Ophthalmology Clinics & Research
OCR, 2(1): 48-63
www.scitcentral.com

ISSN: 2638-115X

Original Research Article: Open Access

Retinal Function and Structure after Intravitreal Injections in Patients with Macular Edema Following Central Retinal Vein Occlusion in Clinical Practice

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Received April 20, 2019; Accepted April 27, 2019; Published April 28, 2019

ABSTRACT

Purpose: To investigate the clinical and electrophysiological effects of serial intravitreal injections of dexamethasone implant and aflibercept for macular edema after central retinal vein occlusion (CRVO).

Methods: Fifteen patients with macular edema after CRVO were examined with full-field electroretinography (ERG) within 1 month of symptom onset and 2 and 12 months after the start of treatment. They were divided into a non-ischemic and an ischemic CRVO group. All the CRVO patients had undergone clinical ophthalmological examination at the CRVO debut, monthly for 6 months and then every second month for 18 months.

The primary outcome measures were the change in the retinal function 2 and 12 months after treatment. Secondary outcome measures included best corrected visual acuity, intraocular pressure, central foveal thickness (CFT) and the presence of neovascular glaucoma (NVG).

Results: Of the 15 patients, 4 (27%) had non-ischemic and 11 (73%) had ischemic CRVO. A significant reduction in CFT, compared with baseline values, was observed in the whole group of CRVO patients at 2, 12 and 24 months (p=0.001, 0.017 and 0.022, respectively). A significant decrease in b-wave amplitudes of combined rod-cone response and of single-flash cone response of the full-field ERG was observed 12 months after treatment, while the reduction in the b-wave amplitudes of 30 Hz flicker response of the full-field ERG was significant compared with baseline values in all studied CRVO patients at both 2 and 12 months (p=0.046, 0.008, 0.021 and 0.030, respectively). Three of the eleven patients with ischemic CRVO (27%) developed NVG, on average, 18 months after CRVO debut.

Conclusion: This study revealed a decrease in retinal function at 12 months in CRVO patients undergoing serial intravitreal injections for macular edema after CRVO. The treatment did not prevent the development of NVG in ischemic CRVO.

Keywords: Central retinal vein occlusion, Intravitreal injections, Full-field electroretinography, Retinal function

INTRODUCTION

Central retinal vein occlusion (CRVO) is a common sight-threatening retinal vascular disease in the elderly. CRVO affects 0.8 per 1000 persons and the incidence increases significantly with age [1]. Systemic hypertension and vascular disease are important risk factors for CRVO in patients older than 50 years [2]. Further risk factors for CRVO have been found to be diabetes mellitus, hyperlipidemia, black race, male sex, diagnosis of stroke, blood hyper viscosity and thrombophilia. Ophthalmic risk factors for CRVO have also been reported, including ocular hypertension, glaucoma and changes in the retinal arteries [2,3].

Studies on the natural visual outcome of CRVO have shown the major causes of vision loss to be macular edema and neovascularization with secondary neovascular glaucoma (NVG) and/or vitreous hemorrhages [4-6]. CRVO can be divided into non-ischemic and ischemic types. The risk of neovascular complications in patients with CRVO is related to the extent of retinal capillary non-perfusion, which can be evaluated with fluorescein angiography (FA) [7-9] and full-field electroretinography (full-field ERG). The cone b-wave implicit times, in both photopic and scotopic 30 Hz flicker ERG have been found to be significantly correlated with the degree of retinal ischemia [10-14], as well as with the concentration of vascular endothelial growth factor (VEGF) in the aqueous humor of CRVO eyes [15].

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Citation: Wittström E, Meinert M & Samuelsson D. (2019) Retinal Function and Structure after Intravitreal Injections in Patients with Macular Edema Following Central Retinal Vein Occlusion in Clinical Practice. Ophthalmol Clin Res, 2(1): 48-63.

An evidence-based systemic study on clinical course of CRVO showed that untreated CRVO eyes, including non-ischemic CRVO, had poor visual acuity, which declined further over time. One third of eyes with non-ischemic CRVO became ischemic over a 3 year period, while in 30% of the non-ischemic CRVO eyes macular edema resolved and NVG was rare. In ischemic CRVO eyes, NVG developed in at least 23% of the eyes within 10 months and ischemic CRVO cases had poor baseline and final vision [16].

VEGF is a hypoxia-inducible angiogenic peptide; a potent growth factor for vascular endothelial cells, which promotes neovascularization and increases vascular permeability in patients with ischemic retinal diseases [17-21]. Anti-VEGF therapy at an early stage of retinal disease has been shown to be beneficial for visual recovery [19-21]. Retinal ischemia and vascular damage in CRVO eyes result in a breakdown of the inner blood-retinal barrier and disruption of this barrier is associated with complex cellular processes that lead to the release of angiogenic and inflammatory cytokines [22]. These cytokines have been found to be overexpressed in the aqueous humor or vitreous fluid of CRVO eyes [23-27]. Both anti-VEGF-therapy and treatment with intravitreal corticosteroid-based agents have been found to be effective in reducing the intraocular level of cytokines and in the reduction of macular edema due to CRVO [25-27].

Since 2010, intravitreal anti-VEGF agents, such as ranibizumab, bevacizumab and recently aflibercept and corticosteroid-based agents, such as dexamethasone and preservative-free triamcinolone, have been used for the treatment of macular edema-associated with CRVO and replaced the recommendations of the Central Retinal Vein Occlusion Study (CVOS) [28,29]. Three large prospective randomized controlled studies on the treatment of macular edema after CRVO (CRUISE, GALILEO and COPERNICUS) have demonstrated that repeated intravitreal injections of ranibizumab (in the CRUISE study) and aflibercept (in the GALILEO and COPERNICUS studies) improved visual and anatomic outcomes at follow-up compared to observation [30-33].

Anti-VEGF intravitreal injections were generally well tolerated and their use quickly replaced standard of care for CRVO-associated macular edema recommended by CVOS [28,29,34-36]. However, long-term results from the extension studies for CRUISE, COPERNICUS and GALILEO demonstrated a decline in visual and anatomic improvements in CRVO eyes when CRVO patients were monitored at least every 3 months and treated with fewer anti-VEGF injections [37-39]. Corticosteroid-based intravitreal injections for the treatment of macular edema-associated with CRVO, including the dexamethasone implant and triamcinolone acetonide used as off-label agent, decrease macular edema in CRVO eyes in the same way as anti-VEGF agents, by reducing vascular permeability, downregulating inflammatory mediators and inhibiting VEGF [40,41]. In the SCORE and GENEVA studies it has been found that intravitreal injections of corticosteroids for the treatment of macular edema associated with CRVO were superior to observation regarding visual and anatomical improvements in CRVO eyes [40-42]. Long-term visual and anatomical outcomes have been reported to be similar to those with dexamethasone implants and anti-VEGF agents in CRVO eyes treated for macular edema [43]. However, intravitreal corticosteroid treatment has been associated with a higher frequency of adverse effects, including the elevation of intraocular pressure (IOP) and cataract formation or progression [35,40,43-47].

It has been suggested that anti-VEGF therapy may not only reduce macular edema in CRVO eyes and improve vision, but may also prevent the deterioration of retinal perfusion and promote reperfusion [48-51]. In contrast, the SCORE study and post hoc analysis of the pooled data from the GENEVA study showed that intravitreal corticosteroid treatment was not associated with lower incidences of neovascular events or less global (peripheral and macular) non-perfusion compared with observation. The area of global non-perfusion increased from baseline to the end of the studies and was similar in treated and untreated eyes [52,53]. Using wide-field FA (WFFA), it has been shown that the area of peripheral retinal non-perfusion may vary in CRVO eyes and may affect the clinical course and the response to treatment of these eyes [54]. Wykoff et al. [55] performed serial WFFA on 12 ischemic CRVO eyes over a period of 3 years. All eyes demonstrated extensive areas of retinal peripheral non-perfusion at baseline, and the area of retinal non-perfusion increased in all eyes during treatment with ranibizumab, with a mean loss of approximately 8.1% of the perfused retinal area per year.

The Rubeosis Anti-VEGF (RAVE) study [56] and two retrospective studies [57,58] on neovascular events in eyes with CRVO treated with anti-VEGF showed that anti-VEGF therapy could improve retinal anatomy and vision in eyes with ischemic CRVO, but it did not prevent ocular neovascularization.

Quantifying the extent of global retinal non-perfusion in patients with CRVO using FA or WFFA is very difficult and very subjective and an electrophysiological method such as full-field ERG may be a more appropriate, objective method for the evaluation of the total retinal function before and after anti-VEGF or intravitreal corticosteroid therapy for macular edema associated with CRVO. Only a few studies have been performed to evaluate the retinal function before and after intravitreal treatment of CRVO patients using full-field ERG [59,60].

The aim of this prospective study was thus to evaluate the retinal function and structure in patients with macular edema due to non-ischemic and ischemic CRVO, using full-field

ERG and optical coherence tomography (OCT), before and after serial intravitreal injections.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of Lund University and all participants gave their written informed consent according to the principles outlined in the Universal Declaration of Helsinki.

Fifteen patients with macular edema secondary to CRVO who were examined with full-field ERG within 1 month of symptom onset and treated with intravitreal injections (dexamethasone implant and aflibercept) were included in this study. They were also examined with full-field ERG 2 and 12 months after the start of the intravitreal treatment. Patients with glaucoma, ocular inflammation or cloudy media due to cataract, keratopathy or vitreous hemorrhage were excluded. The patients were divided into two groups: a non-ischemic (n=4) and an ischemic CRVO group (n=11). Two patients in the ischemic CRVO group did not undergo full-field ERG at 12 months; one because of death (not related to the intravitreal treatment) and the other refused to undergo full-field ERG but completed all other tests at 12 months. All 15 patients received one intravitreal dexamethasone implant injection at the beginning of the study, after which they had the possibility to switch to aflibercept or continue with dexamethasone. Only three patients continued with dexamethasone treatment (two of them had two intravitreal dexamethasone implant injections and one of them had five intravitreal dexamethasone implant injections before changing to aflibercept).

CRVO was classified as non-ischemic if the cone b-wave implicit time in the 30 Hz flicker ERG was ≤ 37 ms and as ischemic if the cone b-wave implicit time was >37 ms [11]. Visual and ophthalmoscopic findings and capillary non perfusion findings on FA were also used to classify CRVO in the present study [7-10]. Macular edema was retreated if the best corrected visual acuity (BCVA) decreased by more than five ETDRS-letters and/or the central foveal thickness in OCT increased by more than 100 µm. Patients with 2 clock hours' iris neovascularization or any angle neovascularization and IOP greater than 22 mm Hg were defined as having NVG.

Ocular examination

All the CRVO patients had undergone clinical ophthalmological examination including BCVA, Early Treatment Diabetic Retunopathy Study (ETDRS-letters), measurement of IOP (Goldman applanation tonometry), slit-lamp examination, biomicroscopy, gonioscopy and OCT examination at the debut of CRVO and then monthly for 6 months, and thereafter every two months for 18 months.

Full-field electroretinography

Full-field electroretinograms were recorded with an Espion E2 analysis system (Diagnosys, LLC, Lowell, MA, USA) after the pupil had been dilated with topical 1% cyclopentolate and 10% phenylephrine, and the subject's eyes had been dark-adapted for 40 min. After topical anesthesia of the eye, a Burian-Allen bipolar contact lens was applied to the cornea, and the ground electrode to the forehead. Responses were obtained with a wide-band filter (-3 dB at 1 Hz and 500 Hz), while stimulating with brief (30 µs) full-field flashes of dim blue light (0.0045 cd•s/m^2) to elicit rod response and with white light (3 cd•s/m^2) to elicit the combined rod-cone response. Cone responses were obtained with 30 Hz flickering white light (3 cd•s/m^2) averaged over 20 sweeps and single-flash white light (3 cd•s/m^2). The background luminance was 30 cd/m^2. The recording procedures were the same as those prescribed in the standard protocol for clinical electroretinography recommended by the International Society for Clinical Electrophysiology of Vision (ISCEV) [61].

Optical coherence tomography

OCT was performed using the spectral domain 3D OCT-1000, version 3.00 software (Topcon, Tokyo, Japan). The 3D macular scan option was used in all scans in this study, centered on the fovea, covering 6 × 6 mm, with a resolution of 512 × 128, creating an image of the whole macular area. The fast macular thickness scan protocol was used. The central foveal thickness (CFT) was used in the analysis. The macular thickness measurements are given as numerical values (µm).

The primary outcome measures were the change in the total retinal function at 2 and 12 months after treatment, as demonstrated by full-field ERG and the secondary outcome measures were BCVA, IOP, CFT and presence of NVG.

Treatment procedure

All 15 patients received the initial intravitreal dexamethasone implant injections (Ozurdex, Allergan; Inc., Irvine, CA, USA) via the pars plana under sterile conditions. The patients were then allowed to change to 2 mg intravitreal aflibercept injections (Bayer, Healthcare Pharmaceuticals, Berlin, Germany) or continue with dexamethasone implant injections as needed.

STATISTICAL ANALYSIS

The data were analyzed using SPSS version 21 (SPSS Inc., Chicago, IL, USA). The Wilcoxon signed-rank test was used to determine whether significant changes had occurred between baseline, 2 and 12 months and the final examination within each CRVO group and the Mann-Whitney U-test was used to compare ordinal parameters between the two study groups. Categorical variables were compared between the two study groups using Fisher's exact test. Values of $p \leq 0.05$ were considered to show statistical significance.

RESULTS

Of the 15 patients studied 4 (27%) had non-ischemic CRVO and 11 (73%) had ischemic CRVO. No significant difference was observed between the non-ischemic and ischemic CRVO groups regarding sex, age, time from CRVO debut to treatment, follow-up period, number of dexamethasone implant or aflibercept injections, ocular complications or lens status **(Table 1)**.

Table 1. Clinical characteristics of CRVO patients treated with intravitreal injections for macular edema.

Parameters	CRVO Total (n=15)	Non-ischemic CRVO (n=4)	Ischemic CRVO (n=11)	p
Sex				
Male	10/15 (67%)	4/4 (100%)	6/11 (55%)	0.231
Female	5/15 (33%)	0/4 (0%)	5/11 (45%)	
Age (years)				
Mean ± SD	70.1 ± 15.1	67.0 ± 2.0	71.4 ± 18.0	0.056
Time from CRVO-debut to treatment (months)				
Mean ± SD	2.7 ± 2.0	2.1 ± 2.0	3.0 ± 2.0	0.343
Follow-up period (months)				
Mean ± SD	24.1 ± 12.1	27.0 ± 10.0	23.2 ± 13.1	0.661
Number of injections (Mean ± SD)				
Dexamethasone	1.4 ± 1.1	1.0 ± 0.0	1.6 ± 1.2	0.489
Aflibercept	2.8 ± 3.0	4.3 ± 3.1	2.3 ± 2.2	0.280
Ocular complications (Mean ± SD)				
Ocular hypertension	7/15 (47%)	3/4 (75%)	4/11 (36%)	0.475
NVG	3/15 (20%)	0/4 (0%)	3/11 (27%)	
Lens status (Mean ± SD)				
Phakic	11/15 (73%)	3/4 (75%)	8/11 (73%)	1.000
Pseudophakic	4/15 (27%)	1/4 (25%)	3/11 (27%)	
Cataract formation	4/15 (27%)	1/4 (25%)	3/11 (37%)	

Abbreviations: CRVO: Central Retinal Vein Occlusion; SD: Standard Deviation; NVG: Neovascular Glaucoma

Analysis of the whole group of CRVO patients

A significant improvement in BCVA (ETDRS-letters) was observed, from 46.0 ± 17.0 letters to 60.0 ± 20.4 letters (p=0.001) 2 months after the intravitreal injections. The mean BCVA decreased at 12 months to 45.0 ± 28 letters (p=0.789) and was almost unchanged, 45.0 ± 27.0 letters, 24 months after retreatments, compared with baseline (p=0.972) **(Figure 1 and Table 2)**. A significant increase in IOP was observed, from 19.0 ± 6.0 mm Hg at baseline to 23.0 ± 8.0 mm Hg (p=0.045) 2 months after the intravitreal injection. The mean IOP decreased both 12 and 24 months after treatment and there was no significant difference compared with baseline (p=0.893 and 0.953, respectively) **(Figure 2 and Table 2)**. The mean CFT decreased significantly, from 679.0 ± 166.2 µm at baseline to 284.0 ± 107.1 µm (p=0.001) 2 months after the intravitreal injection. A different but still significant improvement in CFT was also observed both 12 and 24 months after treatment, compared with baseline (p=0.017 and 0.022, respectively) **(Figure 3 and Table 2)**.

Table 2. Changes in VA, IOP and CFT before, 2 months, 12 months and at the final visit after intravitreal injections in eyes with CRVO.

Parameters	All CRVO subjects (n=15 at 2 months and n=14 at 12 months and final visit)						
	Baseline	2 months	p^1	12 months	p^2	Final visit	p^3
BCVA (ETDRS-letters) Mean ± SD	46.0 ± 17.0	60.0 ± 20.4	0.001*	45.0 ± 28.0	0.789	45.0 ± 27.0	0.972
IOP (mm Hg) Mean ± SD	19.0 ± 6.0	23.0 ± 8.0	0.045*	20.0 ± 7.0	0.893	20.0 ± 7.3	0.953
CFT (µm) Mean ± SD	679.0 ± 166.2	284.0 ± 107.1	0.001*	403.0 ± 375.0	0.017*	423.0 ± 378.0	0.022*
	Non-ischemic CRVO (n=4)						
BCVA (ETDRS-letters) Mean ± SD	58.0 ± 10.0	73.3 ± 4.0	0.068	70.0 ± 7.0	0.066	67.0 ± 12.0	0.144
IOP (mm Hg) Mean ± SD	19.0 ± 3.2	27.0 ± 8.0	0.109	16.0 ± 3.0	0.273	20.0 ± 2.1	0.593
CFT (µm) Mean ± SD	641.0 ± 70.0	221.3 ± 49.0	0.068	252.0 ± 55.0	0.068	245.3 ± 42.3	0.068
	Ischemic CRVO (n=11 at 2 months and 10 at 12 months and at the final visit)						
BCVA (ETDRS-letters) Mean ± SD	44.4 ± 17.0	55.1 ± 22.0	0.007*	35.0 ± 26.4	0.236	37.4 ± 27.0	0.514
IOP (mm Hg) Mean ± SD	18.4 ± 6.2	22.1 ± 8.0	0.154	21.3 ± 8.1	0.307	18.1 ± 9.0	0.752
CFT (µm) Mean ± SD	692.2 ± 191.0	307.0 ± 115.0	0.003*	463.0 ± 433.2	0.083	493.4 ± 431.2	0.114

*Notes: $p^{1, 2, 3}$, p-values (Wilcoxon signed-rank test (baseline vs. 2 months, 12 months and the final visit, respectively); *, denotes statistical significance*

Abbreviations: BCVA: Best Corrected Visual Acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; IOP: Intraocular Pressure; CFT: Central Foveal Thickness; CRVO: Central Retinal Vein Occlusion

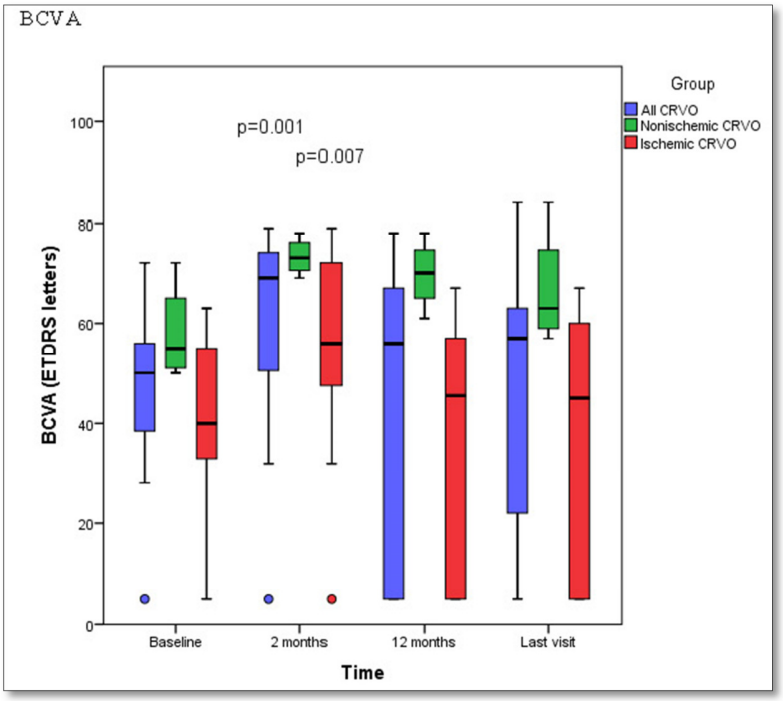

Figure 1. Best corrected visual acuity (BCVA) for the whole group of central retinal vein occlusion (CRVO) patients, and the non-ischemic and ischemic CRVO group.
Note: Box plots showing BCVA, Early Treatment Diabetic Retinopathy Study (ETDRS-letters), at baseline, 2 months, 12 months and final visit after treatment.

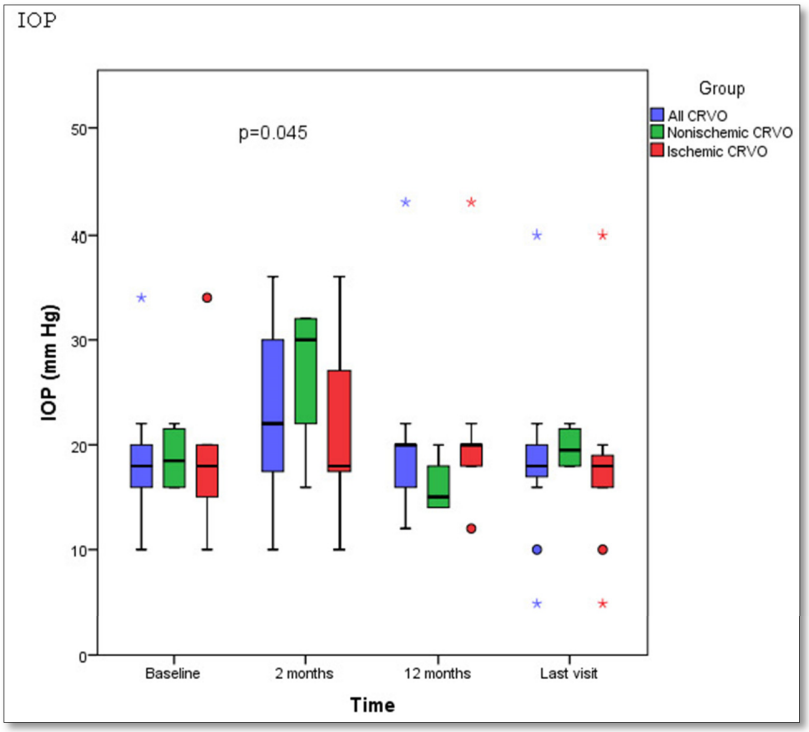

Figure 2. Intraocular pressure (IOP) for the whole group of central retinal vein occlusion (CRVO) patients, and the non-ischemic and ischemic CRVO group.
Note: Box plots showing IOP (mm Hg) at baseline, 2 months, 12 months and at final visit after treatment.

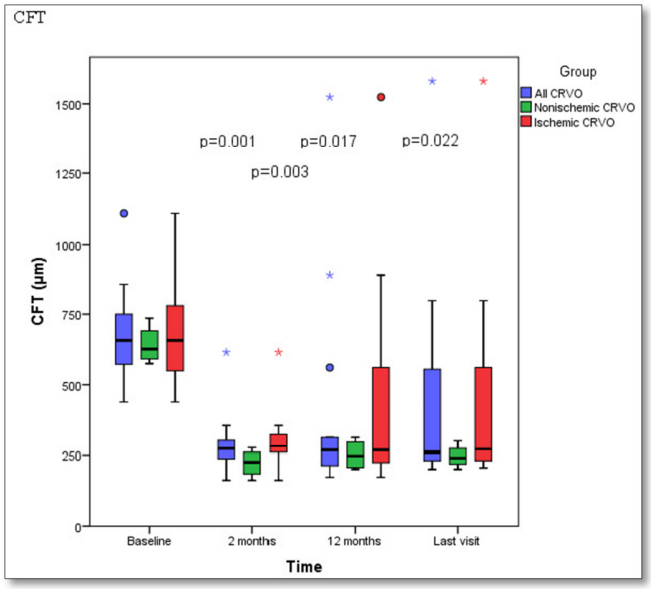

Figure 3. Central foveal thickness (CFT) for the whole group of central retinal vein occlusion (CRVO) patients, and the non-ischemic and ischemic CRVO group.
Note: Box plots showing CFT (µm) at baseline, 2 months, 12 months and at final visit after treatment.

The changes in full-field ERG response for the whole group of CRVO patients during the study period are given in **Table 3**. The a- and b-wave amplitudes of combined rod-cone and single-flash response and the b-wave of rod and 30 Hz flicker response of the full-field ERG decreased both 2 and 12 months after treatment, compared with baseline values **(Figures 4-6 and Table 3)**. The b-wave amplitudes of combined rod-cone response and of single-flash cone response were significantly decreased 12 months after treatment, compared with baseline (p=0.046 and 0.008, respectively) **(Figures 4 and 5 and Table 3)**. The b-wave amplitudes of 30 Hz flicker response (cone response) decreased significantly in all CRVO patients studied, both 2 and 12 months after treatment, compared with baseline (p=0.021 and 0.030, respectively) **(Figure 6 and Table 3)**.

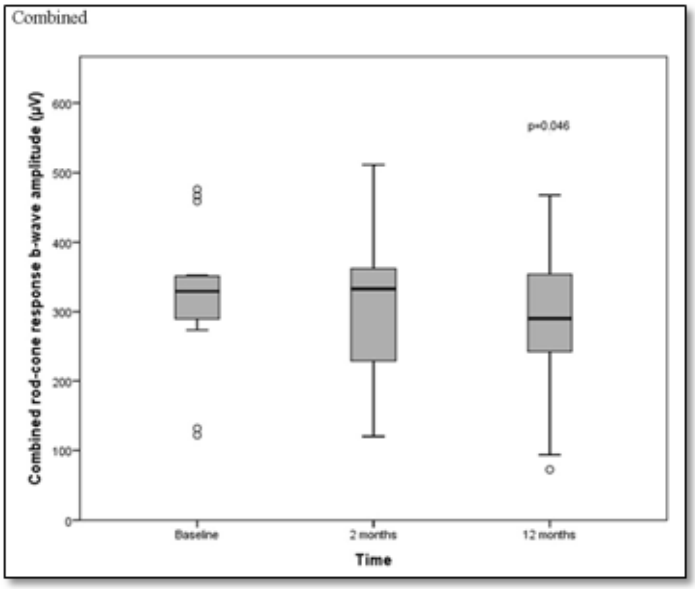

Figure 4. Mean b-wave amplitudes of combined rod-cone response of the full-field electroretinogram for the whole group of patients with central retinal vein occlusion.
Note: Box plots showing the mean b-wave amplitudes (µV) of combined rod-cone response of the full-field electroretinogram at baseline, 2 months and 12 months after treatment.

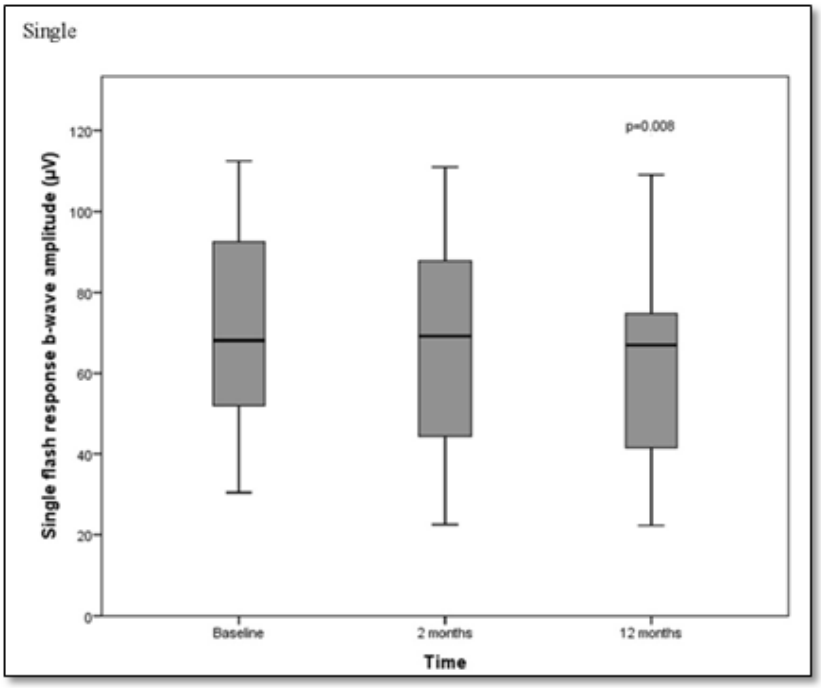

Figure 5. Mean b-wave amplitudes of single-flash response of the full-field electroretinogram for the whole group of patients with central retinal vein occlusion.
Note: Box plots showing the mean b-wave amplitudes (µV) of single-flash response of the full-field electroretinogram at baseline, 2 and 12 months after treatment.

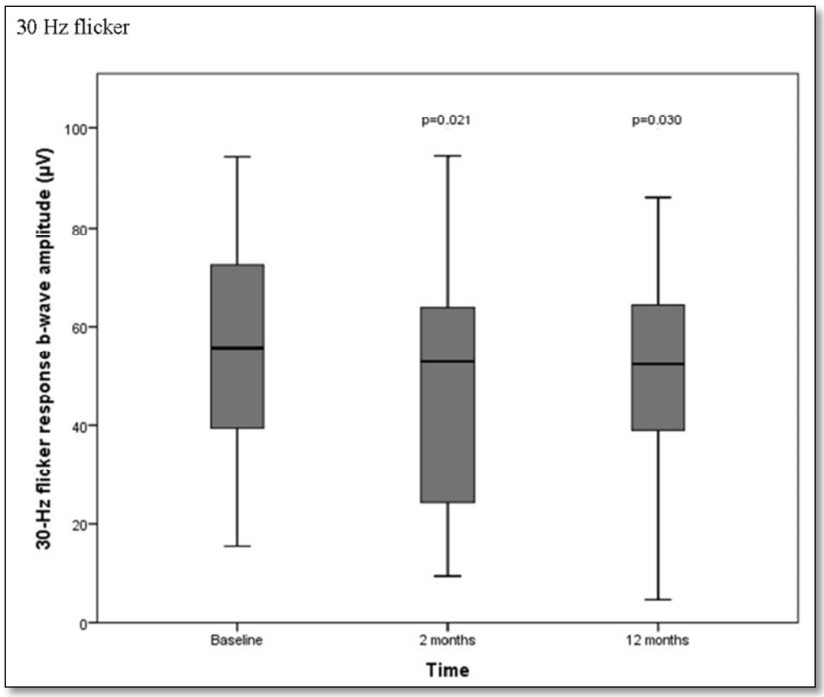

Figure 6. Mean b-wave amplitudes of 30 Hz flicker response of the full-field electroretinogram for the whole group of patients with central retinal vein occlusion.
Note: Box plots showing the mean b-wave amplitudes (µV) of 30 Hz flicker response of the full-field electroretinogram at baseline, 2 and 12 months after treatment.

Table 3. Results of full-field electroretinography (mean values ± SD: a- and b-wave amplitudes (µV) and implicit times (ms) at baseline, 2 and 12 months) in patients with macular edema due to CRVO treated with intravitreal injections

Parameters	Normal controls (n=10)	All CRVO subjects (n=15 at 2 months and n=13 at 12 months)				
		Baseline	2 months	p^1	12 months	p^2
Rod response						
b-wave amplitude	235.2 ± 47.4	147.3 ± 61.5	146.0 ± 89.3	0.460	122.2 ± 78.0	0.099
b-wave implicit time	65.0 ± 5.8	85.3 ± 10.1	85.0 ± 12.0	0.777	79.1 ± 13.0	0.230
Combined rod-cone response						
a-wave amplitude	208.8 ± 47.9	177.6 ± 53.3	171.9 ± 41.8	0.551	152.2 ± 57.4	0.328
a-wave implicit time	16.2 ± 1.7	23.6 ± 3.2	22.7 ± 3.9	0.189	23.6 ± 5.1	0.189
b-wave amplitude	391.0 ± 68.5	324.1 ± 102.4	306.0 ± 123.0	0.820	290.3 ± 116.2	0.046*
b-wave implicit time	46.7 ± 5.0	57.0 ± 6.1	55.1 ± 7.7	0.198	55.4 ± 8.4	0.345
Single-flash response (cone)						
a-wave amplitude	26.2 ± 10.3	23.8 ± 10.0	21.4 ± 7.2	0.272	18.0 ± 8.0	0.100
a-wave implicit time	14.4 ± 1.6	17.0 ± 1.8	17.0 ± 1.7	0.919	18.0 ± 3.6	0.532
b-wave amplitude	81.1 ± 14.1	70.0 ± 26.4	66.4 ± 27.5	0.177	61.0 ± 27.0	0.008*
b-wave implicit time	33.2 ± 1.8	38.0 ± 4.1	37.4 ± 4.5	0.899	40.6 ± 7.6	0.169
30 Hz flicker response (cone)						
b-wave amplitude	83.0 ± 22.0	56.0 ± 23.3	48.2 ± 26.0	0.021*	48.0 ± 25.0	0.030*
b-wave implicit time	28.2 ± 1.3	38.3 ± 3.0	37.2 ± 4.1	0.086	38.0 ± 25.0	0.480

*Notes: p^1, Wilcoxon signed-rank test (baseline vs. 2 months); p^2, Wilcoxon signed-rank test (baseline vs. 12 months); *, denotes statistical significance*
Abbreviation: CRVO: Central Retinal Vein Occlusion

Analysis of the group with non-ischemic CRVO

No significant improvement in BCVA was observed 2 months after treatment (73.3 ± 4.0 letters) compared with baseline values (58.0 ± 10.0 letters) (p=0.068) and the mean BCVA decreased slightly 12 and 24 months after treatment, compared with baseline values (p=0.066 and 0.144) **(Figure 1 and Table 2)**. No significant changes in IOP were observed during the whole study period, compared with baseline **(Figure 2 and Table 2)**. The mean CFT decreased from 641.0 ± 70 µm at baseline to 221.3 ± 49.0 µm 2 months after treatment and increased slightly at 12 and 24 months after treatment, compared with baseline values (p=0.068, 0.068 and 0.068, respectively) **(Figure 3 and Table 2)**.

The b-wave amplitudes of rod, combined rod-cone and 30 Hz flicker response of the full-field ERG increased 2 months after treatment, compared with baseline, but the increase did not reach statistical significance (p=0.460, 0.465 and 0.465, respectively) **(Table 4)**. In contrast, the b-wave amplitudes of rod, combined rod-cone and 30 Hz flicker response of the full-field ERG showed a decrease 12 months after treatment, compared with baseline, but the decrease did not reach statistical significance (p=0.099, 0.465 and 0.465, respectively) **(Table 4)**.

Table 4. Results of full-field electroretinography (mean values ± SD; a- and b-wave amplitudes (µV) and implicit times (ms) at baseline, 2 and 12 months) in patients with macular edema due to non-ischemic CRVO treated with intravitreal injections.

Parameters	Normal controls (n=10)	Non-ischemic CRVO (n=4)				
		Baseline	2 months	p^1	12 months	p^2
Rod response						
b-wave amplitude	235.2 ± 47.4	189.4 ± 46.1	229.1 ± 45.0	0.460	147.0 ± 74.0	0.099
b-wave implicit time	65.0 ± 5.8	80.6 ± 5.4	78.8 ± 7.2	0.777	78.0 ± 5.5	0.230
Combined rod-cone response						
a-wave amplitude	208.8 ± 47.9	206.0 ± 68.2	205.1 ± 38.0	1.000	191.5 ± 46.1	0.655
a-wave implicit time	16.2 ± 1.7	23.6 ± 5.1	20.6 ± 3.1	0.109	23.8 ± 2.5	0.655
b-wave amplitude	391.0 ± 68.5	393.0 ± 90.4	420.1 ± 79.0	0.465	344.5 ± 85.3	0.465
b-wave implicit time	46.7 ± 5.0	54.4 ± 3.1	52.8 ± 5.0	0.109	48.5 ± 7.0	0.068
Single-flash response (cone)						
a-wave amplitude	26.2 ± 10.3	31.7 ± 16.3	26.1 ± 2.3	0.285	23.6 ± 2.8	0.655
a-wave implicit time	14.4 ± 1.6	17.5 ± 0.5	15.8 ± 1.7	0.285	16.0 ± 2.1	0.655
b-wave amplitude	81.1 ± 14.1	82.0 ± 30.3	81.0 ± 21.6	0.593	85.0 ± 34.2	0.655
b-wave implicit time	33.2 ± 1.8	35.3 ± 1.5	35.4 ± 1.7	1.000	37.0 ± 3.5	0.655
30 Hz flicker response (cone)						
b-wave amplitude	83.0 ± 22.0	65.4 ± 23.0	68.1 ± 18.4	0.465	61.1 ± 17.3	0.465
b-wave implicit time	28.2 ± 1.3	35.2 ± 1.8	33.4 ± 2.0	0.068	35.0 ± 4.0	0.581

Notes: p^1, Wilcoxon signed-rank test (baseline vs. 2 months); p^2, Wilcoxon signed-rank test (baseline vs. 12 months)
Abbreviation: CRVO: Central Retinal Vein Occlusion

Analysis of the group with ischemic CRVO

A significant improvement was observed in BCVA, from 44.4 ± 17.0 letters at baseline to 55.1 ± 22.0 letters 2 months after the intravitreal injection, compared with baseline values (p=0.007) **(Table 2)**. No significant changes in IOP were observed at any point in time during the study, compared with baseline values **(Table 2)**. The mean BCVA decreased from 44.4 ± 17.0 letters at baseline to 35.0 ± 26.4 letters at 12 months and to 37.4 ± 27.0 letters at 24 months (p=0.236 and 0.514, respectively) **(Table 2)**.

The mean CFT decreased significantly, from 692 ± 191.0 µm at baseline to 307.0 ± 115.0 µm 2 months after the intravitreal injection (p=0.003). No significant improvement in CFT was observed after 12 or 24 months of treatment, compared with baseline (0.083 and 0.114, respectively) **(Table 2)**.

The a-wave and b-wave amplitudes of rod, combined rod-cone, single-flash and the b-wave amplitudes of 30 Hz flicker response of the full-field ERG decreased both 2 and 12 months after treatment, compared with baseline, but the decrease was only statistically significant for b-wave amplitudes of single-flash response 12 months after treatment, compared with baseline values (p=0.008) and for b-wave amplitudes of 30 Hz flicker response both 2 and 12 months after treatment, compared with baseline (p=0.006 and 0.033, respectively) **(Table 5)**.

Table 5. Results of full-field electroretinography (mean values ± SD: a- and b-wave amplitudes (μV) and implicit times (ms) at baseline, 2 and 12 months) in patients with macular edema due to ischemic CRVO treated with intravitreal injections.

Parameters	Normal controls (n=10)	Ischemic CRVO (n=11, n=9 at 12 months)				
		Baseline	2 months	p^1	12 months	p^2
Rod response						
b-wave amplitude	235.2 ± 47.4	132 ± 61.0	115.3 ± 82.3	0.929	114.0 ± 81.2	0.173
b-wave implicit time	65.0 ± 5.8	87.0 ± 11.2	87.4 ± 12.3	0.919	80.0 ± 15.0	0.674
Combined rod-cone response						
a-wave amplitude	208.8 ± 47.9	170.0 ± 50.0	160.0 ± 45.3	0.594	144.0 ± 58.0	0.260
a-wave implicit time	16.2 ± 1.7	24.0 ± 4.0	24.0 ± 4.0	0.507	24.0 ± 6.0	0.507
b-wave amplitude	391.0 ± 68.5	299.0 ± 98.1	278.0 ± 115.4	0.859	263.0 ± 123.4	0.051
b-wave implicit time	46.7 ± 5.0	58.0 ± 7.0	56.0 ± 8.5	0.398	58.4 ± 7.3	0.953
Single-flash response (cone)						
a-wave amplitude	26.2 ± 10.3	22.0 ± 7.1	20.0 ± 8.0	0.374	17.0 ± 8.2	0.098
a-wave implicit time	14.4 ± 1.6	17.0 ± 2.0	17.3 ± 1.6	0.182	18.1 ± 4.0	0.311
b-wave amplitude	81.1 ± 14.1	67.0 ± 26.0	61.2 ± 28.4	0.362	55.4 ± 24.1	0.008*
b-wave implicit time	33.2 ± 1.8	39.0 ± 4.3	38.1 ± 5.0	0.755	42.0 ± 8.1	0.208
30 Hz flicker response (cone)						
b-wave amplitude	83.0 ± 22.0	52.2 ± 24.0	41.0 ± 25.0	0.006*	42.0 ± 29.0	0.033*
b-wave implicit time	28.2 ± 1.3	39.3 ± 2.0	39.0 ± 4.0	0.373	40.0 ± 5.0	0.362

*Notes: p^1, Wilcoxon signed-rank test (baseline vs. 2 months); p^2, Wilcoxon signed-rank test (baseline vs. 12 months); *, denotes statistical significance*
Abbreviation: CRVO: Central Retinal Vein Occlusion

Three of 11 (27%) patients with ischemic CRVO developed NVG (8, 19 and 29 months after CRVO debut or after 18 months, on average). There were no incidents of endophtalmitis, retinal tears or retinal detachment. No serious non-ocular adverse events occurred.

DISCUSSION

Intravitreal injections of dexamethasone implant and aflibercept were effective in bringing about a significant reduction of CFT, compared with baseline values, in the whole group of CRVO patients during the treatment period in the present study. Patients with non-ischemic CRVO showed a more marked reduction in CFT than those with ischemic CRVO. A significant reduction in CFT, compared with baseline values, has been reported 6 months after anti-VEGF therapy, which was maintained 12 months after repeated ranibizumab injections for macular edema following CRVO in the CRUISE study [30,31] and after repeated aflibercept injections in the COPERNICUS study [32] and the GALILEO study [33].

The mean BCVA improved significantly 2 months after the treatment in the whole group of CRVO patients, compared with baseline values, but the visual gains were diminished 12 and 24 months after treatment, despite the monitoring every two months and repeated aflibercept or dexamethasone implant injections as needed. Patients with ischemic CRVO exhibited the greatest visual loss, nearly 20 letters, both at 12 and 24 months, while patients with non-ischemic CRVO showed insignificant visual loss, ≤ 3 letters, 12 and 24 months after treatment. These findings are in contrast to the results of several previous studies, where it was reported that visual gains achieved with 6 monthly injections of ranibizumab, bevacizumab or aflibercept in patients with macular edema after CRVO were maintained 12 months after treatment [30,31,59,62].

The reason for the poorer worse visual results observed after 12 months in the present study could be the high percentage of patients with ischemic CRVO. In the present study 73% of the patients had ischemic CRVO, while in the

COPERNICUS study [32] only 30% of the patients had ischemic CRVO, 14% in the GALILEO study [33], 0.5% in the CRUISE study [31], while all the CRVO patients in the study by Mayer et al. [62] had non-ischemic CRVO. The deterioration in the visual acuity 12 months after treatment in the present study was unchanged up to 24 months in both ischemic and non-ischemic CRVO patients. It has been reported in other studies that neither the improvements in visual acuity nor the reductions in the CFT were maintained after the first year of anti-VEGF and dexamethasone therapy for macular edema after CRVO [37-39,63,64].

To the best of our knowledge, the present study is the first clinical pilot study on the treatment of CRVO patients with both repeated dexamethasone implant and aflibercept injections using full-field ERG to evaluate the total retinal function 2 and 12 months after treatment. A significant decrease in the b-wave amplitudes of combined rod-cone and of single-flash cone response was observed 12 months after treatment, compared with baseline values in all studied CRVO patients, while the reduction in b-wave amplitudes of 30 Hz flicker response was significant compared with baseline values in all studied CRVO patients of this study both 2 and 12 months after treatment. All patients with ischemic CRVO also showed a significant reduction in b-wave amplitudes for single-flash response 12 months after treatment and for b-wave amplitudes of 30 Hz flicker response 2 and 12 months after treatment.

The findings of the current study indicate a decrease in retinal function in the whole group of CRVO patients studied, especially in patients with ischemic CRVO, 12 months after treatment with repeated intravitreal injections as needed. Previous electrophysiological studies on retinal function after anti-VEGF treatment have revealed no significant changes in the scotopic or the photopic full-field ERG amplitudes or implicit times at the end of the follow-up period, compared with baseline values [65-68]. However, other studies also showed a non-significant reduction in the b-wave amplitudes of the rod, combined rod-cone and 30 Hz flicker response in scotopic full-field ERG at the end of the follow-up period, compared with baseline values, indicating long-term deterioration of photoreceptor function [69,70].

We have previously found a more marked reduction in retinal function in patients with ischemic CRVO treated with bevacizumab and PRP than in those treated with PRP only, 6 months after treatment [60]. In contrast, Topčić et al. [59] reported significantly improved retinal function 6 and 12 months after bevacizumab treatment of macular edema resulting from CRVO. After separating ischemic from non-ischemic CRVO, the authors of the above study found no improvement in the retinal function of patients with ischemic CRVO 12 months after treatment.

There are two possible reasons for the decrease in retinal function in CRVO patients after intravitreal injections in this study. The first could be progressive ischemia associated with the natural development of CRVO. Hayreh et al. [6] and McIntosh et al. [16] have reported that progressive ischemia develop when CRVO is untreated. It has also been reported that up to 34% of eyes with non-ischemic CRVO become ischemic CRVO over a 3 year period and that 23% of eyes with ischemic CRVO developed NVG within 15 months [16]. In the present study, 3 of 11 of the patients with ischemic CRVO (27%) developed NVG an average of 18 months after CRVO debut, and treatment with intravitreal injections did not prevent the progression of retinal ischemia in the eyes of these patients.

The second factor that could contribute to the decrease in retinal function could be direct effects of the dexamethasone or aflibercept on the function of the photoreceptors through damage to the choriocapillaris or the photoreceptors, especially in patients with ischemic CRVO. A significant reduction in choriocapillaris endothelial cell fenestration and segmental occlusion by thrombocytes and leukocytes, which influenced circulation and impaired nutritional provision to the photoreceptors, has been found in primate eyes treated with bevacizumab [71].

Marneros et al. [72] have also shown that VEGF was essential for the development and maintenance of the choriocapillaris. Mutant mice that lack VEGF expression in the retinal pigment epithelium showed morphologic abnormalities in the retinal pigment epithelium and photoreceptors. Furthermore, both a and b wave amplitudes of scotopic full-field ERG response were significantly reduced in these mice compared to the full-field ERG response of control mice [72]. VEGF-A has been recognized as an important survival factor for the retinal neurons and a critical neuroprotectant during ischemic injury by increasing the blood flow to the retina and decreasing the number of apoptotic retinal cells. Chronic inhibition of VEGF-A by anti-VEGF agents reduces macular edema and the neovascularization, but also simultaneously reduces the neuro protective effect of VEGF-A [73]. Anti-VEGF injections have been associated with increased apoptosis in retinal photoreceptor cells, reduced retinal thickness of the inner and outer layer of the retina and a significant reduction in both a and b wave amplitudes of full-field ERG response [74,75]. VEGF blocking may increase the progression of retinal non perfusion and, secondarily, decrease retinal function as measured by full-field ERG. However, it was not possible to ascertain this it in the present study as we did not evaluate untreated CRVO eyes longitudinally. Leaving patients untreated would be unethical.

Although a significant reduction in CFT was seen in CRVO patients undergoing serial intravitreal injections in this study, the retinal function was not improved at 12 months and the treatment did not prevent the development of NVG in ischemic CRVO. NVG occurred in 27% of patients with ischemic CRVO undergoing anti-VEGF therapy in this study an average of 18 months after CRVO debut. Our findings

concerning NVG are similar to those in previous studies on CRVO patients undergoing serial anti-VEGF injections [56-58].

Ryu et al. [57] reported that NVG occurred at 19.7 months after CRVO debut and they concluded that although anti-VEGF therapy for macular edema, especially in patients with ischemic CRVO, does not prevent the development of ocular neovascularization, it may be delayed compared to the natural development of CRVO-associated neovascularization. The RAVE study [56] has also shown that anti-VEGF therapy can improve retinal anatomy and vision in eyes with ischemic CRVO, but neurovascular complications were not prevented by VEGF inhibition, only delayed. The SCORE-study [52] has also shown that triamcinolone treatment was not associated with lower incidences of neurovascular events or non-perfusion status, compared with observation. In a more recent study by Wykoff et al. [55] using WFFA, a progressive loss of the retinal perfusion was observed in ischemic CRVO eyes undergoing anti-VEGF therapy. However, Campochiaro et al. [48] reported anti-VEGF therapy to have a protective effect on retinal vascular perfusion.

Our study has several limitations, including the small number of patients in each group, the lack of a control group to evaluate untreated CRVO eyes longitudinally and a short follow-up period.

CONCLUSION

This study revealed a decrease in total retinal function, measured by full-field ERG, at 12 months in patients undergoing repeated intravitreal injections of dexamethasone implant and aflibercept using as needed dosing. The treatment did not prevent the development of NVG in ischemic CRVO. Further electrophysiological studies with longer follow-up periods and a control group consisting of untreated CRVO eyes are needed to clarify the long-term effects of anti-VEGF therapy on the retinal photoreceptor cells, especially in retinal diseases with severe retinal ischemia.

ACKNOWLEDGEMENT

This study was supported by Stiftelsen för synskadade I f.d. Malmöhus län and Skane University Hospital.

DISCLOSURE

The authors report no conflicts of interest in this work.

REFERENCES

1. Rogers S, McIntosh RL, Cheung N, Lim L, Wang J, et al. (2010) The prevalence of retinal vein occlusion: Pooled data from population studies from the United States, Europe, Asia and Australia. Ophthalmology 117: 313-319.
2. Stem MS, Talwar N, Comer GM, Stein JD (2013) A longitudinal analysis of risk factors associated with central retinal vein occlusion. Ophthalmology 120: 362-370.
3. Kolar P (2014) Risk factors for central and branch retinal vein occlusion: A meta-analysis of published clinical data. J Ophthalmol 2014: 724780.
4. The Central Vein Occlusion Study Group (1997) Natural history and clinical management of central retinal vein occlusion. Arch Ophthalmol 115: 486-491.
5. Hayreh SS, Podhajsky PA, Zimmerman MB (2011) Natural history of visual outcome in central retinal vein occlusion. Ophthalmology 118: 119-133.
6. Hayreh SS, Zimmerman MB (2012) Ocular neovascularization associated with central and hemi central retinal vein occlusion. Retina 32: 1553-1565.
7. Magargal LE, Brown GC, Augsburger JJ, Parrish RK (1981) Neurovascular glaucoma following central retinal vein occlusion. Ophthalmology 88: 1095-1101.
8. Evans K, Wishart PK, McGalliard JN (1993) Neurovascular complications after central retinal vein occlusion. Eye 7: 520-524.
9. Laatikainen L, Kohner EM (1976) Fluorescein angiography and its prognostic significance in central retinal vein occlusion. Br J Ophthalmol 60: 411-418.
10. Larsson J, Bauer B, Cavallin-Sjöberg U, Andréasson S (1998) Fluorescein angiography versus ERG for predicting the prognosis in central retinal vein occlusion. Acta Ophthalmol Scand 76: 456-460.
11. Larsson J, Andréasson S, Bauer B (1998) Cone b-wave implicit time as an early predictor of rubeosis in central retinal vein occlusion. Am J Ophthalmol 125: 247-249.
12. Larsson J, Andréasson S (2001) Photopic 30 Hz flicker ERG as a predictor for rubeosis in central retinal vein occlusion. Br J Ophthalmol 85: 683-685.
13. Kjeka O, Bredrup C, Krohn J (2007) Photopic 30 Hz flicker electro retinography predicts ocular neovascularization in central retinal vein occlusion. Acta Ophthalmol Scand 85: 640-643.
14. Kjeka O, Jansson RW, Bredrup C, Krohn J (2013) Early pan retinal photocoagulation for ERG-verified ischemic central retinal vein occlusion. Acta Ophthalmol 91: 37-41.
15. Yasuda S, Kachi S, Kondo M, Ushida H, Uetani R, et al. (2011) Significant correlation between electro retinogram parameters and ocular vascular endothelial growth factor concentration in central retinal vein occlusion eyes. Invest Ophthalmol Vis Sci 52: 5737-5742.

16. McIntosh RL, Rogers SL, Lim L, Cheung N, Wang J, et al. (2010) Natural history of retinal vein occlusion: An evidence-based systematic review. Ophthalmology 117: 1113-1123.

17. Jin KL, Mao XO, Greenberg DA (2000) Vascular endothelial growth factor: Direct neuro protective effect in in vitro ischemia. PNAS 97: 10242-10247.

18. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, et al. (1994) Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 331: 1480-1487.

19. Adamis AP, Shima DT, Tolentino MJ Gragoudas ES, Ferrara N, et al. (1996) Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a non-human primate. Arch Ophthalmol 114: 66-71.

20. Pe'er J, Folberg R, Itin A, Gnessin H, Hemo I, Keshet E (1998) Vascular endothelial growth factor upregulation in human central retinal vein occlusion. Ophthalmology 105: 412-416.

21. Boyd SR, Zachary I, Chakravarthy U, Allen GJ, Wisdom GB, et al. (2002) Correlation of increased vascular endothelial growth factor with neovascularization and permeability in ischemic central vein occlusion. Arch Ophthalmol 120: 1644-1650.

22. Kaur C, Foulds WS, Ling EA. (2008) Blood-retinal barrier in hypoxic ischemic conditions: Basic concepts, clinical features and management. Prog Retin Eye Res 27: 622-647.

23. Noma H, Funatsu H, Mimura T, Harino S, Hori S (2009) Vitreous levels of interleukin-6 and vascular endothelial growth factor in macular edema with central retinal vein occlusion. Ophthalmology 116: 87-93.

24. Noma H, Funatsu H, Harino S, Mimura T, Eguchi S, Hori S (2011) Vitreous inflammatory factors in macular edema with central retinal vein occlusion. Jpn J Ophthalmol 55: 248-255.

25. Jung SH, Kim KA, Sohn SW, Yang SJ (2014) Association of aqueous humor cytokines with the development of retinal ischemia and recurrent macular edema in retinal vein occlusion. Invest Ophthalmol Vis Sci 55: 2290-2296.

26. Shchuko AG, Zlobin IV, Iureva TN, Ostanin AA, Chernykh ER, Mikhalevich IM (2015) Intraocular cytokines in retinal vein occlusion and its relation to the efficiency of anti-vascular endothelial growth factor therapy. Indian J Ophthalmol 63: 905-911.

27. Rezar-Dreindl S, Eibenberger K, Pollreisz A, Bühl W, Greorgopoulos M, et al. (2017) Effect of intravitreal dexamethasone implant on intra-ocular cytokines and chemokines in eyes with retinal vein occlusion. Acta Ophthalmol 95: e119-e127.

28. The central vein occlusion study group N report (1995) A randomized clinical trial of early pan retinal photocoagulation for ischemic central vein occlusion. Ophthalmology 102: 1434-1444.

29. The central vein occlusion study group M report (1995) Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. Ophthalmology 102: 1425-1433.

30. Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, et al. (2010) Ranibizumab for macular edema following central retinal vein occlusion. Ophthalmology 117: 1124-1133.

31. Campochiaro PA, Brown DM, Awh CC, Lee Y, Gray S, et al. (2011) Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: Twelve month outcomes of a phase III study. Ophthalmology 118: 2041-2049.

32. Brown DM, Heier JS, Clark L, Boyer DS, Vitti R, et al. (2013) Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1 year results from the phase 3 COPERNICUS study. Am J Ophthalmol 155: 429-437.

33. Korobelnik J-F, Holz FG, Roider J, Ogura Y, Simader C, et al. (2014) Intravitreal aflibercept injection for macular edema resulting from central retinal vein occlusion: 1 year results of the phase 3 GALILEO study. Ophthalmology 121: 202-208.

34. Ford JA, Clar C, Lois N, Barton S, Thomas S, et al. (2014) Treatments for macular edema following central retinal vein occlusion: Systematic review. BMJ Open 4: e004120.

35. Yeh S, Kim SJ, Ho AC, Schoenberger S, Bakri S, et al. (2015) Therapies for macular edema associated with central retinal vein occlusion. Ophthalmology 122: 769-778.

36. Ho M, Liu DTL, Lam DSC, Jonas JB (2016) Retinal vein occlusions, from basics to the latest treatment. Retina 36: 432-448.

37. Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, et al. (2012) Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. Ophthalmology 119: 802-809.

38. Heier JS, Clark WL, Boyer DS, Brown DM, Vitti R, et al. (2014) Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion. Ophthalmology 121: 1414-1420.

39. Ogura Y, Roider J, Korobelnik J-F, Holz FG, Simader C, et al. (2014) Intravitreal aflibercept for macular

edema secondary to central retinal vein occlusion: 18 month results of the phase 3 GALILEO study. Am J Ophthalmol 158: 1032-1038.

40. Ip MS, Scott IU, VanVeldhuisen PC, Oden NL, Blodi BA, et al. (2009) A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion. The standard care vs. corticosteroid for retinal vein occlusion (SCORE) study report 5. Arch Ophthalmol 127: 1101-1114.
41. Campochiaro PA, Hafiz G, Mir TA, Scott AW, Sophie R, et al. (2015) Pro-permeability factors after dexamethasone implant in retinal vein occlusion; the ozurdex for retinal vein occlusion (ORVO) study. Am J Ophthalmol 160: 313-321.
42. Haller JA, Bandello F, Belfort R Jr, Blumenkrantz MS, Gillies M, et al. (2010) Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology 117: 1134-1146.
43. Chiquet C, Dupuy C, Bron AM, Aptel F, Straub M, et al. (2015) Intravitreal dexamethasone implant versus anti-VEGF injection for treatment-naïve patients with retinal vein occlusion and macular edema: A 12 month follow-up study. Graefes Arch Clin Exp Ophthalmol 253: 2095-2102.
44. Capone A Jr, Singer MA, Dodwell DG, Dreyer RF, Oh KT, et al. (2014) Efficacy and safety of two or more dexamethasone intravitreal implant injections for treatment of macular edema related to retinal vein occlusion (Shasta study). Retina 34: 342-351.
45. Reid GA, Sahota DS, Sarhan M (2015) Observed complications from dexamethasone intravitreal implant for the treatment of macular edema in retinal vein occlusion over 3 treatment rounds. Retina 35: 1647-1655.
46. Caillaux V, Valtot F, Souied EH, Mimoun G (2015) Intraocular pressure after intravitreal injection of dexamethasone implant for macular edema resulting from retinal vein occlusion. Eur J Ophthalmol 25: 454-458.
47. Garweg JG, Zandi S. (2016) Retinal vein occlusion and the use of a dexamethasone intravitreal implant (Ozurdex) in its treatment. Graefes Arch Clin Exp Ophthalmol 254: 1257-1265.
48. Campochiaro PA, Bhisitkul RB, Shapiro H, Rubio RG (2013) Vascular endothelial growth factor promotes progressive retinal non-perfusion in patients with retinal vein occlusion. Ophthalmology 120: 795-802.
49. Sophie R, Hafiz G, Scott AW, Zimmer-Galler I, Nguyen QD, et al. (2013) Long-term outcomes in ranibizumab-treated patients with retinal vein occlusion; the role of progression of retinal non-perfusion. Am J Ophthalmol 156: 693-705.
50. Campochiaro PA, Hafiz G, Mir TA, Scott AW, Solomon S, et al. (2015) Scatter photocoagulation does not reduce macular edema or treatment burden in patients with retinal vein occlusion. Ophthalmology 122: 1426-1437.
51. Mir TA, Kherani S, Hafiz G, Scott AW, Zimmer-Galler I, et al. (2016) Changes in retinal non-perfusion associated with suppression of vascular endothelial growth factor in retinal vein occlusion. Ophthalmology 123: 625-634.
52. Chan CK, Ip MS, van Veldhuisen PC, Oden NL, Scott I, et al. (2011) SCORE study report 11: Incidences of neovascular events in eyes with retinal vein occlusion. Ophthalmology 118: 1364-1372.
53. Sadda S, Danis RP, Pappuru RR, Keane PA, Jiao J, et al. (2013). Vascular changes in eyes treated with dexamethasone intravitreal implant for macular edema after retinal vein occlusion. Ophthalmology 120: 1423-1431.
54. Singer M, Tan CS, Bell D, Sadda SR (2014) Area of peripheral retinal non-perfusion and treatment response in branch and central retinal vein occlusion. Retina 34: 1736-1742.
55. Wykoff CC, Brown DM, Croft DE, Major JC Jr, Wong TP (2015) Progressive retinal non-perfusion in ischemic central retinal vein occlusion. Retina 35: 43-47.
56. Brown DM, Wykoff CC, Wong TP, Mariani AF, Croft DE Schuetzle KL (2014) Ranibizumab in pre-proliferative (ischemic) central retinal vein occlusion: The rubeosis anti-VEGF (RAVE) trial. Retina 34: 1728-1735.
57. Ryu CL, Elfersy A, Desai U, Hessburg T, Edwards P, Gao H (2014) The effect of anti-vascular endothelial growth factor therapy on the development of neovascular glaucoma after central retinal vein occlusion: A retrospective analysis. J Ophthalmol 2014: 317694.
58. DeCroos FC, Todorich B, Alshareef R, Khuthaila M, Fekrat S, et al. (2014) Neovascular events in eyes with central retinal vein occlusion undergoing serial bevacizumab or ranibizumab intravitreal injections: A retrospective review. J Ophthalmic Vis Res 9: 461-468.
59. Gardašević Topčić I, Šuštar M, Brecelj J, Hawlina M, Mekjavić P (2014) Morphological and electrophysiological outcome in prospective intravitreal bevacizumab treatment of macular edema secondary to

central retinal vein occlusion. Doc Ophthalmol 129: 27-38.

60. Wittström E, Holmberg H, Hvarfner C, Andréasson S (2012) Clinical and electrophysiologic outcome in patients with neovascular glaucoma treated with and without bevacizumab. Eur J Ophthalmol 22: 563-574.
61. McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, et al. (2015) ISCEV Standard for full-field clinical electroretinography (2015 update). Doc Ophthalmol 130: 1-12.
62. Mayer WJ, Wolf A, Kernt M, Kook D, Kampik A, et al. (2013) Twelve-month experience with Ozurdex for the treatment of macular edema associated with retinal vein occlusion. Eye 27: 816-822.
63. Campochiaro PA, Sophie R, Pearlman J, Brown DM, Boyer DS, et al. (2014) Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab. The RETAIN study. Ophthalmology 121: 209-219.
64. Moisseiev E, Goldstein M, Waisbourd M, Barak A, Loewenstein A (2013) Long-term evaluation of patients treated with dexamethasone intravitreal implant for macular edema due to retinal vein occlusion. Eye 27: 65-71.
65. Lüke M, Warga M, Ziemssen F, Gelisken F, Grisanti S, et al. (2006) Effects of bevacizumab on retinal function in isolated vertebrate retina. Br J Ophthalmol 90: 1178-1182.
66. Stahl A, Feltgen N, Fuchs A, Bach M (2009) Electrophysiological evaluation of retinal photoreceptor function after repeated bevacizumab injections. Doc Ophthalmol 118: 81-88.
67. Ziemssen F, Lüke M, Messias A, Beutel J, Tatar O, et al. (2008) Safety monitoring in bevacizumab (Avastin) treatment: Retinal function assessed by psychophysical (visual fields, color vision) and electrophysiological (ERG/EOG) tests in two subgroups of patients. Int Ophthalmol 28: 101-109.
68. Januschowski K, Schnichels S, Hagemann U, Koch V, Hofmann J, et al. (2014) Electrophysiological toxicity testing of VEGF Trap-Eye in an isolated perfused vertebrate retina organ culture model. Acta Ophthalmol 92: e305-e311.
69. Shetty R, Pai SA, Vincent A, Shetty N, Narayana KM, et al. (2008) Electrophysiological and structural assessment of the central retina following intravitreal injection of bevacizumab for treatment of macular edema. Doc Ophthalmol 116: 129-135.
70. Bjerg Pedersen K, Møller F, Sjølie AK, Andréasson S (2010) Electrophysiological assessment of retinal function during 6 months of bevacizumab treatment in neovascular age-related macular degeneration. Retina 30: 1025-1033.
71. Peters S, Heiduschka P, Julien S, Ziemssen F, Fietz H, et al. (2007) Ultra structural findings in the primate eye after intravitreal injection of bevacizumab. Am J Ophthalmol 143: 995-1002.
72. Marneros AG, Fan J, Yokoyama Y, Gerber HP, Ferrara N, et al. (2005) Vascular endothelial growth factor expression in the retinal pigment epithelium is essential for choriocapillaris development and visual function. Am J Pathol 167: 1451-1459.
73. Nishijima K, Ng Y-S, Zhong L, Bradley J, Schubert W, et al. (2007) Vascular endothelial growth factor-A is a survival factor for retinal neurons and a critical neuro protectant during the adaptive response to ischemic injury. Am J Pathol 171: 53-67.
74. Avci B, Avci R, Inan ÜÜ, Kaderli B (2009) Comparative evaluation of apoptotic activity in photoreceptor cells after intravitreal injection of bevacizumab and pegaptanib sodium in rabbits. Invest Ophthalmol Vis Sci 50: 3438-3446.
75. Saint-Geniez M, Maharaj ASR, Walshe T, Tucker BA, Sekiyama E, et al. (2008) Endogenous VEGF is required for visual function: Evidence for a survival role on Müller cells and photoreceptors. PLoS 3: e3554.