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CLINICAL STUDY

Twelve-month experience with Ozurdex for the treatment of macular edema associated with retinal vein occlusion

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Abstract

Purpose **To evaluate the efficacy and safety of a dexamethasone implant (Ozurdex) alone or in combination with bevacizumab.**

Methods **Sixty-four eyes were prospectively investigated. Group 1 (22 central retinal vein occlusion (CRVO) and 16 branch retinal vein occlusion (BRVO)) was treated with Ozurdex alone, and group 2 (14 CRVO and 12 BRVO) was treated with three consecutive bevacizumab injections followed by Ozurdex. Recurrences were treated with Ozurdex only. Patients were seen preoperatively and thereafter in monthly intervals. The primary end point was best-corrected visual acuity (BCVA) at 12 months.**

Results **In group 1, BCVA improved by 6.6 (±1.7) letters in CRVO and 7.8 (±2.9) in BRVO patients, and in group 2 by 9.8 (±1.0) *vs* 9.4 (±2.1) letters. A significant difference was only seen between CRVO patients in group 1 and 2 at 12 months ($P<0.05$). Recurrence after the first Ozurdex injection occurred after 3.8 (CRVO) and 3.5 months (BRVO) in group 1, *vs* 3.2 and 3.7 months in group 2. Elevated intraocular pressure (>5 mm Hg) was measured in approximately 40% cataract progression requiring surgery in about 50% of eyes after three Ozurdex injections.**

Conclusion **Combined treatment showed slightly better functional outcome for CRVO patients. Increased intraocular pressure and cataract progression was frequent and should be considered when an individual treatment is planned.**

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Keywords: macular edema; retinal vein occlusion; dexamethasone; bevacizumab

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Introduction

In industrialized countries, retinal vein occlusion (RVO) is a common vascular disorder of the retina and a cause of visual impairment only second to diabetic retinopathy. In both types, branch RVO (BRVO) and central RVO (CRVO), one cause of visual loss is macular edema. With time, retinal ischemia and iris neovascularization may occur and lead to severe complications, including secondary glaucoma and blindness, in eyes with CRVO.[1] The pathogenesis of macular edema in RVO is not completely understood. However, some causative factors have been identified such as the role of hydrostatic effects from increased venous pressure, the presence of inflammatory cytokines (eg, prostaglandins and interleukin-6), and the upregulation of endothelial tight junction proteins,[2] or increased vascular endothelial growth factor (VEGF) expression.[3] Risk factors for RVO include arterial hypertension, hypercholesterolemia, diabetes mellitus, and glaucoma.[4]

Recently, two pharmacological treatment regimes have been introduced for the treatment

of macular edema associated with RVO, including intravitreal injection of VEGF inhibitors such as bevacizumab or ranibizumab and corticosteroids, that is, dexamethasone. Although bevacizumab remains an off-label treatment, the sustained-release dexamethasone implant (Ozurdex, Allergan, Inc., Irvine, CA, USA) and ranibizumab have been approved.[5–9]

We previously described the response to a pharmacological treatment of macular edema associated with RVO using the present treatment strategy with an Ozurdex monotherapy as a first-line treatment regime compared with an anti-VEGF-loading dose using three bevacizumab injections followed by a dexamethasone implant.[10] However, with regard to the potential side effects of a long-term treatment using dexamethasone, such as a raise of intraocular pressure and cataract formation, we feel the importance to report on the safety and efficacy over a 12-month follow-up of our patients.

Materials and methods

In this prospective, consecutive, non-randomized case series, 64 eyes of 64 patients with RVO, 39 males and 25 females (mean age 68 years), with a maximum duration of symptoms of 4 months were included. Thirty-six patients presented with (non ischemic) CRVO and 28 with BRVO. We excluded patients with a known history of glaucoma or steroid response, as well as vitrectomy and neovascularization, in the anterior or posterior segment.

Informed consent was taken from all patients, and this research was approved by the Institutional Review Board (IRB) of the Department of Ophthalmology, Ludwig-Maximilians University, Munich. Patients were recruited in a consecutive manner between September 2010 and January 2011, starting with the combination treatment group. Group 1 included 38 (59.4%) patients (22 with CRVO and 16 with BRVO) and was treated with an Ozurdex injection from the beginning. Group 2 included 26 (40.6%) patients (14 with CRVO and 12 with BRVO) and was treated with three consecutive injections of bevacizumab at a monthly interval, followed by a Ozurdex injection 4 weeks after the last bevacizumab injection. Thereafter, both groups received Ozurdex injections in case macular edema reoccurred. The criteria for such a retreatment were as follows: loss of best-corrected visual acuity (BCVA) of more than five letters (ETDRS) and/ or an increase in retinal thickness in OCT of $>100\,\mu$m. We examined BCVA (ETDRS chart), central retinal thickness (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany), as well as intraocular pressure, and we performed wide-angle retinal images (Optomap OPTOS, Bruchsal, Germany) at the initiation of treatment and then at monthly intervals. Cataract progression was assessed using the Lens Opacities Classification System III (LOCS III). Fluorescein angiography was performed initially and after 3 months.

The primary clinical end point was BCVA 12 months after the first intravitreal treatment. Secondary end points were central retinal thickness, lens opacity, and the safety of the procedure.

Statistical analysis

Data were collected using Microsoft Excel spread sheets (Microsoft Excel 2010). Statistical analysis was performed using SPSS (IBM SPSS Version 20, IBM, New York, NY, USA). Student's *t*-test and Wilcoxon range test were used to compare both data cohorts and to calculate significance. All performed tests were two-sided. Variations were expressed as SEM. A P-value <0.05 was considered significant.

Results

Efficacy

Visual acuity outcome At baseline, mean BCVA was 22.4 letters (SD of ± 12.3 letters) in CRVO and 26.3 letters (SD of ± 9.9 letters) in BRVO patients in group 1, and 15.5 letters (SD of ± 10.6) *vs* 28.5 letters (SD of ± 10.3) in group 2 ($P=0.38$ for CRVO and $P=0.49$ for BRVO between groups), respectively. Mean macular thickness measured in OCT was 604.4 μm (SD of $\pm 230.5\,\mu$m) in CRVO and 500.5 μm (SD of $\pm 106\,\mu$m) in BRVO patients in group 1, and 601.1 μm (SD of $\pm 252.5\,\mu$m) *vs* 469.8 μm (SD of $\pm 151.7\,\mu$m) in group 2, respectively.

In group 1, an increase of BCVA (± 1 SD) of 2.5 (± 1.6) letters was observed at 6 months and of 6.6 (± 1.7) letters at 12 months after initiation of therapy in CRVO patients (Figure 1a). In BRVO patients, a gain of 13.0 (± 3.2) letters at 6 months and 7.8 (± 2.9) letters at 12 months was observed (Figure 1b).

In group 2, CRVO patients showed an increase of BCVA of 5.9 (± 0.4) letters (Figure 1a) at 6 months and 9.8 (± 1.0) letters at 12 months compared with 3.8 (± 2.4) and 9.4 (± 2.1) letters at 6 and 12 months, respectively, in BRVO patients (Figure 1b).

A gain of BCVA of ≥ 15 letters was observed in 16 (72.7%) CRVO patients 2 months after initial therapy using an Ozurdex injection (group 1) and in 9 (64.3%) patients 2 months after initial therapy using bevacizumab injections (group 2) but not thereafter during the period of treatment. In contrast, a similar improvement of ≥ 15 letters could not be achieved in BRVO patients at any time point. In BRVO patients, the maximum improvement of BCVA was 13 letters at 6

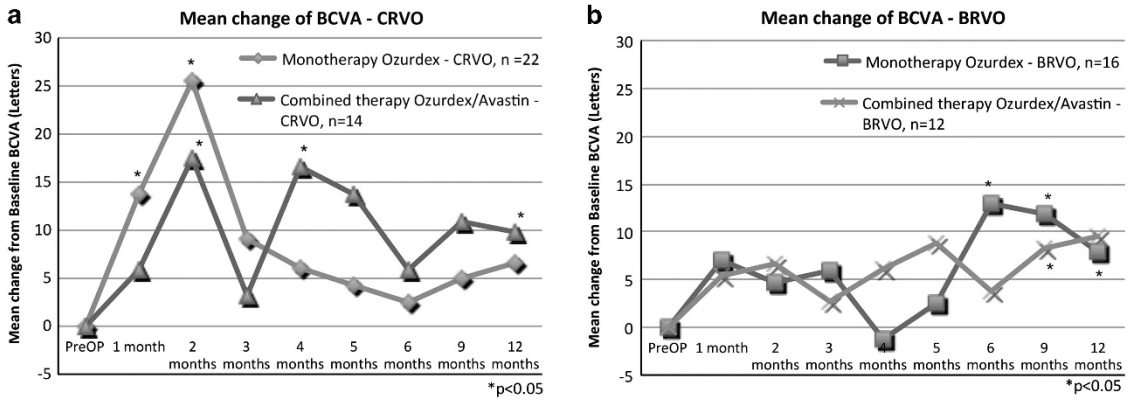

Figure 1 (a, b) Efficacy of VA compared with baseline: 12-month follow-up in both treatment groups after initial therapy in patients with CRVO (a) and BRVO (b).

months in group 1 and 9.4 letters after 12 months in group 2.

When comparing groups 1 and 2 with respect to the type of vein occlusion, a significant advantage for the combined treatment regime compared with Ozurdex monotherapy ($P<0.05$, Figures 1a and b) could be observed after 12-month follow-up only for CRVO patients. This was also confirmed by an area under the curve analysis, where higher values were seen for those CRVO patients treated with the combination regime (108.3 *vs* 68.6, $P<0.05$). In contrast, no significant differences were found in BRVO patients (60.6 *vs* 68.4, $P=0.40$).

Fluorescein angiography revealed a non ischemic status in all CRVO patients initially and during follow-up period.

Recurrences and number of treatments In group 1, 16/22 (72.7%) CRVO patients presented with a recurrence (criteria see above) after a mean period of 3.8 months (± 1.25 months) *vs* 6/16 (37.5%) BRVO patients after a mean period of 3.5 months (± 0.63 months) after the first Ozurdex injection.

In group 2, recurrences after the first Ozurdex injection (following three consecutive injections of bevacizumab) occurred after a mean follow-up of 3.2 months (± 0.5 months) in 9/14 (64.3%) CRVO patients, and after 3.7 months (± 0.75 months) in 7/12 (58.3%) BRVO patients (Table 1).

During the entire period of 12 months, patients in group 1 required 52/2.4 (total/mean) injections for CRVO and 28/1.8 for BRVO *vs* 34/2.4 (CRVO) and 24/2 (BRVO) in group 2.

Macular thickness OCT measurements showed a significant reduction of central retinal thickness after 12 months in both groups and for CRVO ($P=0.02$, Figures 2a and 3a–c) and BRVO patients ($P=0.04$, Figure 2b).

Cataract progression

Overall, 12 patients were already pseudophakic at baseline. After 12 months, LOCS III analysis revealed an incidence of lens opacities interfering with VA and requiring cataract extraction with implantation of a posterior chamber lens in 12 CRVO patients after a mean of 2.7 injections (54.5%, LOCS III score of 1.8 compared with baseline) and 8 BRVO patients after a mean of 1.9 injections (50%, LOCS III score of 2.0 compared with baseline) in group 1. In group 2, cataract surgery was indicated in six CRVO patients after 2.8 injections (42.9%, LOCS III score of 2.3 compared with baseline) and five BRVO patients after 2.2 injections (41.7%, LOCS III score of 2.4 compared with baseline; Table 1). Therefore, at the 12-month control visit, 43/64 eyes were pseudophakic.

Safety

Before initiation of treatment, intraocular pressure was within normal range in all patients. A relevant increase of intraocular pressure was defined as an increase of >5 mm Hg compared with baseline. During the 12 months of review, 15/38 (39.5%) patients in group 1 experienced an increase of intraocular pressure (9 (40.9%) out of 22 CRVO patients, and 6 (37.5%) out of 16 BRVO patients). In group 2, an increase of intraocular pressure was seen in 11/26 (42.3%) patients (6 (42.9%) out of 14 CRVO, and 5 (41.7%) out of 12 BRVO patients; Table 1). Intraocular pressure exceeding normal range was controlled by topical drugs. One eye in group 1 required cyclo-photocoagulation after the second Ozurdex injection.

One CRVO patient of group 1 presented with a localized retinal detachment 3 weeks after implantation,

Table 1 Overview of the 12-month follow-up of all groups after primary intravitreal therapy

	VA (ETDRS letter score)			*Recurrence*	*Ozurdex IVT*	*OCT (μm)*			*IOP* (n/%)		*Cataract progression*					
					(Total/Ø)				*Increase >5 mm Hg*		*Pre OP*			*12 months*		
	Pre OP	*6 months*	*12 months*	(n/*months*)	*12 months*	*Pre OP*	*6 months*	*12 months*	*6 months*	*12 months*	*Clear*	*Mild Cataract*	*PCL*	*Progression + CE/ PCL/Ø Ozurdex IVT*	*No progression/Ø Ozurdex IVT*	
Monotherapy Ozurdex—CRVO, $n=22$	22.4	24.9	26.8	16/3.8	52/2.4	604.4	438.1	301.7	14/63.6	9/40.9	0	20	2	12/2.7	8/2	
Monotherapy Ozurdex—BRVO, $n=16$	26.3	39.2	34.1	6/3.5	28/1.8	500.5	324.8	330.4	8/50.0	6/37.5	1	10	4	8/1.9	4/1.5	
Combined therapy Ozurdex/Avastin—CRVO, $n=14$	15.5	21.4	30.4	9/3.2	34/2.4	543.1	436.7	472.7	8/57.1	6/42.9	2	11	1	6/2.8	7/1.6	
Combined therapy Ozurdex/Avastin—BRVO, $n=12$	28.6	32.4	37.8	7/3.7	24/2	479.6	422.3	278.6	6/50.0	5/41.7	0	7	5	5/2.2	2/0.7	

Abbreviations: CE, cataract extraction; PCL, posterior chamber lens.

which was successfully reattached with a scleral buckle. No other adverse events such as intravitreal hemorrhage or endophthalmitis were noted.

Discussion

Until recently, treatment strategy for patients with BRVO and CRVO was mainly based on the results of the BRVO and CRVO clinical trials,[11,12] suggesting deferred focal laser for macular edema in BRVO patients with BCVA <20/40. Peripheral laser was advocated in cases with severe ischemia in BRVO and CRVO in order to treat or prevent vitreous hemorrhage and neovascular glaucoma, especially in CRVO. Laser photocoagulation of the macular region provided no functional benefit in eyes with CRVO.[11]

Today, under the light of new treatment options, including intravitreal application of corticosteroids[6,7] and VEGF inhibitors,[5,8] patients with RVO, both CRVO and BRVO, have a better perspective of visual recovery. The rationale for both pharmacological approaches is based on pathogenetic factors that have been identified to have a key role in the development of macular edema associated with retinal vascular occlusion, such as the expression of VEGF[13]and a cascade of inflammatory processes.[14–18]

In clinical trials, VEGF inhibitors such as ranibizumab revealed a beneficial effect on visual function and reduced central macular thickness in eyes with BRVO and CRVO.[5,8,9,19] However, with respect to the shorter half-life of ranibizumab,[20] numerous injections are required to achieve and maintain this therapeutic effect. This is also valid for bevacizumab as shown by Epstein *et al*[21], who performed injections every 6 weeks for 12 months with a significant improvement of visual acuity (VA) and reduction of macular edema. Compared with the present study, the VA outcome as achieved by the strict treatment regime appeared better, although one needs to consider different study settings. Patients receiving delayed treatment have a limited visual improvement. Of note, ranibizumab was not approved for the treatment of RVO at the beginning of this study. Therefore, based on published clinical data,[22,23] bevacizumab was used for treatment in an off-label setting after IRB approval.

Corticosteroids not only have an anti-inflammatory effect (eg, inhibition of fibrin deposition, leukocyte movement, suppression of homing, and migration of inflammatory cells) but also interfere with the synthesis of VEGF and other cytokines.[2,24] Studies concerning intravitreal triamcinolone acetonide or intravitreal bevazicumab treatment showed mainly similar effects on macular edema reduction and VA improvement.

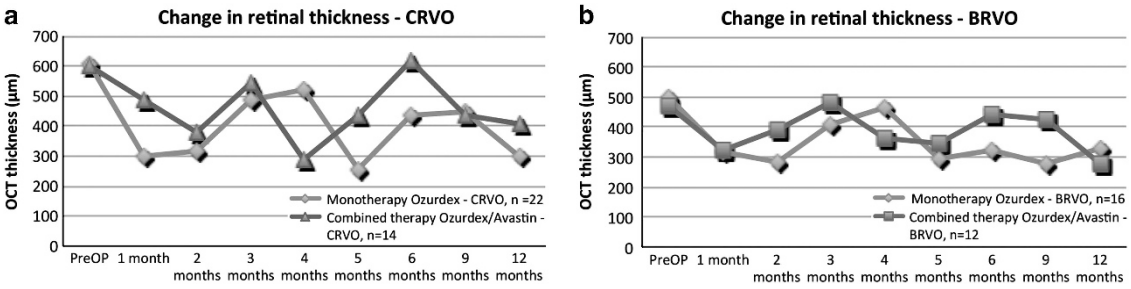

Figure 2 (a, b): Change in retinal thickness using spectral domain OCT: 12-month follow-up in both treatment groups after initial therapy in patients with CRVO (a) and BRVO (b).

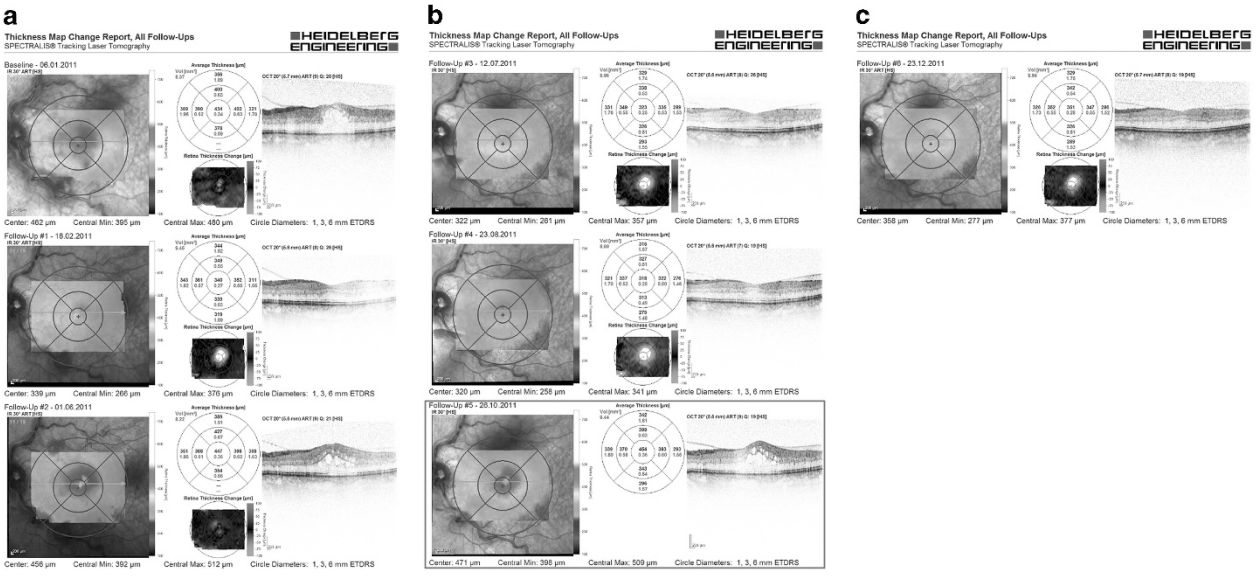

Figure 3 (a–c): Spectralis OCT images of the macular area of a male CRVO case: 12-month course of primary dexamethasone implant therapy.

However, a higher rate of side effects was reported using intravitreal triamcinolone acetonide.[25–28]

Dexamethasone is a potent, water-soluble corticosteroid that can be delivered into the vitreous cavity either by injection of a dexamethasone solution with a very short half-life[29] or by the implantation of an approved dexamethasone intravitreal implant using a customized applicator system (Ozurdex)[6] releasing dexamethasone over a prolonged period until complete resolution of the matrix as shown in the GENEVA trial.[6] Using this approach, a beneficial effect on VA and retinal thickness in patients with macular edema associated with BRVO and CRVO[6] has been reported. However, a retreatment was not allowed before 6 months after the initial implantation according to the protocol of this trial.[6]

The aim of the present study was to evaluate the efficacy and safety of Ozurdex in a clinical setting where reinjections were performed according to defined criteria, including a decrease of BCVA and an increase in retinal thickness. In addition, we wanted to see whether an upload therapy of three consecutive injections with an anti-VEGF drug provides any advantage or disadvantage when the treatment is continued with Ozurdex.

Comparing both treatment strategies 1 year after initiation of treatment, we observed a significant difference of gain in letters only for patients with CRVO, favouring eyes that were initially treated with bevacizumab (increase of 9.8 letters at 12 months). This may in part be explained by the fact that patients in this group had a lower BCVA (15.5 *vs* 22.4 ETDRS letters) at study entry, indicating that there was a greater window for improvement. However, even in CRVO eyes with an initial mean BCVA of 22.4 letters, an improvement of 6.6 letters was seen after 12 months. In BRVO patients, no significant difference between both groups was seen (7.8 *vs* 9.4 letters improvement at 12 months), and it seems noteworthy that there was no significant difference of initial BCVA (26.3 *vs* 28.5 letters) comparing both groups.

We hypothesized that a pre-treatment with a VEGF inhibitor may have an impact on the time until a recurrence of macular edema following the first Ozurdex implantation is seen. However, it appeared that the time to recurrence could not be prolonged, which is in contrast to a recent study of Singer *et al*[30], using a single bevacizumab injection followed by an Ozurdex implantation. Recurrences occurred after a period of 3.2 and 3.8 months and were in line with the known pharmacokinetics of the Ozurdex implant and the results of the GENEVA trial, which revealed a decrease of the treatment effect at about 3–4 months after implantation.[6] Interestingly, the number of recurrences (and subsequent retreatments) in patients receiving a monotherapy with the dexamethasone implant was lower in BRVO compared with CRVO patients, which may be well explained by the more favorable natural course of macular edema associated with BRVO. Therefore, considering the potential adverse effect of a corticosteroidal implant, BRVO patients seem better candidates for this treatment as a first-line option compared with CRVO patients, as the latter require more retreatments as described in other trials too.[8,9]

As to be expected for a corticosteroid, we observed an elevation of intraocular pressure of >5 mm Hg compared with baseline in approximately 40% of patients, irrespective of the treatment regime. One patient required cyclo-photocoagulation following the second steroid implant. In all other cases, the intraocular pressure was well controlled using topical medications. Interestingly, we observed no additive effect on intraocular pressure, although one might hypothesize that subsequent implantations after 3–4 months may increase the risk for an elevation of intraocular pressure, as the partially degraded first implant still releases dexamethasone into the vitreous cavity, though on a lower lever. In the GENEVA trial, no such additional effect had to be expected, as reinjections were not permitted within 6 months. Although we had no uncontrolled case with elevated intraocular pressure, based on our 12-month experience using Ozurdex, we suggest excluding patients with a known history of glaucoma and steroid response from this treatment.

Similar thoughts may theoretically apply for the formation or progression of cataracts in phacic eyes. In our series, it became apparent that lens opacities interfering with VA and requiring cataract extraction occurred after the second and finally after the third Ozurdex implantation in about 50% of treated eyes, and this is in line with previous reports in the literature.[7] This observation should be considered when choosing a treatment option for the individual RVO patient. From our perspective, young phacic patients should be treated with a VEGF inhibitor in order to preserve a clear lens. In addition, a combination of Ozurdex with an anti-VEGF drug or a switch from a Ozurdex monotherapy to an anti-VEGF strategy may be an option in selected cases, for example, especially in CRVO patients, where the natural history is quite poor compared with patients with BRVO, and more treatments seem to be required to maintain function.[8,9]

The limitation of the present study is the small number of patients included. We are also aware that the results seen for bevacizumab may not necessarily be transferred to the results one may obtain using ranibizumab in a similar setting. Of note, ranibizumab was not approved for the treatment of RVO at the initiation of our trial. A longer period of review will be needed to document whether the re-treatment effect observed in our study can be maintained. In addition, especially the safety issues such as secondary glaucoma and cataract progression need to be investigated in a prolonged period or review. However, we believe that the present investigation contributes interesting and helpful information on the use of Ozurdex in a setting that reflects its use in clinical practice.

In conclusion, combined treatment using Avastin and Ozurdex showed slightly better functional outcome for CRVO patients. Increased intraocular pressure and cataract progression was frequent and should be considered when an individual treatment is planned.

Summary

What was known before

- Treatment of macular edema due to retinal vein occlusion using anti-VEGF.

What this study adds

- Using a dexamethasone implant in case of retinal vein occlusion, in addition to the known treatment strategies.
- Comparison of dexamethasone implant monotherapy *vs* combined treatment using bevacizumab and dexamethasone implant in case of macular edema due to retinal vein occlusion.
- Showing efficacy and safety of the used treatment strategies in a long time period.

Conflict of interest

The authors declare no conflict of interest.

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