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RETINA®

THE JOURNAL OF RETINAL AND VITREOUS DISEASES

OZURDEX® (dexamethasone intravitreal implant) 0.7 mg for Treating Macular Edema Following Retinal Vein Occlusion: A Case-Based Discussion

Indications and Usage
Diabetic Macular Edema
OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of diabetic macular edema.

Retinal Vein Occlusion
OZURDEX® is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis
OZURDEX® is indicated for the treatment of noninfectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION
Contraindications
Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Please see additional Important Safety Information on the following pages.

On November 12, 2017, a group of experts in retinal diseases convened in New Orleans, LA, to discuss their experience with OZURDEX® (dexamethasone intravitreal implant) for the treatment of macular edema (ME) following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). They shared their thoughts on the role of OZURDEX® in the treatment of RVO, reviewed data from a clinical trial program of OZURDEX® in RVO, and discussed patient cases.

Profile of Retina Experts

Michael S. Ip, MD
Professor of Ophthalmology,
Doheny Eye Institute
University of California in
Los Angeles
Los Angeles, CA

Michael S. Ip, MD, is a retina specialist and professor of ophthalmology at the Doheny Eye Institute at the University of California in Los Angeles. He treats various retinal vascular diseases, with expertise in retina image analysis.

Sophie J. Bakri, MD
Professor of Ophthalmology,
Mayo Clinic
Rochester, MN

Sophie J. Bakri, MD, is a professor of ophthalmology at Mayo Clinic in Rochester, Minnesota, and a vitreoretinal specialist focused on medical and surgical treatment of patients with retinal vascular diseases.

Daniel Roth, MD
Associate Clinical Professor
of Ophthalmology
NJ Retina
Department of Ophthalmology
Rutgers Robert Wood Johnson
Medical School
New Brunswick, NJ

Daniel Roth, MD, is an associate clinical professor in the Department of Ophthalmology and a vitreoretinal specialist at NJ Retina, a part of Rutgers Robert Wood Johnson Medical School. He is a medical and surgical retina specialist, with an emphasis on treating macular disease.

Aleksandra Rachitskaya, MD
Assistant Professor of
Ophthalmology, Cleveland
Clinic Lerner College of
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Cole Eye Institute,
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Cleveland, OH

Aleksandra Rachitskaya, MD, is a vitreoretinal specialist at the Cole Eye Institute at the Cleveland Clinic and Assistant Professor of Ophthalmology at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. She treats patients with a wide range of diseases of the retina, using both medical and surgical approaches.

INTRODUCTION

Dr. Ip first presented some background information on RVO and its diagnosis and treatment, and then opened the floor for discussion among the group.

RVO is the second most common type of retinal vascular disease,[1,2] and it can occur when the circulation in the central retinal vein or a branch retinal vein becomes partially or completely blocked.[3,4] Based on pooled data from 68,751 patients standardized by age and sex in the United States, Europe, Asia, and Australia, the estimated prevalence of CRVO is 0.65 per 1000 and BRVO is 3.77 per 1000.[5] Both CRVO and BRVO can lead to ME,[2,6] and patients may experience impaired vision, "floaters," and metamorphopsia.[7]

Patients with BRVO usually complain of a sudden, painless decrease in vision or a visual field defect in the affected eye or eyes.[2] Intraretinal hemorrhages, retinal edema or ME, and cotton wool spots can be seen in the portion of the fundus affected by the involved retinal vein.[2] In chronic BRVO, hemorrhages may be absent and ME may be the only sign of disease present.[8] Retinal neovascularization may be seen in eyes with large areas of nonperfusion. This may in turn lead to vitreous hemorrhage and tractional retinal detachments, which can create retinal breaks leading to combined rhegmatogenous and tractional retinal detachments. Neovascular glaucoma and neovascularization at the disc are rare.[8] In patients with reduced vision, fluorescein angiography can help identify vision loss secondary to ME or macular ischemia.[2]

Patients with CRVO usually complain of a sudden, painless, unilateral loss of vision.[2] CRVO usually presents as widespread, deep, and superficial hemorrhages, cotton wool spots, retinal edema, and dilated tortuous veins.[2]

Disease Presentation and Diagnosis

Dr. Aleksandra Rachitskaya: After diabetic retinopathy, RVO is the second most common medical retinal vascular problem that I see, in about 10% of my patients. In an average clinic day, I see at least 1 to 2 patients with RVO, and some of these patients are referred to my practice with very complex disease. BRVO is more common than CRVO.

Dr. Michael Ip: I have practiced in 2 different areas of the country—at the University of Wisconsin, a relatively rural area, and at UCLA Doheny, which is more urban—but the frequency of RVO was very similar in both. It's frequent enough that it is always top of mind.

Dr. Sophie Bakri: Typically, I see RVO in older patients, usually over the age of 60. These patients tend to have hypertension and either have a history of glaucoma or are newly diagnosed with glaucoma. Younger patients with RVO are rare. Patients are referred to me from either ophthalmology or optometry. Patients referred from optometry have RVO with or without ME or ischemia, while those referred from ophthalmologists tend to have more severe disease, with ME or rubeosis.

Dr. Rachitskaya: My RVO patients also tend to be older and are split between phakic and pseudophakic. They have similar risk factors: diabetes, hypertension, and arteriosclerosis.[9] If RVO patients are current smokers, I counsel about smoking cessation. In younger patients, I get concerned about hypercoagulable diseases.

Dr. Ip: Diagnosis is usually fairly straightforward in the acute phase: with both CRVO and BRVO, there is a painless decrease in visual acuity, with typical intraretinal hemorrhage, cotton wool spots, and dilated veins in all four quadrants.[10-12]

Dr. Daniel Roth: There are subtle cases, however, in which you have to look carefully, not just at hemorrhages, but also at the optic nerve, for shunt vessels, for tortuosity—the vascular patterns that indicate a vein occlusion.[10,13]

Discussion—Prognosis

Dr. Rachitskaya: With regard to prognosis, the biggest issue with both BRVO and CRVO patients, and the reason why their vision is affected, is ME. Particularly in CRVO, there is also an additional risk of macular ischemia, neovascularization of the iris, and neovascular glaucoma that can negatively affect prognosis and treatment outcomes.[11,12,14] For both BRVO and CRVO, vitreous hemorrhage and tractional detachments may be present.[11]

I usually start treating ME if it is symptomatic and affecting vision; even if the patient has a good response, though, I keep the potential complications in mind. For patients with a small BRVO, I might not worry about neovascularization, but they still have the underlying risk factors and may develop disease in the other eye.[12]

Dr. Bakri: Ultimately, RVO can be seen as a spectrum of disease; the CRVO patient with impaired vision and ischemia is going to have a worse prognosis than a patient with a small, localized BRVO.[12] In some cases, I might decide to observe the patient with a small BRVO rather than immediately initiate treatment.

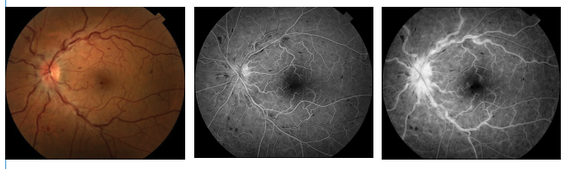
Dr. Roth: CRVO and BRVO are different entities. The patient with CRVO has a higher risk of iris neovascularization and neovascular glaucoma than a patient with BRVO.[12] A patient with BRVO can develop CRVO.[12] It is important to closely monitor all RVO patients, but in general, the patient with a more distal RVO with less occlusion will have a better prognosis than more proximal RVOs with greater ischemia.

While visual acuity at presentation is an important predictor of outcome, I would say that visual acuity after the initiation of treatment is a stronger predictor.[15] Take a patient with 900 µm of ME and very poor vision who improves dramatically after treatment; this patient will usually have a good prognosis if he or she does not become ischemic or develop neovascularization. However, if this patient does not show improvement in ME in response to treatment, it may be due to underlying ischemic changes, poor perfusion, macular pigmentation, or signs of chronicity, which are disease features that will negatively affect his or her outcomes.[15,16]

Dr. Rachitskaya: I used to think that the presenting visual acuity predicts outcomes, but I have been surprised by some patients who have severe CRVO and who responded very nicely to treatment. For this reason, I give every patient who presents with severe disease a trial of treatment.

Discussion—Imaging

Dr. Bakri: For evaluating patients with suspected RVO, I use wide-angle fluorescein angiography and optical coherence tomography (OCT), sometimes with color photos. Occasionally, I will also use OCT angiography.



Dr. Roth: I get the fundus photo not only to monitor edema and perfusion, but also to look at hemorrhages and cotton wool spots.

Dr. Ip: There is some evidence that hemorrhage is a biomarker for severity of disease, similar to how intraretinal microvascular abnormality (IrMA) is a marker of diabetic retinopathy severity.[17] There is a need to develop a severity scale for retinal vein occlusion.[18]

Dr. Roth: The presence of hemorrhages increases the risk of recurrent ME.[16]

Dr. Ip: Even when ME is resolved, if hemorrhages are still present, that helps me decide the treatment approach to take.

Dr. Rachitskaya: I find value in getting an angiogram to evaluate whether there is any ischemia that might have been missed on the exam and to look for other RVO biomarkers and hemorrhages. If there is a lot of hemorrhaging, it can be hard to establish how much ischemia is present. Also, as I progress with treatment, I might repeat fluorescein angiography.

Dr. Roth: I do not do wide-field angiography routinely. It can be helpful to obtain fluorescein angiography to evaluate ischemia and poor perfusion, but it is not clear whether the presence of peripheral ischemia or nonperfusion, as opposed to central ischemia, predicts the risk of neovascularization. Wide-field periphery may not be helpful, at least clinically.[12]

INFLAMMATION AND RVO

Inflammatory processes are critical factors in the pathogenesis of retinovascular disorders, including RVO.[19] Retinal hypoxia and ischemia induced by RVO promote the release of various inflammatory mediators,[20] which in turn increase retinal capillary permeability, leading to breakdown of the blood-retinal barrier, vascular leakage, and ME.[6] Reducing inflammation early in the treatment of RVO, using treatments that target multiple inflammatory cytokines, can help treat ME.[21,22]

Discussion—Inflammation in RVO

Dr. Ip: In terms of the etiology of ME in patients with RVO, we know that it is multifactorial and has an inflammatory component, which is why I sometimes also consider alternative therapy.

Dr. Bakri: Both vascular endothelial growth factor (VEGF) and inflammation are involved; it is possible that some patients may have a larger inflammatory component to their disease.

Dr. Roth: I completely agree. If there is vascular occlusion and edema, then inflammation is present.[19] Although inflammation may not be the primary treatment target, it still needs to be treated. In some of my younger RVO patients and patients without clear vascular pathology, the disease may be predominantly inflammatory.[23]

For my patients who have RVO with an inflammatory component, I would try OZURDEX® (dexamethasone intravitreal implant) at that point and watch them closely to evaluate the clinical response, including vision. I use OZURDEX® when I need a corticosteroid to treat inflammation. I use an anti-VEGF to address VEGF.

Dr. Rachitskaya: Something I take into account is how frequently my RVO patients need to visit the office. Many of them are working adults, so it's difficult for them to frequently take time away from their jobs.

OZURDEX® IN ME SECONDARY TO RVO

OZURDEX® is a sustained-release, biodegradable steroid implant containing 0.7 mg of the corticosteroid dexamethasone, approved for the treatment of ME following either BRVO or CRVO.[22] Dexamethasone has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines, resulting in decreased edema, fibrin deposition, capillary leakage, and migration of inflammatory cells.[22]

Continued on next page.

OZURDEX® IN ME SECONDARY TO RVO (continued)

The efficacy of OZURDEX® (dexamethasone intravitreal implant) for the treatment of ME following BRVO or CRVO was assessed in the Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA (GENEVA) trial program.[24,25] GENEVA included two multicenter, randomized, phase 3 studies that included a 6-month, double-masked period (initial-treatment period) and a 6-month open-label extension period (Figure 1).

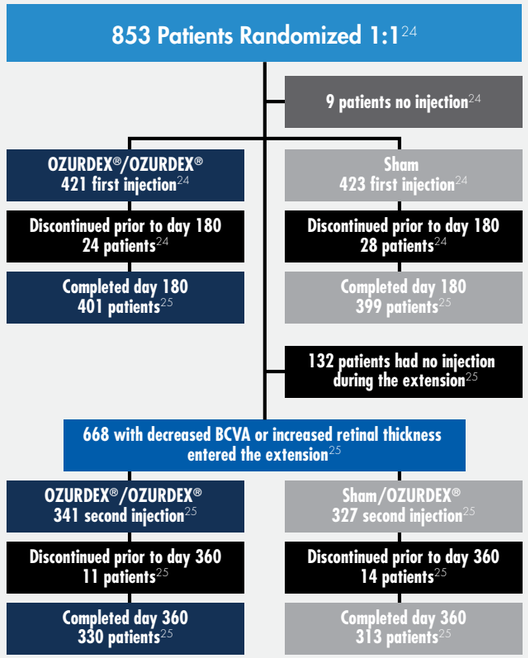
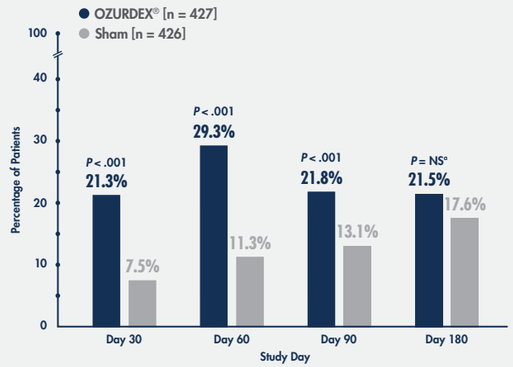


Figure 1.

The average patient age (64 years), best-corrected visual acuity (BCVA) (54 letters), and retinal thickness by OCT (551 µm) at baseline were similar between the 2 treatment groups. The majority of patients had a disease duration of ≥ 90 days and approximately twice as many patients had BRVO as had CRVO.[24]

The proportion of patients achieving at least a 15-letter (3-line) improvement from baseline BCVA was significantly greater in the OZURDEX® group than in the sham group from day 30 through day 90 (Figure 2).[24] Patients treated with OZURDEX® gained 3 lines of vision significantly faster than did those treated with sham ($P < .01$) based on time to achieve a ≥ 3-line improvement in BCVA cumulative response rate curves.[22] The onset of a ≥ 15-letter improvement in BCVA with OZURDEX® occurred within the first 2 months after implantation in approximately 20% to 30% of patients (vs 7%-12% in the sham group), and the effect persisted approximately 1 to 3 months after onset (Figure 2).[22] The greatest response in the OZURDEX® group was seen at day 60, when approximately 29% of patients achieved at least a 15-letter improvement from baseline compared with approximately 11% in the sham group.[26]

Percentage of RVO Patients With ≥ 15 Letter Gains From Baseline in BCVA[24,26]



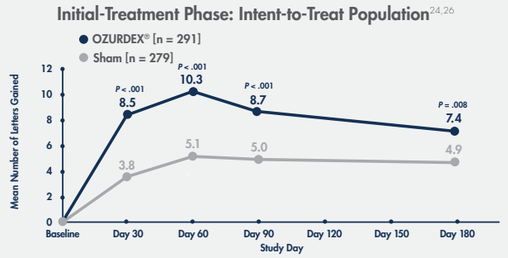
Pooled results of two phase 3, multicenter, randomized, masked, sham-controlled, 6-month trials in patients with macular edema following BRVO or CRVO.
* NS = not significant.

Figure 2.

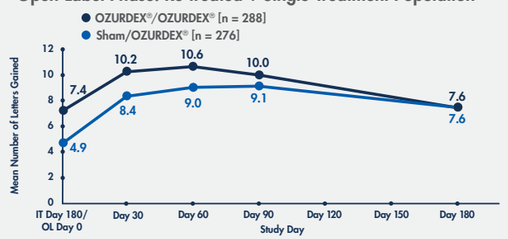
During the initial treatment phase, BRVO patients who received OZURDEX® gained up to 10.3 letters from baseline, and CRVO patients gained up to 8.7 letters (Figures 3 and 4).[24,26]

Mean Change From Baseline BCVA in BRVO Patients

Initial-Treatment Phase: Intent-to-Treat Population[24,26]



Open-Label Phase: Re-treated + Single-Treatment Population[26,a,b]

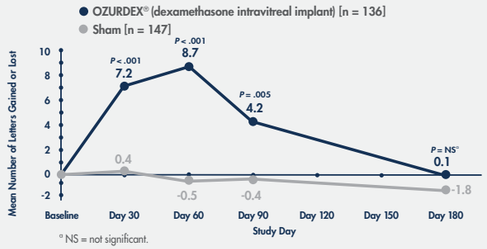


[a] Excludes randomized patients who did not receive treatment (OZURDEX® or sham) in the initial-treatment phase.
[b] Patients in the single-treatment group received OZURDEX® in the initial-treatment phase, but not in the open-label phase (n = 61).[26]

Figure 3.

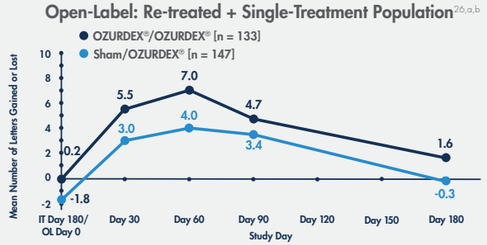
Mean Change From Baseline BCVA in CRVO Patients

Initial-Treatment Phase: Intent-to-Treat Population[24,26]



* NS = not significant.

Open-Label: Re-treated + Single-Treatment Population[26,a,b]



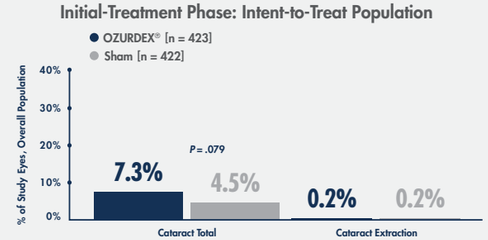
[a] Excludes randomized patients who did not receive treatment (OZURDEX® or sham) in the initial-treatment phase.
[b] Patients in the single-treatment group received OZURDEX® in the initial-treatment phase, but not in the open-label phase (n = 19).[26]

Figure 4.

During the entire initial 180-day treatment phase of the GENEVA study, the rates of cataracts in the overall population were 7.3% for OZURDEX® patients and 4.5% for sham patients ($P = .079$). 0.2% of OZURDEX® patients required cataract surgery vs 0.2% of sham patients through month 6 (Figure 5).[24] Following a second injection of OZURDEX® in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

Overall Population: Incidence of Cataract and Surgery Over 6 Months[24]

Initial-Treatment Phase: Intent-to-Treat Population



373 OZURDEX® treated eyes and 387 sham-treated eyes were phakic at baseline.

Phakic Population: Incidence of Cataract and Surgery Over 12 Months[25]

Initial Treatment + Open-Label Extension: Re-treated + Sham/OZURDEX® Phakic Population

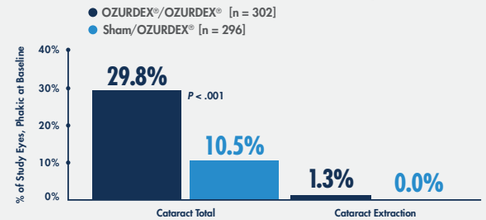


Figure 5.

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IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
Retinal Vein Occlusion and Posterior Segment Uveitis
Adverse reactions reported by greater than 2% of patients in the first 6 months following injection of OZURDEX® (dexamethasone intravitreal implant) for retinal vein occlusion and posterior segment uveitis include: intraocular pressure increased (25%), conjunctival hemorrhage (22%), eye pain (8%), conjunctival hyperemia (7%), ocular hypertension (5%), cataract (5%), vitreous detachment (2%), and headache (4%).

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
Retinal Vein Occlusion and Posterior Segment Uveitis (continued)
Increased IOP with OZURDEX® (dexamethasone intravitreal implant) peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

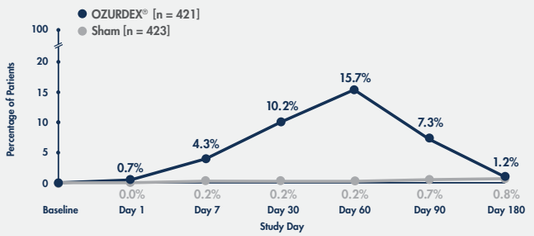
Please see additional Important Safety Information on the following pages.

OZURDEX® IN ME SECONDARY TO RVO (continued)

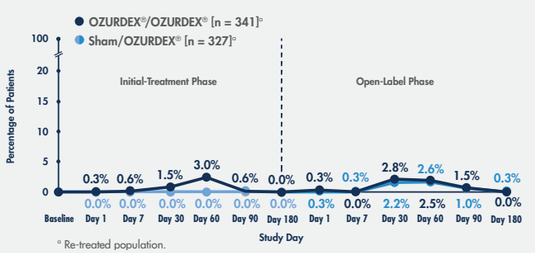
In the GENEVA trial, intraocular pressure (IOP) increases of ≥ 10 mm Hg from baseline occurred in about 16% of OZURDEX® (dexamethasone intravitreal implant) patients (vs 0.2% of sham patients) at day 60 (Figure 6). 26.6% of OZURDEX® patients had IOP increases of ≥ 10 mm Hg from baseline at any study visit (vs 1.4% of sham patients).[26] Pressure levels typically returned to baseline levels by 180 days post treatment.[25] IOP ≥ 35 mm Hg was low across the initial- and extended-treatment phase studies and peaked at day 60 after the first treatment and around days 30 and 60 after the second treatment (Figure 6).[26]

In the GENEVA trial, most patients with increased IOP were managed with observation or topical IOP-lowering medications.[24] At any time during the 6-month initial treatment phase, around 30% of OZURDEX® patients required IOP-lowering medication vs almost 4% of sham patients. At the final study visit (day 180), 23% of OZURDEX® patients and 4% of sham patients were on IOP-lowering medications; among those patients, 16% of OZURDEX® patients and 3% of sham patients were on 1 IOP-lowering medication.[26] Three patients who received OZURDEX® required surgery for elevated IOP.[22,24]

Percentage of Patients With ≥ 10 mm Hg Increase From Baseline IOP[25,26]



Percentage of Patients With IOP ≥ 35 mm Hg[25,26]



* Re-treated population.

Figure 6.

Discussion—Clinical Trial Experience

Dr. Roth: The GENEVA study demonstrated the efficacy of OZURDEX® in the first 90 days after 1 injection for the treatment of ME in RVO (Figure 2).[24]

Dr. Ip: The BRVO and CRVO data show the same thing: a peak effect of OZURDEX® between day 30 and 60 that tapers off (Figures 3 and 4).[24]

It's interesting that the area under the curve looks smaller in the group assigned to sham then OZURDEX® compared to the group that received 2 doses of OZURDEX®. There may be a "penalty" in waiting to treat; the patients who received the sham injection in the first 6 months theoretically would have had more ME for a longer period of time before receiving OZURDEX®.[26] When you see ME, it's important to treat it.

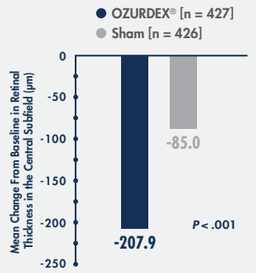
Dr. Roth: You may have a "penalty" when you start treatment late. That being said, I don't think it's always wrong to wait a month or 2 to see if a BRVO with a little bit of edema will resolve on its own, or if that rare CRVO will resolve or not progress. There are certain features of a patient's systemic illness or lifestyle that can be modified to have a dramatic effect on RVO.[27]

Dr. Rachitskaya: It's important to note that the majority of patients in the trial had ME for more than 90 days at baseline.[24]

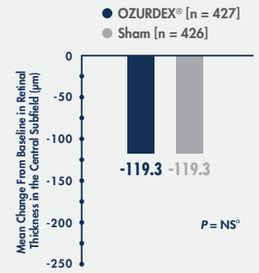
Dr. Roth: It was an average of 156 days, so the patients in the sham group would be 6 months into the trial plus 156 days before reaching the open-label part of the trial—that is a long time to have untreated ME.[24]

Dr. Ip: Turning to the anatomical outcomes, OZURDEX® also had a significant difference vs sham at 90 days with respect to mean change from baseline in central retinal thickness on OCT compared to the sham group ($P < .001$), but not at day 180 (Figure 7).[24]

Mean Change in Retinal Thickness at Day 90[26]



Mean Change in Retinal Thickness at Day 180[26]



Pooled results of two phase 3, multicenter, randomized, masked, sham-controlled, 6-month trials in patients with macular edema following BRVO or CRVO. Four hundred twenty-seven patients received OZURDEX® 0.7 mg and 426 patients received sham injections. Central retinal subfield thickness was measured using optical coherence tomography (OCT). Baseline retinal thickness (central subfield): 562.0 µm for OZURDEX® vs 538.6 µm for sham.[24,26]
* NS = not significant.

Figure 7.

Dr. Ip: With regard to the IOP rise, the higher rates in the OZURDEX® group compared to the sham group are expected (Figure 6), but it is also important to note that very few patients needed surgery (3 patients in the OZURDEX® group).[24]

Medical management[26]

IOP-Lowering Medication	OZURDEX®	Sham
At baseline	5.7% (24/421)	2.4% (10/423)
During the 6-month study	29.7% (125/421)	3.8% (16/423)
At the final study visit	22.8% (96/421)	3.8% (16/423)

Table 1.

Dr. Rachitskaya: This is consistent with what I see in practice. That said, this is a population of patients who are already prone to developing cataracts because of their age, and if a patient is receiving repeat OZURDEX® injections, you're probably going to see some cataract formation.[22]

In terms of IOP elevations, I find that in most cases they are transient—once the effects of the steroid wear off, the patient generally returns to normal pressure. If I do see an increase in pressure, I usually start IOP-lowering drops and monitor the patient. Usually, if a patient has an IOP elevation in the 20 mm Hg range, I can bring it down with the drops and the steroid effect eventually wears off.

If I can't control the IOP with one drop, then I might refer the patient to a glaucoma specialist.

If I see anything concerning with the optic nerve, though, or I'm worried that the patient might need more aggressive treatment, then I would definitely refer the patient. RVO patients are more likely to have glaucoma or be diagnosed with glaucoma, so if I have any concerns, it's very easy for me to refer.[12]

Dr. Bakri: If it's a case of ocular hypertension and not glaucoma, which invariably it is in the beginning stages of treatment, then I feel comfortable initiating IOP-lowering drops. If it gets to the point that I start having to add multiple drops, I might be comfortable adding a second drop, but after that, I refer the patient to the glaucoma specialist.

I'll also get a baseline OCT of the nerve. Sometimes I will order visual fields, but if it's an ocular hypertension issue, it may be transient and may improve as the steroid wears off.

Dr. Roth: I agree that cataract development is not as common with a single OZURDEX® injection as compared with repeated injections.

An IOP rise is more likely in the 15%-to-20% range, but it's usually manageable and generally not that long-lasting. I would manage it with 1, 2, or even 3 drops before referring the patient to a glaucoma specialist. It's less frequent for me to encounter an IOP elevation that is so difficult to manage with medical therapy that I need to refer the patient to a glaucoma specialist.

However, if I feel a patient who has elevated pressure issues really needs a steroid, I would get a glaucoma specialist involved at the outset. It is important to try OZURDEX® to see if it will be an effective treatment option for ME following RVO; one trial of OZURDEX® may be helpful. If OZURDEX® ends up being an effective treatment for a patient, then you have to weigh the benefit of improving their vision by treating ME against the potential for a cataract or IOP elevation.

Dr. Roth: It's very important to monitor their nerve and not let them get nerve damage.

IMPORTANT SAFETY INFORMATION (continued)
Contraindications
Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

IMPORTANT SAFETY INFORMATION (continued)
Contraindications (continued)
Glaucoma: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

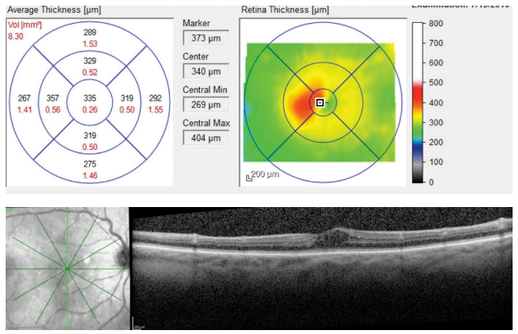
Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

Please see additional Important Safety Information on the following pages.

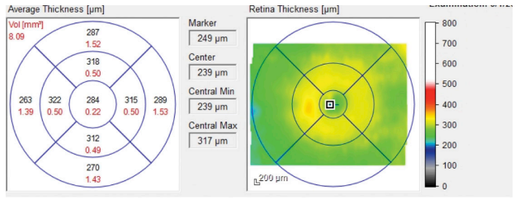
CASE STUDY 1: Response to OZURDEX® (dexamethasone intravitreal implant) in ME following CRVO

Presented by Sophie Bakri, MD

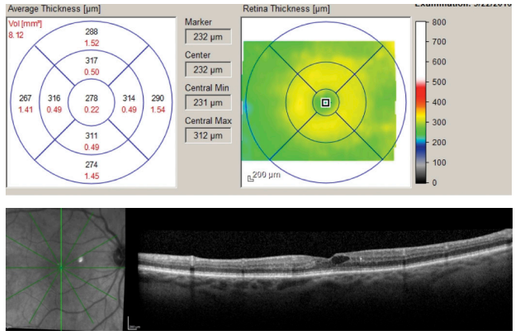
- 85-year-old white female
- Diagnosis: CRVO OD
- Visual acuity (VA): 20/60 OD (20/70 OS)
- At baseline, OD OCT was 335 µm and IOP was 16 mm Hg
- **After previous treatments, an OZURDEX® implant was inserted OD**



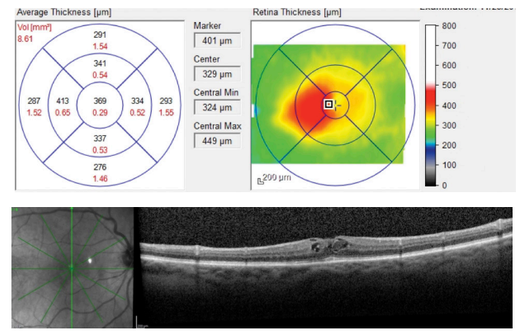
One month later, visual acuity improved to 20/40 and her OCT showed a 51-µm improvement in central retinal thickness (CRT).



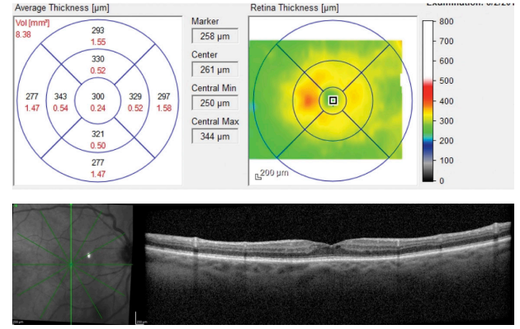
At 3 months, her vision was maintained (20/40) and the CRT showed an additional decrease of 6 µm (total decrease of 57 µm). IOP was 16 mm Hg.



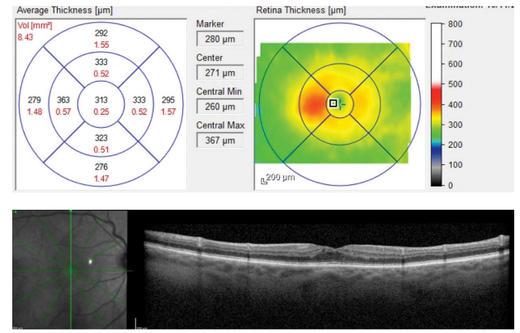
At 4.5 months after placement of OZURDEX® (dexamethasone intravitreal implant), the patient's vision had returned to the baseline of 20/60 and CRT had increased by 91 µm. IOP was 14 mm Hg. **A second OZURDEX® implant was placed OD.**



The patient returned for evaluation 3 months later, and her vision improved to 20/30. CRT had decreased by 69 µm and IOP remained stable at 17 mm Hg. Only trace cystoid macular edema (CME) was present, and so no additional treatment was given.



The patient was seen again 3 months later (6 months after placement of the second OZURDEX®) and she had 20/40 vision, stable CRT, and an IOP of 16 mm Hg.



Case Study 1: Discussion

Dr. Ip: I think this case exemplifies an individual experience with managing ME in RVO.

Dr. Bakri: For some of my patients, I know their interval and it's almost like clockwork. I know when they are going to need another OZURDEX® implant.

Dr. Roth: It's not so much "treat and extend" as it is "maintain with a patient-specific treatment interval."

CASE STUDY 2: Treatment of ME following CRVO with OZURDEX® (dexamethasone intravitreal implant)

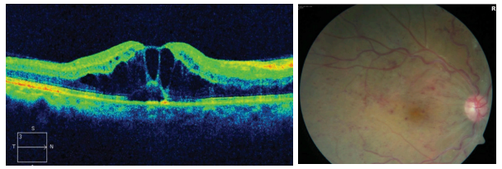
Presented by Daniel Roth, MD

- 52-year-old female with systemic hypertension, on medication
- Diagnosis: CRVO OD
- VA: 20/50 OD, 20/25 OS

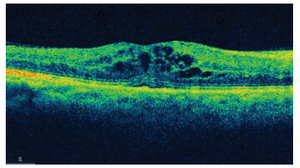
Physician notes:

- Complains of blurred vision OD
- Patient also has cystoid macular edema (CME) and vision loss
- Some cotton wool spots in the retina

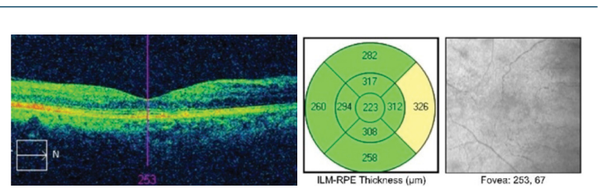
- At baseline, OD OCT CRT was 616 µm and IOP was 13 mm Hg; minimal to no cataract (lens: 1+ nuclear sclerotic cataract [NSC], 1+ cortical clouding [CC])
- Previously treated OD
- **The patient started on OZURDEX® OD**



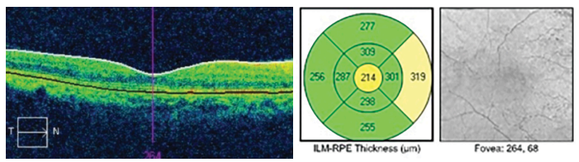
She returned approximately 6 months later, with no change in the blurred vision. Her vision remained the same (20/50), as did the IOP (13 mm Hg) and lens (1+ NSC, 1+ CC), but her CRT had decreased to 382 µm.
A second OZURDEX® was placed OD.



The patient returned for evaluation 4 weeks later and reported improvements in her blurred vision symptoms. Her visual acuity was 20/20, the IOP was down slightly to 12 mm Hg, and the lens was stable at 1+ NSC, 1+ CC. The CRT had decreased further to 223 µm. The patient was observed with no additional treatment.



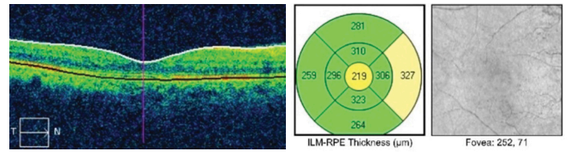
The patient returned 4 weeks later (2 months after the second OZURDEX®) with mildly blurred vision, though her vision was still 20/20. Her IOP was back to the baseline of 13 mm Hg, but her lens remained the same at 1+ NSC, 1+ CC. Because her CRT was slightly lower at 214 µm, the patient continued to be observed, with no additional treatment.



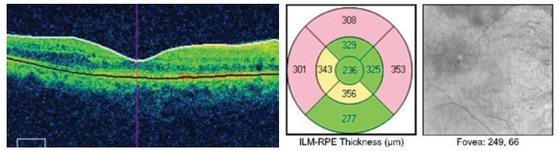
IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
Diabetic Macular Edema (continued)
Increased Intraocular Pressure (continued): The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6-month period).

Cataracts and Cataract Surgery: The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® (dexamethasone intravitreal implant) group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects versus 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

At 4 months after placement of the second OZURDEX® (dexamethasone intravitreal implant), the patient was experiencing recurrent blurred vision, and her visual acuity had worsened to 20/30-. Her IOP had increased to 16 mm Hg and her lens was 1+ NSC, 1+ CC, 1+ posterior subcapsular cataract (PSC). The CRT had increased only slightly to 219 µm, so observation was continued.



At 6 months after the second OZURDEX®, the patient reported more blurred vision OD, while her vision remained at 20/30-. CRT was 236 µm. IOP had continued to rise to 21 mm Hg, with her lens at 1+ NSC, 1+ CC, 1+ PSC.
The patient eventually underwent cataract surgery with further visual improvement.



Patient Case Summary

- 52-year-old female with ME following CRVO
- Response to continued treatments of OZURDEX®
- Developed PSC
- VA recovery to 20/20- after CE/IOL
- IOP elevations transient and managed with drops
- No glaucoma drops
- Lens: PCIOL
- Received multiple OZURDEX® injections

Case Study 2: Discussion

Dr. Roth: I like to see patients approximately 8 weeks after OZURDEX® placement because that is when increased IOP has been shown to peak. The patient would report that she started to lose vision again just before the 5-month mark. She received multiple OZURDEX® implants.

Dr. Ip: Would you have inserted OZURDEX® before the cataract surgery?

Dr. Roth: I would typically have the cataract surgery performed after the patient has OZURDEX® in the eye. For this patient, I went ahead and placed the OZURDEX® before the cataract extraction and IOL was performed.[26]

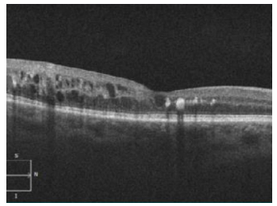
IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
Retinal Vein Occlusion and Posterior Segment Uveitis
Adverse reactions reported by greater than 2% of patients in the first 6 months following injection of OZURDEX® (dexamethasone intravitreal implant) for retinal vein occlusion and posterior segment uveitis include: intraocular pressure increased (25%), conjunctival hemorrhage (22%), eye pain (8%), conjunctival hyperemia (7%), ocular hypertension (5%), cataract (5%), vitreous detachment (2%), and headache (4%).

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Please see additional Important Safety Information on the following pages.

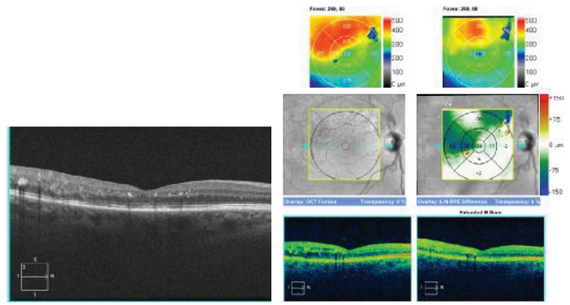
CASE STUDY 3: OZURDEX® (dexamethasone intravitreal implant) in a patient with ME following BRVO

Presented by Aleksandra Rachitskaya, MD; case courtesy of Peter Kaiser, MD

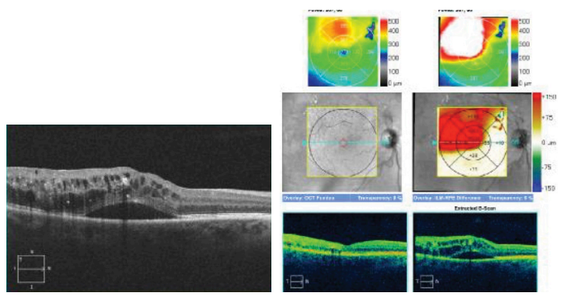


- 56-year-old male with very active BRVO for 4 years
- Previous focal grid laser
- At baseline, VA was 20/50, IOP was 16 mm Hg, and central subfoveal thickness (CSF) was 302 µm
- **A trial of OZURDEX® was started**

Two months later, the patient had improved VA of 20/40, IOP of 17 mm Hg, and a reduction in CSF thickness to 278 µm.



At 4 months after the OZURDEX® implant, his VA was slightly worse (20/50), with an IOP of 13 mm Hg, and an increased CSF thickness of 350 µm.
A second OZURDEX® implant was placed.



The patient continued to receive OZURDEX®, with stable IOP. He underwent cataract surgery, and his VA was 20/50 with CSF thickness of 363 µm.

Case Study 3: Discussion

Dr. Rachitskaya: When I treat BRVO patients, my primary goal is to improve VA and to address ME. It was nice to see that in this case, as in the other cases, OZURDEX® treatment improved his vision, even though CSF thickness fluctuated. If the interval period can be determined, then retreatment can be timed to the point that the patient starts to reaccumulate fluid.

Dr. Bakri: In this patient, OZURDEX® is effective in treating ME due to RVO. The treatment goals in both BRVO and CRVO are to treat ME and improve vision, and OZURDEX® can help do this.

IMPORTANT SAFETY INFORMATION (continued)
Contraindications
Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

DISCUSSION—COMMUNICATING WITH PATIENTS

Dr. Bakri: I let my patients know about the benefits of OZURDEX® (dexamethasone intravitreal implant) in the treatment of ME following RVO: reduction of fluid in the retina and improved vision, as well as reduction in inflammation to "quiet down" the eye. I tell them that about 1 in 3 patients requires eye drops to lower eye pressure, but that it is very rare that surgery will be needed to lower the pressure. I also explain that the risk of developing cataract increases with an increasing number of injections, but that if OZURDEX® is needed, a cataract can be removed.

Dr. Rachitskaya: I take a similar approach to educate patients on the benefits that OZURDEX® can provide in treating their disease and improving vision. If the patient is phakic, I mention the risk of cataract progression, with the incidence higher with repeated treatments. Additionally, I discuss with them how some patients may experience an elevation of their IOP after an injection and the importance of monitoring the IOP. I may treat patients who experience IOP elevations with pressure-lowering drops and, in rare instances, with surgery if recommended by my glaucoma colleagues.

Introducing OZURDEX® to Your Patients

- The swelling in your retina can be caused by several factors[28]
- OZURDEX® is a corticosteroid and works to help reduce the inflammation in your retina. OZURDEX® helps by improving visual acuity[22]
- OZURDEX® is a tiny implant that slowly releases medication over time, without monthly injections. It will dissolve over months and will not need to be removed[22]
- OZURDEX® is injected directly into the back of the eye, with minimal systemic absorption[29]
- There is a chance of an increase in eye pressure that generally returns to where it started. If you experience this, it will need to be managed with eye drops, and rarely, with surgery[22]
- After repeated OZURDEX® injections, a cataract may occur. If this occurs, your vision will decrease and you will need a procedure to remove the cataract and restore your vision[22]
- In clinical studies, OZURDEX® improved vision in patients without the need for monthly injections[22]

IMPORTANT SAFETY INFORMATION (continued)
Contraindications (continued)
Glaucoma: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

Dosage and Administration
FOR OPHTHALMIC INTRAVITREAL INJECTION. The intravitreal injection procedure should be carried out under controlled aseptic conditions. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Please see accompanying full Prescribing Information or visit https://www.rxabbvie.com/pdf/ozurdex_pi.pdf

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