthalmol. 2021 Nov;105(11):1571–6.
20 Gale R, Pikoula M, Lee AY, Denaxas S, Egan C, Tufail A, et al. Real world evidence on 5,661 patients treated for macular oedema secondary to branch retinal vein occlusion with intravitreal anti-vascular endothelial growth factor, intravitreal dexamethasone or macular laser. Br J Ophthalmol. 2021 Apr;105(4):549–54.
21 Narayanan R, Kelkar A, Abbas Z, Goel N, Soman M, Naik N, et al. Sub-optimal gain in vision in retinal vein occlusion due to under-treatment in the real world: results from an open-label prospective study of Intravitreal Ranibizumab. BMC Ophthalmol. 2021 Jan 12;21(1):33.
22 Guichard MM, Xavier AR, Türksever C, Pruente C, Hatz K. Spectral-domain optical coherence tomography-driven treat-and-extend and pro Re nata regimen in patients with macular oedema due to retinal vein occlusion: 24-month evaluation and outcome predictors. Ophthalmic Res. 2018;60(1):29–37.
23 Glacet-Bernard A. A Treat and Extend regimen to treat retinal vein occlusion in the real-life practice. Paris: [Conference presentation] Maculart Meeting; 2015.
24 Mascali R, Glacet-Bernard A, Srour M, Capuano V, Chevreaud O, Caillaux V, et al. Experience in real life of the "Treat and Extend" for retinal venous occlusions. [Conference presentation]. Paris, France: Soc Fr Ophtalmol; 2015.
25 Addou Regnard M, Glacet-Bernard A, Sekfali R, Miere A, Souied E. Anti-VEGF treatment of macular edema using a treat-and-extend regimen in retinal vein occlusion in clinical practice: 18 months follow-up [Conference poster]. Baltimore, USA: The Association for Research in Vision and Ophthalmology; 2017.
26 Rahimy E, Rayess N, Brady CJ, Regillo CD. Treat-and-Extend regimen for macular edema secondary to central retinal vein occlusion: 12-month results. Ophthalmol Retina. 2017 Mar–Apr;1(2):118–23.
27 Eleftheriadou M, Nicholson L, D'Alonzo G, Addison PKF. Real-life evidence for using a treat-and-extend injection regime for patients with central retinal vein occlusion. Ophthalmol Ther. 2019 Jun;8(2):289–96.
28 Ashraf M, Souka AAR, Singh RP. Central retinal vein occlusion: modifying current treatment protocols. Eye. 2016;30(4):505–14.
29 Spooner K, Fraser-Bell S, Hong T, Chang A. Prospective study of aflibercept for the treatment of persistent macular oedema secondary to retinal vein occlusions in eyes not responsive to long-term treatment with bevacizumab or ranibizumab. Clin Exp Ophthalmol. 2020 Jan;48(1):53–60.
30 Chatziralli I, Theodossiadis G, Chatzirallis A, Parikakis E, Mitropoulos P, Theodossiadis P. Ranibizumab for retinal vein occlusion: predictive factors and long-term outcomes in real-life data. Retina. 2018 Mar;38(3):559–68.
31 Yiu G, Welch RJ, Wang Y, Wang Z, Wang PW, Haskova Z. Spectral-domain OCT predictors of visual outcomes after ranibizumab treatment for macular edema resulting from retinal vein occlusion. Ophthalmol Retina. 2020 Jan;4(1):67–76.
32 Khokhlova DY, Drozdova EA, Kurysheva NI, Loskutov IA. Optical coherence tomographic patterns in patients with retinal vein occlusion and macular edema treated by ranibizumab: a predictive and personalized approach. EPMA J. 2021 Mar;12(1):57–66.
33 Sen P, Gurudas S, Ramu J, Patrao N, Chandra S, Rasheed R, et al. Predictors of visual acuity outcomes after anti-vascular endothelial growth factor treatment for macular edema secondary to central retinal vein occlusion. Ophthalmol Retina. 2021 Nov;5(11):1115–24.