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CLINICAL STUDY

Anatomical and functional recurrence after dexamethasone intravitreal implants: a 6-month prospective study

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Abstract

Purpose **To evaluate the efficacy, safety, and delay of anatomical and functional recurrence after a first intravitreal injection of dexamethasone implant in eyes with cystoid macular edema (CME) secondary to retinal vein occlusion (RVO).**

Methods **A 6-month prospective, monocentric and noncomparative case-series of 26 eyes of 26 patients. Best-corrected visual acuity (BCVA) and central subfield thickness (CST) were measured at baseline and each visit at 1 week, and months 1, 2, 3, 4, 5, and 6 after a first treatment. Primary efficacy outcome was the proportion of eyes with a minimum three-line improvement from baseline BCVA at each visit and at 6 months. We also defined different patterns of recurrence: qualitative anatomical recurrence, quantitative anatomical recurrence and functional recurrence. A *P*-value $<5\%$ was considered statistically significant.**

Results **Mean population age was 69.3 years (SD = 12.2; range = 42–94 years). Mean ME duration before treatment was ~9.2 months (SD = 11.43; range = 0.4–40 months). Eighty eight percent of eyes achieved a three-line improvement from baseline at 2 months ($P = 0.02$). The mean delay from baseline until qualitative anatomical, functional, or quantitative anatomical recurrence was 4.11 months (±0.86), 4.31 months (±1.33), and 4.40 months (±1.14), respectively. Qualitative anatomical recurrence occurred on average 14.4 days (SD = 42.18) before a minimum of one-line BCVA impairment (functional recurrence).**

Conclusion **Dexamethasone intravitreal treatment seems to be effective for ME after RVO even with long-duration ME or poor visual acuity before treatment. Other longer studies should assess the delay of recurrence after second and further treatments with DEX implants or combined therapies for ME after RVO.**

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Introduction

Macular edema is one of the leading causes of vision loss among patients with retinal vein occlusion (RVO). Current evidence suggests that the pathological processes leading to ME involve the numerous inflammatory cells, cytokines, growth factors, and intercellular adhesion molecules that are associated with increased vascular permeability, the breakdown of the blood–retinal barrier, the remodeling of the extracellular matrix, and the upregulation of proangiogenic factors.[1–4]

Dexamethasone is one of the most potent corticosteroids, with an anti-inflammatory activity that is sixfold greater than that of triamcinolone and 30-fold greater than cortisol.[5,6] In the dexamethasone implant, the active drug is dispersed through a biodegradable copolymer of lactic acid and glycolic acid (PLGA), forming a matrix structure (Novadur, Allergan Inc).[7] Dexamethasone intravitreal implants (DEX implants) can both reduce the risk of further vision loss and increase the chances of improving visual acuity in eyes with macular edema after BRVO or CRVO.

One major goal of this 6-month study was to evaluate the mean delay before anatomical and functional recurrence after DEX implant injection in eyes with vision loss due to ME associated with BRVO or CRVO. The second goal was to estimate the efficacy and the safety profiles after treatment. All parameters were

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The study was performed with informed consent and following all the guidelines for experimental investigation in human subjects required by the local Ethics Committee (number CE_20130319_8_BWF).

reported prospectively and each month throughout the duration of the study.

Materials and methods

Study design

We conducted a prospective, observational, monocentric, and noncomparative case-series study in the Ophthalmology Department of the University Hospital of Lyon, France. The study was performed under informed consent in compliance with the Declaration of Helsinki and following all the guidelines for experimental investigations on human subjects. We obtained authorization from the local ethics committee (number CE_20130319_8_BWF). We certify that this research complies with all the applicable institutional and governmental regulations concerning the ethical use of human volunteers.

Study population

All patients in the study were at least 18 years of age and had decreased visual acuity as a result of clinically detectable macular edema (ME) associated with either CRVO or BRVO. The lower limit for the duration of ME (defined as the time since the initial ME diagnosis) was 2 weeks. There was no upper limit for the duration of ME. We selected one eye per patient as the study eye. Previous treatment of ME in the study eye was accepted as an inclusion criterion only if an intravitreal injection of Triamcinolone, Ranibizumab, or Bevacizumab had been given >6 months before inclusion. No previous intravitreal injection of DEX implants in either eye was accepted. Eligible patients had to have best-corrected visual acuity (BCVA) of $\leq 20/50$ Snellen equivalent (+0.4 LogMAR) in the study eye and better than 20/200 (+1.0 LogMAR) in the nonstudy eye. Central subfield thickness (CST) had to be $\geq 300\,\mu$m in the study eye. Patients with glaucoma requiring more than one drug treatment to control IOP were included only if they had had no steroid-induced IOP increase of >5 mm Hg in either eye after 8 days of topical treatment with dexamethasone eye drops (4 times daily) before inclusion.

The main exclusion criteria included the presence of active or a history of, choroidal neovascularization, active retinal, or optic disc neovascularization, clinically significant epiretinal membrane, presence of rubeosis iridis or retinal ischemia, any active infection, aphakia, or anterior-chamber intraocular lens, or a history of steroid-induced IOP increase ≥ 5 mm Hg for patients with glaucoma. Patients were also excluded if they had diabetic or hypertensive retinopathy in either eye, had any uncontrolled systemic disease, or were currently using, or anticipating the use of, systemic steroids or anticoagulants during the study.

Study treatment

Only topical anesthetic eye drops (Oxybuprocaine hydrochloride 1.6 mg/0.4 ml) were used in the study eye on day 0. The intravitreal injections of the DEX implant were performed according to the standard clinical practices issued by the French Health Authority (AFSSAPS) in January 2011. The DEX implant was inserted into the vitreous cavity through the pars plana using a customized, single-use, 22-gauge applicator. Patients were treated with a topical ophthalmic antibiotic two times daily starting one day before the day of their study procedure (day 0) and continuing for two days after the procedure (Azithromycin 15 mg/g eye drops 0.25 g unit dose preservative free). Moreover, none of the patients included were injected with a second DEX implant before day 180, even if there was a decrease in BCVA and/or a recurrence of ME during the first 6 months of the study, in accordance with the data in the literature and patient management protocols in 2011.

Outcome measures

The primary efficacy outcome measure was the proportion of eyes achieving at least a 3-line improvement from baseline BCVA at each study visit and at 6 months. BCVA was transposed into LogMAR for statistical purposes and was also represented in Snellen equivalent to help readers interpret our visual acuity findings in familiar units.

Secondary efficacy outcome measures were the mean change from baseline BCVA and the mean change from baseline CST measured using spectral-domain optical coherence tomography (Cirrus OCT, Carl Zeiss Meditec, Inc, Dublin, California, USA; version 3.0). Moreover, we also evaluated the mean delay of anatomical recurrence (increase in macular edema) or functional recurrence (decrease in BCVA) after treatment. We considered strict anatomical recurrence when SD-OCT imaging showed few intraretinal new cysts and/or little sub-retinal fluid. In addition, we also defined obvious anatomical recurrence when there was an increase in CST $\geq 50\,\mu$m identified using SD-OCT imaging. Functional recurrence was defined as a loss of BCVA ≥ 1-line in the study eye after treatment. Patients were assessed at baseline and days 8, 30, 60, 90, 120, 150, and 180 after treatment.

BCVA, CST, IOP, biomicroscopy, ophthalmoscopy, and adverse events were assessed at each study visit. Fluorescein angiography was performed at baseline and day 180.

Data analysis and statistical methods

Continuous and categorical variables were assessed using a variance analysis and a Pearson χ^2-test, respectively. Between groups comparisons were made using a Wilcoxon rank-sum test. Statistical significance was set at $P \leq 0.05$. The statistical analysis system (software version 9.1) was used for all parameters.

Results

Twenty-six patients were enrolled in this study between February 2011 and November 2011.

Table 1 Demographic and baseline characteristics

Characteristics total (26)	
Gender	
Male	15 (57.7%)
Female	11 (42.3%)
Age (years)	
Mean (SD)	69.3 (12.2)
Study eye	
Right	15 (57.7%)
Left	11 (42.3%)
Diagnosis in study eye	
BRVO	9 (34.6%)
CRVO	17 (65.4%)
Duration of macular edema	
Mean duration: months (SD)	9.2 (11.43)
≤90 days	11 (42.3%)
91–179 days	3 (11.6%)
≥180 days	12 (46.1%)
Previous intravitreal treatment	
Yes	14 (53.8%)
No	12 (46.2%)
Mean best-corrected visual acuity (BCVA) at baseline	
LogMAR (SD)	0.98 (0.56)
Snellen equivalent	20/200
Mean central subfield thickness at baseline	
μm (range)	619 (398–1006)
Lens status	
Phakic	19 (73.1%)
Pseudophakic	7 (26.9%)
Baseline intraocular pressure status: healthy or Primary Open Angle Glaucoma (POAG)	
Healthy	18 (69.2%)
POAG with 1 treatment	5 (19.2%)
POAG with at least 2 treatments	3 (11.6%)

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

The demographic and baseline characteristics of our population are presented in Table 1.

Efficacy analysis

Visual acuity After treatment with DEX implants, we observed that the improvement in BCVA until day 60 was faster than the loss of vision between day 60 and day 180. The proportion of eyes achieving at least a three-line improvement from baseline reached 24% on day 8 for all types of RVO. Moreover, according to our primary efficacy outcome, 88% of eyes achieved at least a three-line improvement from baseline on day 60. This result was statistically significant (primary outcome measure; Figure 1a; $P = 0.02$). The visual benefit was sustained until day 180 for 27.8% of eyes.

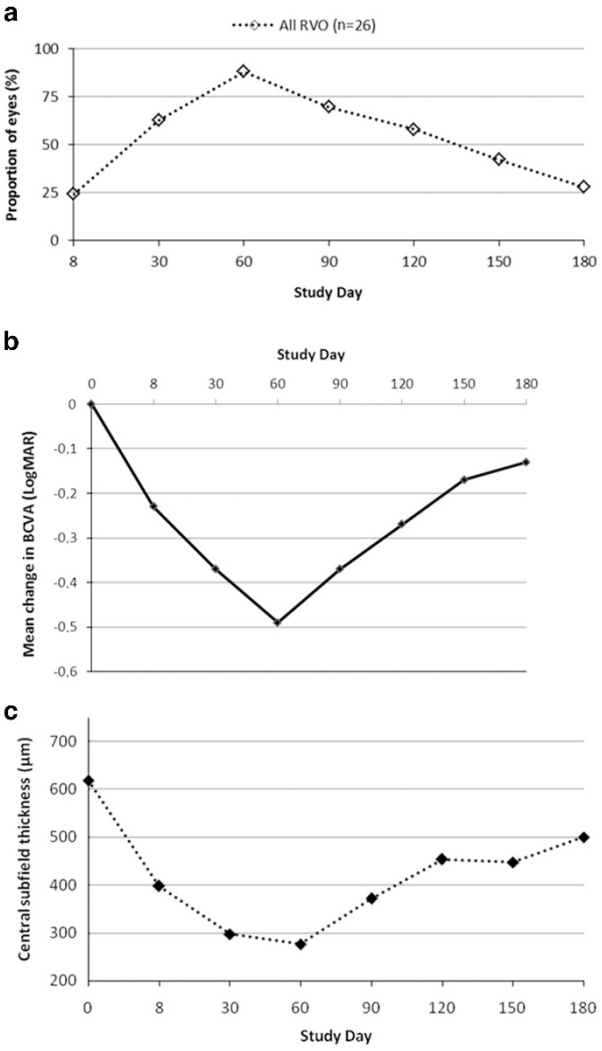

Figure 1 (a) Proportion of eyes achieving at least a three-line improvement from baseline BCVA ($n = 26$). (b) Mean change from baseline BCVA ($n = 26$). (c) Analysis central subfield thickness (CST) at each study visit ($n = 26$).

The greatest mean change from baseline BCVA was −0.49 (0.37) LogMAR on day 60 after treatment. This statistically significant result surrogates an improvement of at least three lines in BCVA (doubling mean visual acuity) (Figure 1b; $P=0.02$) on day 60. Considering all types of RVO, the mean visual benefit was approximately two lines on day 8. Despite the decrease in BCVA after day 60, it was still better than baseline on day 180 with a mean change in BCVA of −0.13(0.19) LogMAR. Furthermore, we found that 26.9% of eyes maintained BCVA of >20/50 Snellen equivalent on day 180.

Retinal thickness Regarding the anatomical outcome, the proportion of eyes with a decrease in central retinal thickness had reached 96%, 95.8%, and 96% on day 8, day 30, and day 60, respectively. The mean central retinal thickness measurement showed a fast reduction in all eyes after the DEX implant, from baseline to day 8. Indeed, there was a 35.7% decrease in retinal thickness identified using SD-OCT, from 619 to 398 μm, on day eight. The peak of anatomical efficacy was measured on day 60 with a mean decrease from baseline of 55.2%, from 619 to 277 μm (Figure 1c). Despite the progressive increase in retinal thickness after day 60, the CST level measured at day 180 was lower than at baseline. The proportion of eyes with CST<300 μm on day 180 was 11.5% ($n=3$).

Subgroup analysis by baseline retinal vein occlusion diagnosis We evaluated our primary efficacy outcome (proportion of eyes achieving at least a three-line improvement from baseline BCVA) for the CRVO and BRVO populations separately (Figure 2a). The CRVO subgroup showed a three-line BCVA improvement for 31.3%, 73.3%, and 82.4% at day 8, day 30, and day 60 after treatment, respectively. The mean change in BCVA was significantly better after treatment for CRVO than BRVO on day 30 ($P=0.02$; CRVO −0.44(0.31); BRVO −0.24 (0.12)) and day 60 (($P=0.04$; CRVO −0.57(0.43); −0.33 (0.05); Figure 2b). However, mean visual acuity was better in the BRVO subgroup at all study visits, but without any significant differences between subgroups.

Subgroup analysis according to the duration of macular edema at baseline Functional efficacy after treatment was often greater in eyes with a shorter duration of macular edema at baseline (≤90 days). However, the proportion of eyes achieving at least a three-line improvement was not statistically significant between subgroup analyses. The anatomical efficacy with SD-OCT measurements was also greater for in patients with a shorter duration of ME (≤90 days).

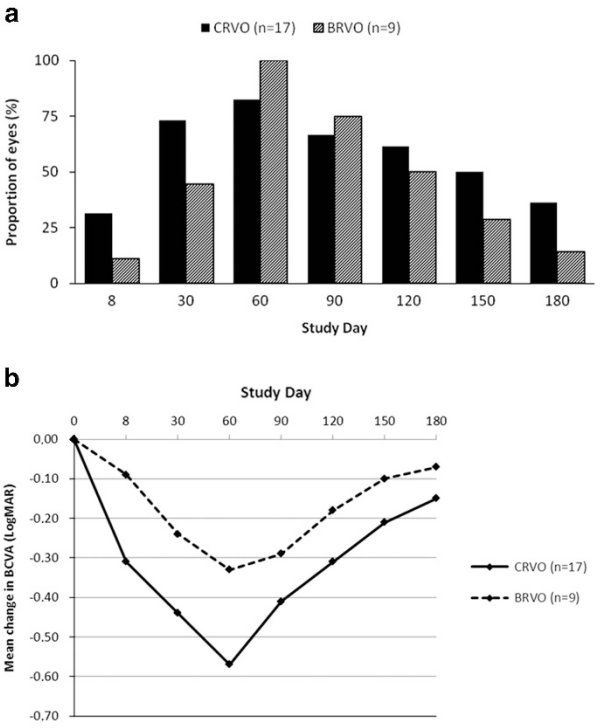

Figure 2 (a) Proportion of eyes achieving at least a three-line improvement of BCVA by baseline retinal vein occlusion diagnosis ($n=26$). (b) Mean change from baseline BCVA by retinal vein occlusion diagnosis ($n=26$).

Anatomical and functional recurrence

The proportion of eyes with qualitative anatomical, quantitative anatomical, or functional recurrence at each study visit is shown in Table 2.

The mean delay from baseline until qualitative anatomical recurrence, functional recurrence and quantitative anatomical recurrence was, respectively, 4.11 months (±0.86), 4.31 months (±1.33), and 4.40 months (±1.14). Qualitative anatomical recurrence occurred 14.40 days (SD=26.22) before quantitative anatomical recurrence on OCT imaging and 14.4 days (SD=42.18) before a loss of vision of at least one line (functional recurrence). The mean delay between quantitative anatomical and functional recurrence was 4.09 days (SD=30.58), with the functional recurrence appearing first.

One patient had no functional recurrence during the 6-month follow-up but the data on anatomical status were missing (Table 2). Only one patient had no functional and no anatomical recurrence. Importantly, all the patients with qualitative anatomical recurrence presented a functional recurrence (loss of visual acuity of at least one line) with a delay of 14.4 days (SD=42.18) on average.

Table 2 Proportion of eyes with qualitative anatomical, quantitative anatomical, or functional recurrence at each study visit

	Day 8	*Day 30*	*Day 60*	*Day 90*	*Day 120*	*Day 150*	*Day 180*	*Recurrence*	*No recurrence*
Functional recurrence	0%	0%	11.5% ($n=3$)	38.5% ($n=10$)	23.1% ($n=6$)	15.4% ($n=4$)	3.8% ($n=1$)	92.3%[a] ($n=24$)	7.7% ($n=2$)
Qualitative anatomical recurrence	0%	0%	5.3% ($n=1$)	47.3% ($n=9$)	31.6% ($n=6$)	5.3% ($n=1$)	0%	89.5%[a] ($n=17$)	10.5% ($n=2$)
Quantitative anatomical recurrence	0%	0%	8% ($n=2$)	36% ($n=9$)	32% ($n=8$)	12% ($n=3$)	4% ($n=1$)	92%[a] ($n=25$)	8% ($n=2$)

[a]Missing data were $n=7$ for qualitative anatomical recurrence and $n=1$ for quantitative anatomical recurrence.

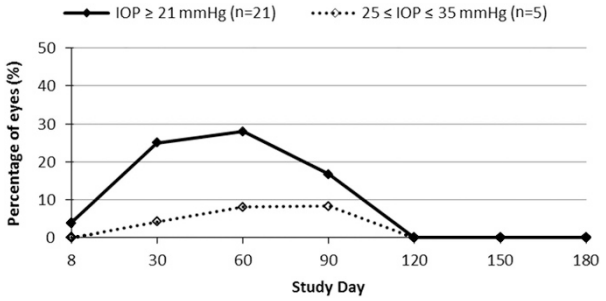

Figure 3 Intra ocular pressure (IOP) levels during the 6-month study ($n=26$).

Safety analysis

The results shown in Figure 3 focus on the issues relating to intraocular pressure. On day 30 and day 60, the measurements reported an IOP level ≥ 21 mm Hg for 25% and 28% of eyes, respectively ($n=26$).

Two patients had an increase in IOP of between 30 and 35 mm Hg at day 60. Those two patients had POAG controlled with two drugs at baseline. For two of the three POAG patients taking two drugs at baseline, we had to perform filtering surgery (trabeculectomy) on day 90 to bring the IOP back under control.

No other serious adverse events were reported except for foreign-body sensation or conjunctival hemorrhage in three patients, immediately after the intravitreal injection of the DEX implant. Rates of cataract-related adverse events in phakic eyes were not estimated because of the limited follow-up (6-month) and only one injection was performed.

Discussion

First of all, the return to both functional and anatomical efficacy was achieved very rapidly after DEX intravitreal treatment. The results in Figure 1a show that on day 8, 24% of eyes achieved at least a three-line improvement from baseline for all type of RVO; furthermore, there was a 35.7% decrease in retinal thickness on SD-OCT, from 619 to 398 μm on day 8 (Figure 3).

Second, the efficacy of the DEX implants increased over time until the 2-month point. Indeed, the mean change from baseline BCVA was statistically significant on day 60 with an improvement of more than three lines (Figure 1b; $P=0.02$). Moreover, 88% of eyes achieved at least a three-line improvement from baseline on day 60. This result was statistically significant (primary outcome measure; Figure 1a; $P=0.02$). The visual benefit was also sustained until day 180 for 27.8% of eyes. As for functional efficacy, the peak in anatomical efficacy was measured on day 60 with a mean decrease in retinal thickness from baseline of 55.2%, from 619 to 277 μm (Figure 1c). Moreover, our population was mostly affected by CRVO ($n=17$; 65%), whereas only a minority had BRVO ($n=9$; 35%). These demographic characteristics are unusual in daily medical practice and could account for differences with other published studies.[7–9] Furthermore, the mean age of the patients enrolled (69.3 years; ± 12.2 years) was higher (although not significantly) than those in the Geneva study group (64.7 years; range 33–90 years).[7] Mean BCVA at baseline was poor in our population (20/200 Snellen equivalent; +0.98(0.56) LogMAR; about 35 letters translated into the ETDRS grading scale) compared to 54.3, 51, and 48 letters in the Geneva study group, SCORE study and CRUISE Trial, respectively.[7,9,10] It is well documented that the lower the initial visual acuity is the greater the visual gain. DEX implants could therefore be very helpful even for patients with poor baseline BCVA. Indeed, our results showed that 71.4% of patients with baseline BCVA $<20/200$ ($n=8$) had at least a three-line improvement on day eight. Even if the mean BCVA after treatment is not as high as for patients with better baseline BCVA, we can imagine the enormous benefits for our patients in terms of their day-to-day lives.

Concerning the subgroup analysis, the results shown in Figures 2a and b demonstrate that the gain in vision after DEX intravitreal treatment was higher for patients with poor baseline visual acuity (patients with CRVO). The percentage of eyes achieving at least a three-line improvement from baseline BCVA was sustained at a slightly higher rate among eyes with CRVO than eyes with BRVO on day 8 and 30 and after day 90. Patients with CRVO had at least a three-line improvement in BCVA (doubling of vision) from baseline, measured from day 8 up until day 120 (Figure 2b), whereas patients with BRVO only achieved a three-line improvement on day 60.

Furthermore, the mean duration of ME at baseline in our study (9.2 months; SD = 11.43) was higher than the other trials, which have assessed intravitreal treatment for ME secondary to RVO. The BRAVO, CRUISE, and GENEVA trials are three studies that have demonstrated the efficacy of anti-VEGF agents and DEX implants, but they cannot serve as comparative studies.[7,8,10] For example, two-thirds of the patients included in the BRAVO and CRUISE (ranibizumab) studies had more recent onset macular edema (short duration $\leq$90 days) than patients in the GENEVA study (only 16% $\leq$90 days). A shorter duration of ME was associated with greater improvements in BCVA after DEX implant.[11] However, the improvement found in this study was not statistically significant regarding the percentage of eyes achieving at least a three-line increase. This may be owing to the specificities of our population (more CRVO than BRVO) and the limited number of patients included in our study. These results suggest that earlier intravitreal treatment with DEX implant after macular edema secondary to RVO is beneficial.

The originality of this work is that we analyzed and found differences between three patterns of recurrence. It was possible during this 6-month prospective study, with monthly functional and anatomical examinations, to evaluate the proportion of eyes with recurrence and the mean delay before recurrence for all patients. The highest proportion of patients with anatomical and functional recurrences was found between 3 and 5 months (Table 2), in accordance with the GENEVA study findings and in our day-to-day clinical practice with DEX implants.[7,11] We determined three patterns of recurrence: qualitative anatomical recurrence occurring on average at 4.11 months (SD = 0.86), functional recurrence at 4.31 months (SD = 1.33), and quantitative anatomical recurrence at 4.40 months (SD = 1.14). One limitation of our study is the small number of eyes included. However, that is mitigated by the prospective follow-up at monthly intervals in order to provide more precise data on the duration of action and recurrences. To our knowledge, no other prospective study has described such patterns of recurrence. Recently Mayer *et al*[12] defined recurrence as a loss of BCVA of more than 5 letters ETDRS and/or an increase in retinal thickness on OCT of >100 microns. They did not separate these two patterns of recurrence and did not provide the delay for each one. They estimated the overall mean delay of recurrence after DEX intravitreal treatment as 3.8 months (CRVO) and 3.5 months (BRVO). Merkoudis *et al*[13] found a recurrence of macular edema between months 4 and 5 after the first DEX implant in eyes treated for RVO. However, other retrospective studies found a mean reinjection interval of 4.5, 5.3, and 5.6 months after treatment with DEX implants,[14–16] with a probable delay between recurrence and reinjection time. However, all patients with qualitative anatomical recurrence on SD-OCT imaging had functional recurrence at 14.44 days (SD = 42.18) on average after the first signs on OCT. These results emphasize the important role of SD-OCT imaging in diagnosing early recurrence after intravitreal treatment. Furthermore, we determined that it was neither necessary nor advisable to wait for an obvious increase in CST on SD-OCT of around 50 μm to confirm recurrence. Indeed, the increase in CST $\geq$ 50 μm was actually the last sign of recurrence, after loss of vision and the recurrence of new intraretinal cysts and/or sub-retinal fluid. All the patients in our study with qualitative anatomical recurrence experienced functional recurrence a few days or weeks later. Early retreatment would therefore seem to be both anatomically and functionally beneficial for patients, and we would therefore recommend retreatment with DEX implants within the 2-week period following the qualitative anatomical recurrence of ME after RVO. The recent multicentric study conducted by Coscas *et al*[17] emphasized the need to retreat patients as soon as possible after the observation of a recurrence of ME, as well as the clinical benefits of doing so. In this study, the mean interval for Ozurdex reinjection was 5.9 months following the first injection and 8.7 months following the second.[17] It would be interesting to conduct a larger study to determine if the delay in anatomical and functional recurrence changes and lengthens after repeat intravitreal injections.

Concerning IOP management, nearly all cases of high IOP were controlled with topical IOP-lowering medication alone. Only two patients with primary open-angle glaucoma (POAG) controlled at baseline, but already receiving two drug treatments, required filtering surgery at day 90. Despite our awareness of the high IOP risks for these two patients before enrolment, we decided on DEX intravitreal treatment owing to a medical history of heart attack that theoretically limited the use of Bevacizumab or Ranibizumab. Moreover, we performed a prior test with DEX eye drops for one week with no increase in IOP. In our case, the filtering surgery succeeded in controlling IOP after day 90 for these two patients. We would advise the strictest compliance with the recommendations on the use of DEX implants in patients with glaucoma. However, compared with 16% in the Geneva Trial, only 8% of all eyes in our study had IOP > 25 mm Hg at its peak (day 60).[7] For the third patient with POAG controlled with two drug treatments and the five other patients with POAG, controlled with just one drug treatment at baseline, there was no significant increase in IOP during the 6-month follow-up period. Prior testing with DEX eye drops before intravitreal treatment is not recommended as part of everyday clinical practice as there is still a risk of an increase in IOP, even if the test results are negative. However, if the test is positive, DEX implants are certain to increase IOP.

Concerning cataract-related adverse events in phakic eyes, the rates were not precisely estimated in our study for three reasons: the limited follow-up of our study (6-month), the mean population age of 69.3 years (SD = 12.2; range = 42–94 years) for which cataract is frequent, and because only one injection was performed for each eye during the study.

In conclusion, the DEX implant is a functionally and anatomically effective treatment for ME after RVO even in cases of ME with a long duration or poor visual acuity before treatment. Moreover, it is well tolerated, producing generally transient, moderate, and readily managed increases in IOP, except for patients treated more than one drug. Further longer studies would be of interest in order to assess the delay of recurrence after a second, third, or further treatment with DEX implants or combined therapies for ME after RVO.

Summary

What was known before

- Ozurdex duration efficacy was known to be between 3 and 6 months after intravitreal injection.

What this study adds

- The delay of anatomical and functional recurrence assessed by a monthly prospective examination during 6 months.
- In daily clinical practice, it is easier to manage a patient knowing this delay to perform a next injection, if necessary, for retreatment.

Conflict of interest

PD serves as a Principal Investigator in advisory boards and recieves lecture fees from Alcon, Alimera, Allergan, EyeTechCare, Théa. LK served as a Principal Investigator for trials sponsored by Novartis, Bausch&Lomb, Théa, Alcon; has sat on advisory boards for Alcon, Alimera, Allergan, Bayer, Bausch&Lomb, Novartis, Théa; recieved lecture fees from Alcon, Alimera, Allergan, Bayer, Bausch&Lomb, Novartis, Théa. VF declares no conflict of interest.

References

1 Noma H, Mimura T, Tatsugawa M, Shimada K. Aqueous flare and inflammatory factors in macular edema with central retinal vein occlusion: a case series. *BMC Ophthalmol* 2013; **13**: 78.
2 Yao J, Chen Z, Yang Q, Liu X, Chen X, Zhuang M *et al.* Proteomic analysis of aqueous humor from patients with branch retinal vein occlusion-induced macular edema. *Int J Mol Med* 2013; **32**(6): 1421–1434.
3 Noma H, Mimura T, Shimada K. Role of inflammation in previously untreated macular edema with branch retinal vein occlusion. *BMC Ophthalmol* 2014; **14**(1): 67.
4 Noma H, Mimura T, Yasuda K, Shimura M. Role of soluble vascular endothelial growth factor receptors-1 and -2, their ligands, and other factors in branch retinal vein occlusion with macular edema. *Invest Ophthalmol Vis Sci* 2014; **55**(6): 3878–3885.
5 Glacet-Bernard A, Coscas G, Zourdani A, Soubrane G, Souied EH. Steroids and macular edema from retinal vein occlusion. *Eur J Ophthalmol* 2011; **21**(Suppl 6): S37–S44.
6 Pielen A, Feltgen N, Isserstedt C, Callizo J, Junker B, Schmucker C. Efficacy and safety of intravitreal therapy in macular edema due to branch and central retinal vein occlusion: a systematic review. *PLoS One* 2013; **8**(10): e78538.
7 Haller JA, Bandello F, Belfort R, Blumenkranz MS, Gillies M, Heier J *et al.* Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. *Ophthalmology* 2011; **118**(12): 2453–2460.
8 Campochiaro PA, Heier JS, Feiner L, Gray S, Saroj N, Rundle AC *et al.* Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology* 2010; **117**(6): 1102–1112 e1.
9 Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Blodi BA, Hartnett ME *et al.* Baseline predictors of visual acuity and retinal thickness outcomes in patients with retinal vein occlusion: Standard Care Versus COrticosteroid for REtinal Vein Occlusion Study report 10. *Ophthalmology* 2011; **118**(2): 345–352.
10 Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N *et al.* Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology* 2010; **117**(6): 1124–1133 e1.
11 Yeh W-S, Haller JA, Lanzetta P, Kuppermann BD, Wong TY, Mitchell P *et al.* Effect of the duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant. *Ophthalmology* 2012; **119**(6): 1190–1198.
12 Mayer WJ, Wolf A, Kernt M, Kook D, Kampik A, Ulbig M *et al.* Twelve-month experience with Ozurdex for the treatment of macular edema associated with retinal vein occlusion. *Eye (Lond)* 2013; **27**(7): 816–822.
13 Merkoudis N, Granstam E. Treatment of macular edema associated with retinal vein occlusion using sustained-release dexamethasone implants in a clinical setting. *Eur J Ophthalmol* 2013; **23**(4): 558–563.
14 Matonti F, Meyer F, Guigou S, Barthelemy T, Dumas S, Gobert F *et al.* Ozurdex in the management of the macular edema following retinal vein occlusion in clinical practice. *Acta Ophthalmol* 2013; **91**(7): e584–e586.
15 Bezatis A, Spital G, Höhn F, Maier M, Clemens CR, Wachtlin J *et al.* Functional and anatomical results after a single intravitreal Ozurdex injection in retinal vein occlusion: a 6-month follow-up—the SOLO study. *Acta Ophthalmol* 2013; **91**(5): e340–e347.
16 Capone A, Singer MA, Dodwell DG, Dreyer RF, Oh KT, Roth DB *et al.* Efficacy and safety of two or more dexamethasone intravitreal implant injections for treatment of macular edema related to retinal vein occlusion (Shasta study). *Retina* 2014; **34**(2): 342–351.
17 Coscas G, Augustin A, Bandello F, de Smet MD, Lanzetta P, Staurenghi G *et al.* Retreatment with Ozurdex for macular edema secondary to retinal vein occlusion. *Eur J Ophthalmol* 2014; **24**(1): 1–9.