Long-term visual outcome and its predictors in macular oedema secondary to retinal vein occlusion treated with dexamethasone implant

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ABSTRACT

Background To evaluate the functional long-term outcome in patients with macular oedema (MO) secondary to central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) treated with dexamethasone implant (DEX implant) and to identify its clinical predictors.

Methods A 24-month, retrospective, multinational, real-world study. Chart review of patients with either naïve or recurrent MO secondary to CRVO/BRVO treated with DEX implant, including best-corrected visual acuity (BCVA), central subfield thickness (CST), demographic baseline characteristics and details of any additional treatment during follow-up.

Results A total of 155 eyes (65 CRVO, 90 BRVO) from 155 patients were included. At 24 months, mean BCVA did not change significantly in CRVO (−2.1±24.5 letters, p=0.96) and BRVO patients (1.3±27.0 letters, p=0.07). A worse baseline BCVA (p<0.001), visual acuity (VA) gain ≥5 letters at 2 months (p=0.006) and no need for adjunctive intravitreal therapy after first DEX implant (p=0.001) were associated with a better final BCVA gain. Treatment-naïve patients (p=0.006, OR: 0.25, 95% CI 0.11 to 0.57) and those with a baseline CST≤400 µm (p=0.02, OR: 0.25, 95% CI 0.10 to 0.63) were identified as being less likely to need additional intravitreal therapy.

Conclusion Clinical baseline characteristics and the early treatment response were identified as possible predictors for long-term outcome and the need of adjunctive intravitreal therapy in MO secondary to BRVO/CRVO treated by DEX implant.

INTRODUCTION

Retinal vein occlusion (RVO) affects around 16 million people around the world accounting for the second most common visual impairing retinal vascular disease.[1 2] A common cause for vision loss in RVO is macular oedema (MO).[3] Aside from intravitreal antivascular endothelial growth factor (anti-VEGF) therapy, the use of intravitreal corticosteroids is a common therapeutic option for MO caused by RVO. The rationale for steroid use is the inhibition of multiple inflammatory mediators causing and contributing to the persistence of MO.[3–6]

The GENEVA study demonstrated the efficacy and safety of dexamethasone intravitreal implant 0.7 mg (DEX implant, Ozurdex; Allergan plc, Dublin, Ireland) for treatment of MO in RVO with faster resolution and greater improvement of vision compared with sham.[7 8] However, even though randomised controlled trials are the 'gold-standard' for providing evidence for the efficacy and safety of a pharmaceutical agent, they may not represent real-world conditions. Strict inclusion and exclusion criteria may lead to under-representation of certain patient groups in these results (eg, elderly, less compliant patients and pretreated patients).[9] As such, functional outcomes from real-world studies of RVO treated with DEX implant, especially with a follow-up beyond 12 months, are limited.[10]

The LOUVRE trial, a prospective multicentre study, showed a mean gain in VA from baseline of 4.6 letters after 24 months. Thirty-one per cent gained ≥15 letters after 6 months and 38.7% after 24 months.[10] Despite the favourable reported overall outcome, certain patient subgroups did not improve sufficiently after DEX implant. In the GENEVA study, 63% of the patients gained <10 letters in vision after 6 months, and even 6% lost ≥15 letters.[7] Predictors for functional outcome in patients with MO due to RVO treated with DEX implant in real-life are not available. An early characterisation of a patient's presumable visual outcome might help to provide individualised treatment and consequent optimal functional outcome and disease management. The main objective of this study was to describe visual outcomes in patients with MO due to RVO treated by DEX implant after 24 months and analyse its clinical predictors in a multinational, real-world setting.

METHODS

This international multicentre study included 10 study sites (see online supplementary material). The research adhered to the tenets of the Declaration of Helsinki. Patient records from 1 January 2012 to 1 August 2017 were reviewed for cases of MO related to RVO treated by intravitreal DEX implant.

Study participants

Patients who met the following criteria were included in the analysis: (1) age 18 years or older; (2) MO (both naïve and refractory to previous anti-VEGF therapy) related to central RVO (CRVO) or branch RVO (BRVO); MO defined clinically and by spectral domain optical coherence tomography (SD-OCT) as retinal thickness of >300 µm in the central subfield (CST); and presence of intraretinal or subretinal fluid; (3) best-corrected visual acuity (BCVA) in the study eye of ≤1.5 log of the minimum angle of resolution (MAR); (4) treatment with DEX implant. If both eyes met the inclusion criteria, only the right eye was included. (5) Data available for 24 months from the first DEX injection. Exclusion criteria included (1) another concomitant ocular disease that causes MO (ie, neovascular age-related macular degeneration, diabetic retinopathy or choroidal neovascularisation due to other reasons, uveitis and recent intraocular surgery possibly causing postsurgical MO); (2) another ocular condition that compromises VA, except for the presence of cataract; (3) previous treatment with intraocular corticosteroids before treatment with the DEX implant; and (4) previous vitreoretinal surgery.

Consecutive patient charts were reviewed for demographic data; presence of concomitant diseases; previous treatments for MO; BCVA before the DEX implant and at 2, 6 12, 18 and 24 months; any form of additional treatment (including further DEX implants, anti-VEGF injection, triamcinolone acetonide injection, macular laser, peripheral laser and vitrectomy); and the performance of cataract surgery during follow-up.

Outcome measures

Primary outcome measure was BCVA gain at 24 months after the first DEX implant and its clinical predictors. Secondary outcome measures were BCVA gain and CST after 2, 6, 12 and 18 months, the need for additional intravitreal therapy (further DEX implants, anti-VEGF or triamcinolone acetonide injections) and its predictors.

Statistical analysis

Difference in BCVA and CST from baseline was tested by Wilcoxon signed rank test. A linear regression model for continuous outcome measure (BCVA gain at 24 months) was run by testing the following confounding variables: (1) age, baseline (2) BCVA and (3) CST, (4) presence of diabetes, (5) previous treatment with intravitreal anti-VEGF prior to DEX, (6) duration of the disease, (7) lens status at 24 months (phakic vs pseudophakic), (8) need of cataract surgery, (9) BCVA gain ≥5 letters at 2 months after first DEX implant and (10) need for additional intravitreal therapy during follow-up. A logistic regression model for binary outcome measure (need for additional intravitreal therapy during follow-up) was run by testing the following confounding variables: (1) age, (2) BCVA>0.7 logMAR at baseline, (3) CST >400 µm at baseline, (4) presence of diabetes, (5) previous intravitreal anti-VEGF treatment and (6) BCVA gain ≥5 letters at 2 months after first DEX implant. Predictors with a p value ≤0.15 in univariate analysis were included in the final regression model. A backward selection procedure was applied that retained only those variables with p<0.05. To control for multiple testing, a Bonferroni correction was carried out, and the p value was adapted accordingly. The last observation carried forward method was used to impute missing data. Statistical analysis was performed with SPSS Statistics V.22.

Table 1 Baseline characteristics of 155 eyes with macular oedema due to retinal vein occlusion treated with dexamethasone (DEX)

	All eyes (n=155)	CRVO (n=65)	BRVO (n=90)
Age, years, mean±SD (range)	64.4±12.4 (30–87)	62.4±13.9 (30–87)	65.8±11.2 (37–86)
Male gender, n (%)	85 (54.8)	42 (64.6)	43 (47.8)
Duration of disease, months, mean±SD (range)	8.9±10.5 (0–72) n=148	7.5±8.9 (0–36) n=63	10.0±11.4 (0–72) n=85
Presence of diabetes mellitus, n (%)	51/150 (34.0)	29/64 (45.3)	22/86 (25.6)
Presence of hypertension, n (%)	89/150 (59.3)	35/64 (54.7)	54/86 (62.8)
Previous treatment			
Anti-VEGF injections, n (%)	105/154 (68.2)	43 (66.2)	62/89 (69.7)
Grid laser, n (%)	25/132 (18.9)	9/55 (16.4)	16/77 (20.8)
No. of previous anti-VEGF injections, mean±SD (range)	5.0±4.9 (1–27) n=105	4.9±4.3 (1–23) n=43	5.1±5.3 (1–27) n=62
Baseline BCVA, logMAR, mean±SD (range)	0.52±0.35 (-0.06–1.50)	0.56±0.35 (0.00–1.50)	0.50±0.35 (-0.06–1.50)
CST at baseline, µm, mean±SD (range)	576±217 (260–1648), n=153	679±248 (268–1648), n=64	501±155 (260–1144) n=89
Pseudophakia at baseline, n (%)	26/153 (17.0)	6 (9.2)	20/88 (22.7)

BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CST, central subfield thickness; VEGF, vascular endothelial growth factor.

RESULTS

The study included 155 eyes from 155 patients. Demographic and baseline characteristics are shown in table 1. The mean age was 64.4±12.4 years (range: 30–87 years), and 54.8% were male. Sixty-five eyes (41.9%) were diagnosed with CRVO, and 90 eyes (58.1%) were diagnosed with BRVO. At baseline, overall mean BCVA was 0.52±0.35 logMAR and mean CST was 576±217 µm.

Functional outcome

Mean BCVA change in CRVO eyes was 10.5±17.8 letters at 2 months (from baseline: p<0.001), 3.4±22.5 letters at 12 months (from baseline: p=0.02) and −2.1±24.5 letters at 24 months (from baseline: p=0.96). BRVO eyes gained 8.5±14.9 letters at 2 months (from baseline: p<0.001), 3.3±19.1 letters at 12 months (from baseline: p=0.05) and 1.3±27.0 letters at 24 months (from baseline: p=0.07). The change in visual acuity is shown in figure 1A and table 2.

Multivariate analysis revealed that a worse baseline BCVA was correlated with a greater final BCVA gain (p<0.001, unstandardized coefficent: 0.46, 95% confidence interval: 0.25 - 0.68) Table 3). Furthermore, patients that gained ≥5 letters at 2 months (p=0.006) and those who did not need additional intravitreal therapy during follow-up (p=0.001) showed a greater BCVA gain after 24 months. In CRVO eyes, pretreatment with anti-VEGF was associated with a reduced BCVA gain (p=0.006).

VA gain at 2 months as predictor for visual outcome

Changes in BCVA after stratifying for subgroups according to the VA gain after 2 months are shown in figure 1B. Of 67 patients

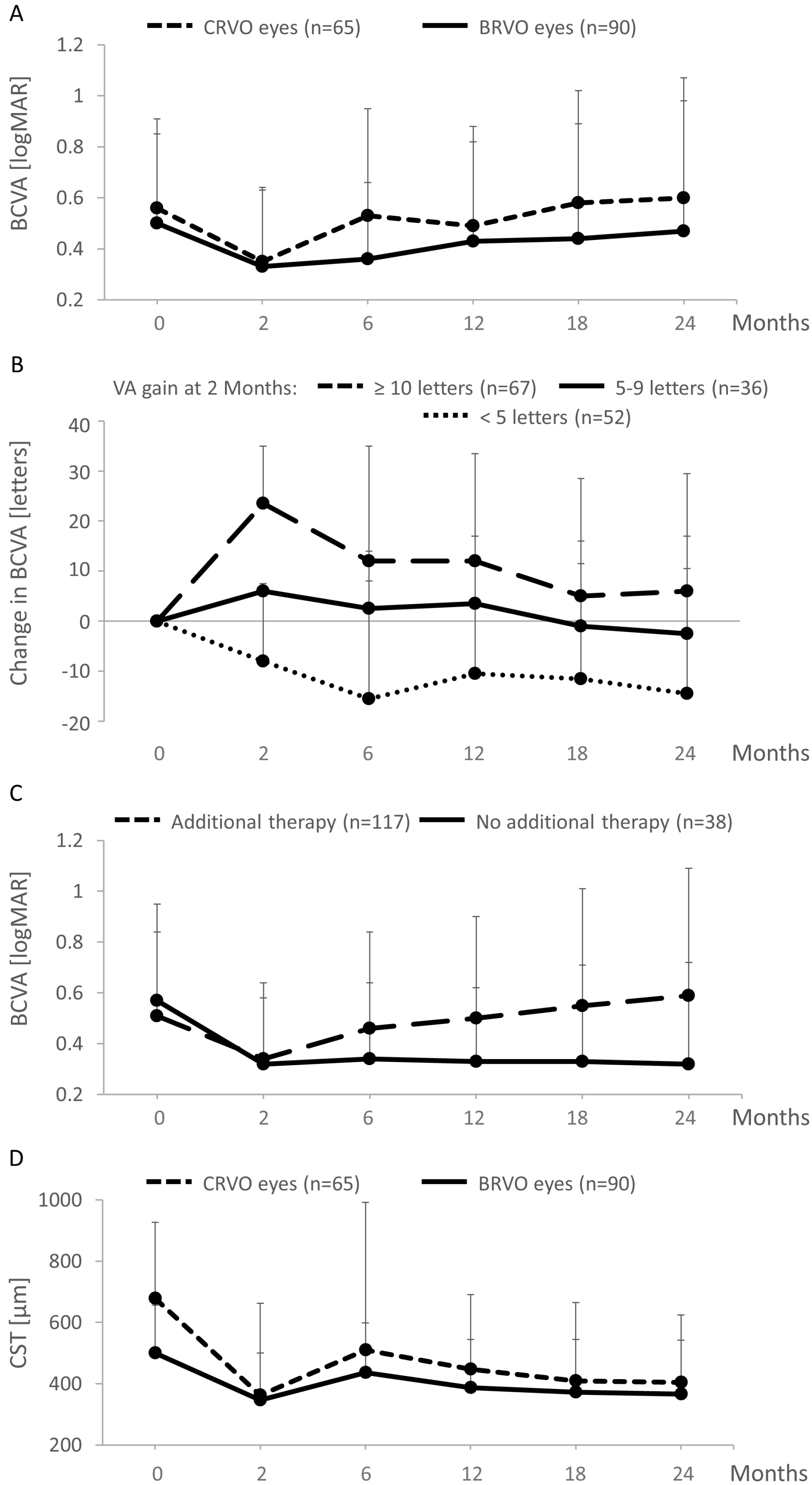

Figure 1 (A) Mean BCVA in CRVO patients and BRVO patients. (B) Change in BCVA stratified for BCVA gain after 2 months. (C) Mean BCVA in patients with and without additional intravitreal therapy during follow-up. (D) Mean CST in CRVO patients and BRVO patients. Values are mean±SD. BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CST, central subfield thickness.

Table 2 BCVA change from baseline in all eyes (n=155) and stratified for CRVO (n=65) and BRVO (n=90)

	All eyes (n=155)	CRVO (n=65)	BRVO (n=90)
BCVA change at 2 months, n (%)			
≥15 letters	51 (32.9)	25 (38.5)	26 (28.9)
≥10 letters	67 (43.2)	32 (49.2)	35 (38.9)
5–9 letters	36 (23.2)	13 (20.0)	23 (25.6)
<5 letters	52 (33.5)	20 (30.8)	32 (35.6)
BCVA loss ≥5 letters at 2 months, n (%)	19 (12.3)	7 (10.8)	12 (13.3)
BCVA gain at 24 months, n (%)			
≥15 letters	33 (21.3)	10 (15.4)	23 (25.6)
≥10 letters	55 (35.5)	21 (32.3)	34 (37.8)
5–9 letters	28 (18.1)	13 (20.0)	15 (16.7)
<5 letters	72 (46.5)	31 (47.7)	41 (45.6)
BCVA loss ≥5 letters at 24 months, n (%)	52 (33.5)	24 (36.9)	28 (31.1)

BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

who gained ≥10 letters at 2 months, 37 patients (55.2%) presented with a VA gain ≥10 letters at 24 months. Accordingly, patients that gained ≥10 letters after 2 months were significantly more likely to show a gain of ≥10 letters also after 24 months ($p<0.001$, OR: 4.81, 95% CI 2.36 to 9.71).

In contrast, 34 out of 52 patients (65.4%) who gained <5 letters after 2 months remained non-responsive (VA gain <5 letters) through the follow-up. Accordingly, patients that gained <5 letters initially were more likely to present with a VA gain of <5 letters also after 24 months ($p=0.001$, OR: 3.23, 95% CI 1.61 to 6.49).

Table 3 Predictors for BCVA gain at 24 months in RVO eyes (n=155) and stratified for CRVO (n=65) and BRVO (n=90), multivariate analysis

	All eyes (n=155) p values	CRVO (n=65) p values	BRVO (n=90) p values
Age	–	–	0.17
Baseline BCVA	**<0.001**	**0.001**	**0.001**
Baseline CST	–	–	–
Presence of diabetes	0.09	0.18	–
Previous treatment with anti-VEGF	0.16	**0.006**	–
Duration of disease	–	–	–
Lens status at 24 months (phakic vs pseudophakic)	–	–-	–
Cataract surgery during F/U	–	–	–
BCVA gain ≥5 letters at 2 months after first DEX implant	**0.006**	0.24	0.02
Need of additional intravitreal therapy within follow-up	**0.001**	–	**0.002**

Predictors with a p value>0.15 in univariate analysis were not included in final multivariate model (–). P value of <0.01 considered as statistical significant (Bonferroni correction).
BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CST, central subfield thickness; DEX, dexamethasone; F/U, follow-Up; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor.

Table 4 Additional therapy within 24 months follow-up, n=155 eyes

Eyes with additional therapy within **1st year** of follow-up, n (%)	125/155 (80.6)
Anti-VEGF injection	49/125 (39.2)
Further DEX implant	76/125 (60.8)
Triamcinolone acetonide	9/125 (7.2)
Focal laser	22/125 (17.6)
Peripheral laser	29/125 (23.2)
PPV+ILM-Peeling	3/125 (2.4)
No. of additional intravitreal injections after first DEX implant within **1st year** of follow-up, mean±SD (range).	
Anti-VEGF	3.0±1.9 (1–7)
DEX implant	1.4±0.6 (1–4)
Triamcinolone acetonide	1.1±0.4 (1–2)
Eyes with additional therapy within **2nd year** of follow-up, n (%)	102/155 (65.8)
Anti-VEGF injection	51/102 (50.0)
Further DEX implant	61/102 (59.8)
Triamcinolone acetonide	5/102 (4.9)
Focal laser	13/102 (12.7)
Peripheral laser	25/102 (24.5)
PPV+ILM-Peeling	0/102 (0)
No. of additional intravitreal injections within **2nd year** of follow-up, mean±SD (range)	
Anti-VEGF	3.5±1.6 (1–10)
DEX implant	1.6±0.7 (1–4)
Triamcinolone acetonide	1.0±0.0 (1–1)
Eyes underwent cataract surgery within 24 months follow-up, n (%), n=127	35/127 (27.6)

DEX, dexamethasone; ILM, inner limiting membrane; PPV, pars plana vitrectomy; VEGF, vascular endothelial growth factor.

Need for additional intravitreal therapy and its predictors

Eighty-one per cent of the patients (125 eyes) required additional therapy in year 1 and 66% (102 eyes) in year 2. Details of additional therapy required during the follow-up period are shown in table 4. Thirty-eight eyes (24.5%) did not require any further intravitreal injections after first DEX implant. Patients without additional intravitreal therapy during follow-up presented with a significant better visual outcome than those who required further intravitreal injections (BCVA gain at 24 months: 12.8±22.3 vs -4.3±25.8 letters, $p=0.001$, figure 1C). Multivariate analysis revealed that treatment-naïve patients ($p=0.006$, OR: 0.25, 95% CI 0.11 to 0.57) and those with baseline CST≤400 µm ($p=0.02$, OR: 0.25, 95% CI 0.10 to 0.63) were less likely to need further intravitreal injections after first DEX implant.

Anatomical outcome

Mean baseline CST was 679±248 µm in CRVO patients and 501±155 µm in BRVO patients. In CRVO eyes, CST was reduced to 448±243 µm after 12 months (from baseline: $p<0.001$) and to 408±219 µm after 24 months (from baseline: $p<0.001$). In BRVO eyes, CST was significantly reduced to 387±158 µm after 12 months (from baseline: $p<0.001$) and to 362±174 µm after 24 months (from baseline: $p<0.001$). Changes in CST are shown in figure 1D.

DISCUSSION

This multinational, real-world study describes the functional and anatomical outcome in patients with MO secondary to RVO treated with DEX implant. At 24 months, mean BCVA did not improve significantly for the whole cohort of CRVO and BRVO eyes. However, one-third of the patients gained ≥10 letters at 24 months. We identified, a worse BCVA at baseline, VA gain ≥5 letters at 2 months and no need of additional intravitreal therapy after first DEX implant as predictive for a greater BCVA gain. Treatment-naïve patients and those with a baseline CST ≤400 µm were less likely to require additional intravitreal therapy after first DEX implant.

Real-world data on long-term functional outcome in patients with MO secondary to RVO treated by DEX implant have thus far been limited. The LOUVRE study reported a significant improvement of 4.8 letters in RVO eyes treated with DEX implant after 24 months.[10] The better outcome reported in this trial compared with our results might be explained by its prospective design and a discontinuation rate of 26%, among others due to lack of treatment efficacy.[10] In our study, only patients with a follow-up of 24 months were included. However, in the real world, patients with a good treatment response without need for further therapy are less likely to be followed up for such a long period. Our study might have selected patients with comparatively worse treatment response with need for retreatment and therefore longer follow-up. This might also explain the lower rate of patients with a BCVA gain ≥15 letters after 24 months in our study (21.3%) compared with LOUVRE study (38.7%), while the rate of patients with BCVA gain ≥15 letters after 6 months was similar in both studies (32.9% vs 31.3% in LOUVRE).[10] Furthermore, data on anatomical outcomes in our study demonstrated that a proportion of the patients might have been undertreated, reflecting the scenario in the real-world setting.

The final change in BCVA ranged from −1.12 to 2.90 logMAR among our patients. That the long-term outcome in RVO eyes treated with DEX implant is characterised by a certain diversity was already revealed by previous reports.[10,11] Thus, we aimed to identify clinical predictors for the functional outcome in patients treated in a real-world setting. To our best knowledge, clinical predictors for visual outcome in patients with MO secondary to RVO treated by DEX implant have not been investigated before. We identified that baseline BCVA is correlated with BCVA gain after 24 months, which is in agreement with previous reports on patients treated with intravitreal anti-VEGF.[12,13]

Similarly, our study demonstrated that the early treatment response to DEX implant was predictive for the final functional outcome. This has also been demonstrated in previous studies of patients treated with anti-VEGF.[14] In our study, patients with a BCVA gain ≥10 letters at 2 months were five times more likely to show a BCVA gain of ≥10 letters also at 24 months. However, 45% of these patients converted to non-good responder during the follow-up. Unfortunately, due to limitations in sample size in this subgroup, our study was not powerful enough to further analyse characteristics of this subgroup and to assess for clinical predictors for the conversion of an initial good responder. Future studies with larger cohorts are required to address this issue.

Patients who did not need any additional intravitreal therapy after first DEX implantation presented with a greater BCVA gain compared with those that required further intravitreal therapy, confirming a previous report.[10] Since our study was of a retrospective nature, the decision whether and what kind of additional therapy a patient needed was made by the clinicians without predefined protocol. Retreatment criteria in clinical practice among the study sites included persistence (CST >250 µm in SD-OCT) or any recurrence of MO. DEX implant retreatment was carried out every 4–6 months, and anti-VEGF injections as pro re nata regimen. Switching to anti-VEGF therapy was routinely considered in case of no CST improvement 1–3 months after DEX implant. Patients who did not require any additional intravitreal therapy showed a marked BCVA improvement at 2 months, which remained stable during the entire follow-up. Patients who had prior anti-VEGF treatment and presented with a CST >400 µm at baseline were four times more likely to require further additional therapy after the first DEX implant. A better understanding of predictors for the need of additional therapy might help to identify these patients at early stage and to adapt follow-up regimens.

Limitations of this study include its retrospective nature and shortcomings of the real-world setting. Even though development of cataract is a known side effect after therapy with intraocular steroids and might compromise functional outcome,[7,8] cataract progression was not included as an outcome measure in this study due to the variability in cataract grading. Furthermore, evaluation of central and peripheral retinal perfusion and morphological characteristics in OCT or OCT angiography as possible anatomical predictors were not included in our study. Central and peripheral perfusion status could prove as being helpful to predict long-term outcome and need of additional therapy in RVO patients treated with DEX implant and might help to understand why a patient convert to a non-responder during the long-term follow-up. Future studies are needed to analyse the predictive value of those anatomical characteristics for functional outcome after treatment with DEX implant, as has been demonstrated in RVO patients treated with anti-VEGF.[15–19]

In conclusion, we described the functional long-term outcomes in a large cohort of patients with MO secondary to RVO in a real-world setting. In this study, baseline characteristics and early treatment response are useful predictors of final visual outcome and patient's need for adjunctive intravitreal therapy. These new findings could help provide details of visual prognosis and treatment course for an individual patient and to help in early identification of patients with likely poor treatment response to DEX implant.

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