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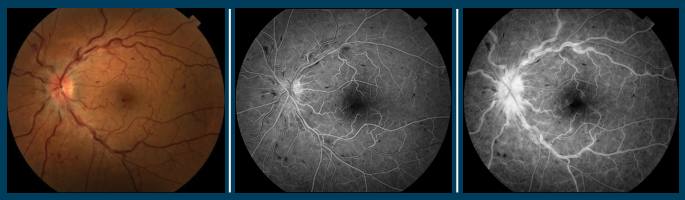

OZURDEX® (Dexamethasone Intravitreal Implant) 0.7 mg as Initial Therapy in Pseudophakic Patients With Diabetic Macular Edema, Macular Edema Following Retinal Vein Occlusion, and Noninfectious Posterior Segment Uveitis: A Case-Based Discussion

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.

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.

In late 2018, a group of experts in ophthalmologic diseases met in Chicago, IL, to discuss their experience with OZURDEX® (dexamethasone intravitreal implant) 0.7 mg for the treatment of diabetic macular edema (DME), macular edema (ME) following retinal vein occlusion (RVO), or noninfectious posterior segment uveitis in pseudophakic patients. They shared their thoughts on how treatment protocols differ for each disease and discussed 4 patient cases.

PROFILES OF EXPERTS

Michael A. Singer, MD
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University of Texas Health Science Center
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Michael A. Singer, MD, is a professor of ophthalmology at the University of Texas Health Science Center and a board-certified ophthalmologist at Medical Center Ophthalmology Associates, where he sees patients with retinal diseases, macular degeneration, and diabetic eye diseases.

Joseph M. Coney, MD
Retina Associates of Cleveland, Inc.
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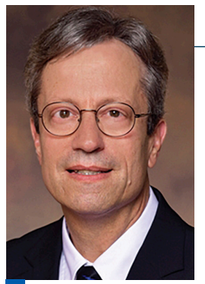
Joseph M. Coney, MD, is a highly recognized, board-certified ophthalmologist at Retina Associates of Cleveland, specializing in the treatment of diabetic retinopathy and age-related macular degeneration.



Kevin J. Blinder, MD
The Retina Institute
Washington University School of Medicine
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Kevin J. Blinder, MD, is a professor of ophthalmology and visual sciences at Washington University School of Medicine and a board-certified ophthalmologist at The Retina Institute, where he treats patients with diabetic retinopathy, macular degeneration, and other retinal and macular diseases.

Reginald J. Sanders, MD
The Retina Group of Washington
Washington, DC

Reginald J. Sanders, MD, is a board-certified ophthalmologist at The Retina Group of Washington and has served as Chief of the Retina Service at Georgetown University/Washington Hospital Center since 2001.

IMPORTANT SAFETY INFORMATION (continued)
Contraindications (continued)
Hypersensitivity: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions
Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

INTRODUCTION: INFLAMMATION IN MACULAR EDEMA

Dr. Singer opened the roundtable with a review of what is known about the role of inflammation in the pathophysiology of retinal vascular diseases. ME is defined as an accumulation of extracellular and/or intracellular fluid in the central part of the retina and is considered a nonspecific sign of retinal vascular diseases, including DME and RVO.[1] Specific inflammatory mediators are present at sites of ME, including chemokines, cytokines, inflammatory cells, and prostaglandins, among others.[1] Vascular disease or primary inflammatory disease, such as uveitis, initiate the release of various inflammatory mediators in the microvessels of the retina, causing disruption of tight junctions.[2] This leads to increased vascular permeability, vasodilation, leukostasis, diapedesis, and a further accumulation of inflammatory factors.[2]

DISCUSSION: TREATING INFLAMMATION IN DME AND RVO

Dr. Singer: What role do you think inflammation plays in macular edema?

Dr. Sanders: These diseases are multifactorial and the extent to which inflammation plays a role in any specific disease is unclear, though there are common pathways involved. We treat patients with anti–vascular endothelial growth factors (VEGF) and with steroids, and either one or both can be effective depending on the patient.

Dr. Blinder: Inflammation plays a role in both DME and RVO, but it seems shortsighted to think that we can just block one pathway and succeed with therapy. If we recognize that these diseases are multifactorial, then we would expect that treatment may need to block many different pathways.

Dr. Coney: Steroids are effective in inhibiting inflammatory pathways in RVO, where the acute injury may be driven by ischemia.[3] In longstanding and chronic conditions such as DME, there is a tipping point where the inflammatory process plays a greater role in disease progression, and at that point, an anti-inflammatory treatment may address the inflammation.[4]

Dr. Singer: RVO is an acute event, with high VEGF levels, a rapid inflammatory response, and ME and central foveal thickness (CFT) changes often seen.[5,6] DME develops slowly, but also involves VEGF-driven processes that underlie microvascular occlusive events, along with chronic inflammation.[4] Taking a multimodal approach may be effective because a steroid addresses inflammation-mediated disease processes and an anti-VEGF addresses VEGF-mediated processes.

Dr. Coney: I do discuss the role of inflammation with my patients because they often already understand that steroids are used to treat inflammation. I make the associations to other chronic medical conditions where additional treatment may be required to optimize management before there is permanent damage.

Dr. Sanders: I also talk to my patients about inflammation in general terms, explaining that we have several treatments that work on different parts of the disease. We will try one treatment that we think will work best for them and if that isn't enough, then often there's something else we can try.

Dr. Blinder: The point at which I might decide to try a steroid as a treatment strategy depends on the disease progression. For example, if vision is deteriorating and edema is not resolving, despite our efforts. The most important thing to communicate to patients is that RVO and DME are chronic conditions with no cure. Once patients realize the chronicity of their pathology and that they may need therapy for a long time, the discussion about treatment options becomes easier.

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions
Diabetic Macular Edema
Ocular adverse reactions reported by greater than or equal to 1% of patients in the two combined 3-year clinical trials following injection of OZURDEX® (dexamethasone intravitreal implant) for diabetic macular edema include: cataract (68%), conjunctival hemorrhage (23%), visual acuity reduced (9%), conjunctivitis (6%), vitreous floaters (5%), conjunctival edema (5%), dry eye (5%), vitreous detachment (4%), vitreous opacities (3%), retinal aneurysm (3%), foreign body sensation (2%), corneal erosion (2%), keratitis (2%), anterior chamber inflammation (2%), retinal tear (2%), eyelid ptosis (2%). Non-ocular adverse reactions reported by greater than or equal to 5% of patients include: hypertension (13%) and bronchitis (5%).

Please see additional Important Safety Information on the following pages.

Dr. Coney: I try to customize therapy for every patient. I individualize the treatment endpoint and threshold for response based on visual acuity and optical coherence tomography (OCT) findings. The OCT helps me to assess response to treatment and disease activity and when I need to consider changing my management. While adjusting my therapy, I am trying to determine the driving force of their disease to maximize efficacy while decreasing the burden.

Managing the patient expectations and concerns is critical. I explain that in clinical studies, OZURDEX® improved vision in patients without the need for monthly injections, but that it also comes with more side effects, specifically cataracts and intraocular pressure (IOP) elevations.[7] I make them aware that they may need to be placed on topical drops if the IOP were to increase and that after repeated injections, they will likely develop a cataract. We typically obtain authorization for OZURDEX® so that it's available if visual acuity is decreased and macular edema is still present at the next visit, and the patient agrees to the treatment. I normally check the IOP again in 4 to 6 weeks after the first injection, since that is when you would expect an elevation, and it's the most common after the first injection. It's rare to have progression in the cataract after the first treatment, but after repeated injections, it will typically worsen, and often need surgery after the fourth cycle.

Dr. Sanders: When choosing a treatment, I also take into account the socioeconomic status of my patients, whether they have insurance, or if they have issues getting to the clinic. I might try OZURDEX® earlier because it dissolves slowly over time without the need for monthly injections.[7] Other patients may have distrust in medicine or do not like the idea of something floating in their eye; I might hold off starting OZURDEX® until I can prepare them for what to expect.

I agree about the impact of seeing changes in both visual acuity and on the OCT. Patients can notice changes in their visual acuity and, when explained to them, the improvement on the OCT is clear.

Dr. Singer: For a patient with DME, I will try several rounds of an anti-VEGF injection and monitor the patient closely. If they have a response below 50% on the OCT after several visits, I will assume this patient's DME is not predominantly VEGF mediated. That is the point at which I will introduce the possibility of OZURDEX® to address the inflammatory processes. I try to start the preauthorization process before this last visit so that when they come in, I can do the insertion. After the OZURDEX® implant injection, I check IOP again in 6 to 8 weeks.

DISCUSSION: TREATING RESIDUAL FLUID IN DME AND RVO

Dr. Singer: How do you treat residual fluid in RVO and DME?

Dr. Blinder: For DME, more than for RVO, I like to get patients as dry as possible. Patients with DME can have good visual acuity even with some residual edema, so many times we will treat until patients are stable and then we will observe.

Dr. Singer: Does treatment change depending on where the fluid is in each disease?

Dr. Coney: This varies depending on the disease state. With all retinovascular diseases, my main goal is to maximize visual acuity as well as achieve complete dryness. In diabetes, in my experience, intraretinal swelling is more resistant to treatment than subretinal fluid (SRF). With resolution of SRF, sometimes there is better vision improvement. The problem is that VA and OCT do not correlate. After I have maximized treatment and the OCTs are stable, I will observe without additional treatment until fluid worsens or VA decreases.

Dr. Coney: Those eyes with persistent fluid do worse than people with less fluid on presentation.[8] That is why I think it is important to try to get the retina as dry as possible, with the recognition that some patients will have fluid no matter what, and in some of those patients, the fluid may not be causing any damage.

Dr. Sanders: It is always a negotiation with DME patients on whether to inject. It can be really hard to convince them they need an injection because they may not necessarily see a benefit in terms of vision. Subretinal fluid may have an effect on vision. In certain patients, there seems to be little correlation between fluid and visual improvement. I have to convince DME patients and explain that they really do need the injection. There is a different mindset in DME patients.

Dr. Singer: OZURDEX® isn't indicated for age-related macular degeneration (AMD), but compared to DME patients, I care more about wetness in AMD patients.

The Comparison of AMD Treatments Trials (CATT) found that subretinal fluid is less worrisome than intraretinal fluid in AMD.[9] I want AMD patients to be as dry as possible but worry less about patients with DME because some of them will resolve on their own.

Dr. Coney: In my experience, DME patients are less compliant than others, and we have to get them to buy into the process. I share the VA test along with ancillary testing, OCTs and FAs, as visual aids to demonstrate their progress with treatment. As I try to extend and customize their treatment, I will show them their fluctuations on the OCT. I also try to set expectations early in the process and let them know that their retinopathy will take time to improve, but over time they may require fewer treatments, as the disease is better controlled. It is important for them to understand that it's a therapy and not a cure. I tell them we can stabilize the disease and reduce the risk of permanent vision loss in most cases if it is caught early and managed appropriately.

Dr. Singer: We looked at cancellation and no-show rates among AMD and DME patients getting injections. Compared to patients with AMD, patients with DME cancelled more often and were no-shows 3 times more often.[10]

DISCUSSION: TRACKING DISEASE PROGRESSION

Dr. Singer: Do you monitor diabetic retinopathy without macular edema?

Dr. Coney: My perspective on monitoring diabetic retinopathy shifted when I saw a patient progress a lot faster than I expected. The rate of developing proliferative disease in an eye with severe nonproliferative diabetic retinopathy (NPDR) is 52% in 1 year.[11] Once patients progress to proliferative diabetic retinopathy (PDR), if left untreated, half will experience severe vision loss within the next 5 years.[11] I now obtain a widefield angiogram as part of my evaluation to assess the peripheral retina for ischemic changes, which is difficult to see clinically. The most important risk factor for progression is the level of retinopathy on presentation.

Dr. Singer: How often do you perform angiography on your diabetic patients and do you use regular or widefield?

Dr. Sanders: We just got a widefield, and I perform it once a year or if I anticipate a medication change.

DISCUSSION: PATIENT FACTORS IN TREATMENT SELECTION FOR DME

Dr. Singer: Does patient compliance factor into your decision making?

Dr. Sanders: I tend to give more aggressive treatment for those patients who tend to be less compliant.

Dr. Coney: My biggest concern is with the patient who doesn't come back after you start treatment and consequently, their disease progresses. Part of my conversation with patients is to gauge their buy-in to the treatment process so that I can assess whether they are likely to be compliant. I will tend to be more aggressive with patients who have multiple medical problems or travel long distances.

Dr. Singer: I have a certain bias based on insurance status. Patients may be less likely to come back if they are uninsured. The other thing that factors in is their hemoglobin A1C. If it is on the high side, I assume that they are noncompliant with their diabetes treatment, so I might be more aggressive in my treatment of DME.

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
Diabetic Macular Edema (continued)
Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX® (dexamethasone intravitreal implant) patients versus 4% of sham patients. 42% of the patients who received OZURDEX® were subsequently treated with IOP-lowering medications during the study versus 10% of sham patients.

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® 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.

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
Diabetic Macular Edema (continued)
Cataracts and Cataract Surgery (continued): Among these patients, 61% of OZURDEX® (dexamethasone intravitreal implant) 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.

Please see additional Important Safety Information on the following pages.

MEAD STUDY

Dr. Singer reviewed the top-line results of the 3-year Macular Edema Assessment of Implantable Dexamethasone in Diabetes, or MEAD, study of OZURDEX® in patients with DME. OZURDEX® sustained clinically significant vision improvement throughout the 3-year study.[8,12] 19.5% of OZURDEX® patients gained 15 or more letters in best-corrected visual acuity (BCVA) at month 39, compared to 10.7% of sham patients (estimated difference 8.8%; 95% confidence interval: 3.4%, 14.3%) (Figure 1).[7,12] The percentages of patients with 3 or more lines of improvement in BCVA were similar in phakic and pseudophakic patients who received OZURDEX®, though a greater proportion of phakic patients lost 3 lines of vision due to cataracts, which occurred with greatest frequency after 4 treatment cycles.[7,8] A post hoc analysis revealed improvement in vision following cataract surgery (Figure 2).[12]

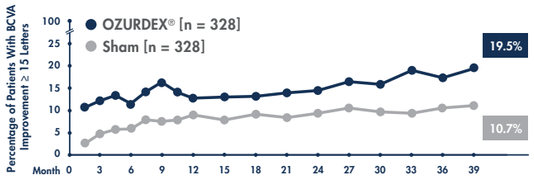
DISCUSSION: MEAD STUDY

Dr. Singer: In the MEAD study, there was a 6-letter gain after 3 months with a single OZURDEX® treatment, compared to 2.6 letters in the sham group (Table 1).[7] What do you think about that?

Dr. Blinder: That is an impressive response.

Dr. Sanders: After that first OZURDEX® injection is the point in time at which you need to get buy-in from the DME patient. It is very important to discuss their progress and talk to them about it and say, "Even though your vision may not have changed, although often it does, stay the course."

Figure 1. Primary Endpoint: Percentage of Patients With ≥ 15-Letter (3-Line) Gains in BCVA[a] From Baseline[8]



Pooled results of all DME randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized, sham-controlled studies. The primary endpoint was the proportion of patients with 15 or more letters' improvement in BCVA from baseline at month 39 or final visit for subjects who exited the study at or prior to month 36. The month 39 extension was included to accommodate the evaluation of safety and efficacy outcomes for subjects who received retreatment at month 36. Only 14% of the study patients completed the month 39 visit (16.8% from OZURDEX® and 12.2% from sham).[8,12]

Table 1. All Randomized Patients: Visual Acuity Outcome at Month 39[8]

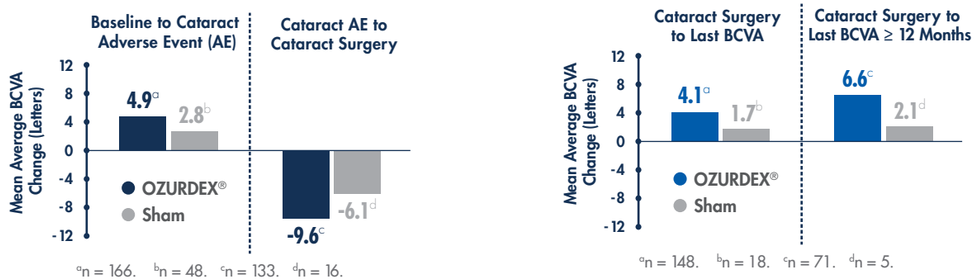
Measurement	OZURDEX® (n = 328)	Sham (n = 328)	Estimated Difference (95% confidence interval [CI])
Patients gaining ≥ 15 letters (3 lines) in BCVA (n)	19.5% (64)	10.7% (35)	8.8% (3.4%, 14.3%)
Patients losing ≥ 15 letters in BCVA (n)	13.7% (45)	10.7% (35)	3.0% (-2.0%, 8.1%)
Mean change in BCVA (letters) (SD[b])	2.2 (15.88)	0.8 (12.72)	1.3 (-0.9, 3.4)

BCVA Change From Baseline After 1 Treatment[8]

After 1 treatment (3-month visit)	6.0 letters gained in OZURDEX® group 2.6 letters gained in sham group

[b]Standard deviation.

Figure 2. Baseline Phakic Patients to the Date Cataract Surgery Was Performed / After Cataract Surgery Was Performed to Last BCVA[8]



[a]n = 166. [b]n = 48. [c]n = 133. [d]n = 16.

[a]n = 148. [b]n = 18. [c]n = 71. [d]n = 5.

Pooled results from 2 multicenter, masked, randomized, sham-controlled, 3-year trials in patients with DME. Subgroup for pooled data with LOCF. BCVA was measured using a standard Early Treatment Diabetic Retinopathy Study (ETDRS) protocol.[7,12]

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%).

GENEVA STUDY

Dr. Singer also reviewed the results of the Global Evaluation of Implantable Dexamethasone in Retinal Vein Occlusion with Macular Edema, or GENEVA, study in patients with RVO (branch or central). By day 30, 21.3% (91/427) of patients treated with OZURDEX® gained 3 or more lines in BCVA vs 7.5% (32/426) of sham patients ($P < .001$).[8,13] Peak improvement was seen at day 60: 29.3% (125/427) of patients treated with one OZURDEX® injection gained 3 or more lines in BCVA vs 11.3% (48/426) of sham patients ($P < .001$) (Figure 3).[8,13] The mean decrease in retinal thickness at 3 months was 207.9 µm for the OZURDEX® group compared to 85 µm in the sham group ($P < .001$), but were not significantly different at day 180 (Figure 4).[8,13]

DISCUSSION: GENEVA STUDY

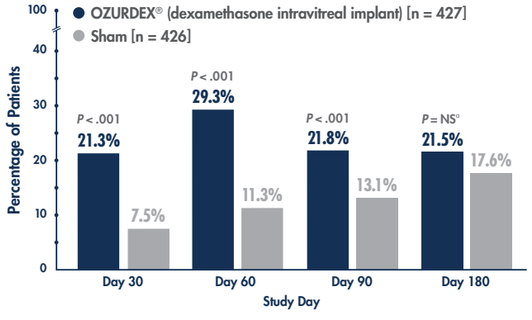
Dr. Singer: What is your impression on how OZURDEX® works in retinal vein occlusion?

Dr. Coney: It is always impressive to see the improvements from OZURDEX® in RVO patients. Depending on the degree of ischemia and damage to the perifoveal capillary network, it is not uncommon to have dryness after 1 injection with significant visual gains. However, rebound swelling can reoccur quickly in contrast to DME, requiring additional treatments.

Dr. Singer: It is a different disease process than DME.

Dr. Coney: In those RVO patients who do require multiple injections, the interval between injections may become shorter once the physician considers all factors.

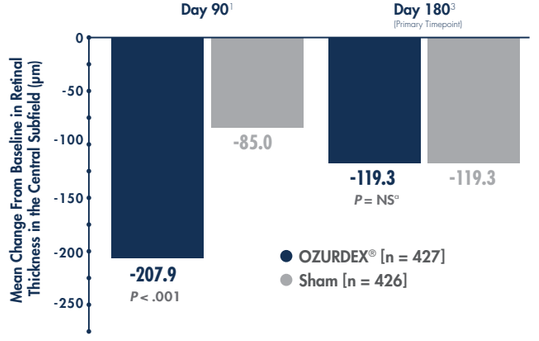
Figure 3. Percentage of RVO Patients With ≥ 3-Line Gains in BCVA From Baseline[8,13]



[a]NS = not significant.

The primary outcome measure was time to achieve a 15-letter improvement in BCVA. Secondary endpoints included BCVA, central retinal thickness, and safety.[7] 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.[7,13] BCVA was measured using a standard ETDRS protocol.[7]

Figure 4. Mean Change in Retinal Thickness[8,13,*]



*Retinal thickness does not correlate with visual acuity.
[a]NS = not significant.

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 OCT. Baseline retinal thickness (central subfield): 562.0 µm for OZURDEX® vs 538.6 µm for sham.[7,8,13]

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.

HURON STUDY

Dr. Singer also quickly reviewed the findings of the Chronic Uveitis: Evaluation of the Intravitreal Dexamethasone Implant, or HURON, study in patients with noninfectious posterior segment uveitis. One injection of OZURDEX® significantly reduced vitreous haze vs sham at 8 weeks (Figure 5). 46.8% of OZURDEX® patients had a vitreous haze score of 0 vs 11.8% of sham patients ($P < .001$).[7,14] At 8 weeks, the OZURDEX® group also had a 13.5-letter gain in mean BCVA vs 1.8 letters in the sham group ($P < .001$) (Figure 6). While baseline central macular thickness measurements were similar in OZURDEX® and sham groups (344.0 µm vs 324.6 µm), at week 8 there was a 99.4-µm drop in mean central macular thickness vs a 12.4-µm drop in the sham group ($P \leq .004$).[8,14] At week 26, the mean change from baseline in central macular thickness was not statistically significant (OZURDEX® -50.2 µm vs sham -35.5 µm, $P \geq .227$).[14]

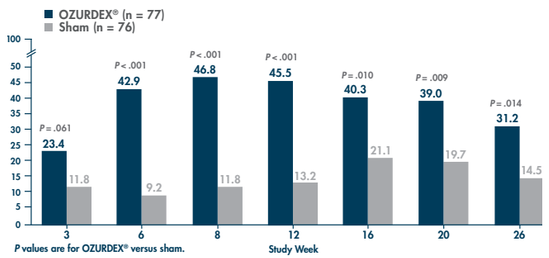
DISCUSSION: HURON STUDY

Dr. Singer: How does the HURON study apply to your patients with noninfectious posterior segment uveitis?

Dr. Sanders: If these patients have macular edema in addition to vitreous haze, I would be more motivated to try OZURDEX®.

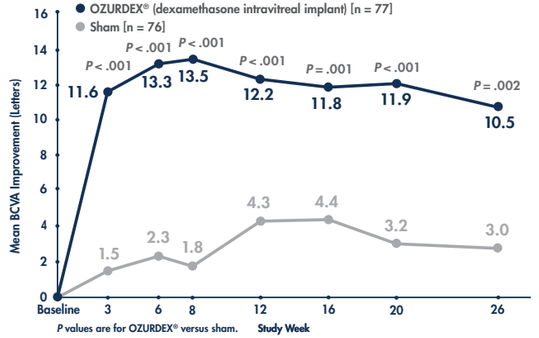
Dr. Coney: If the vision is good and there is limited macular edema with no resolution in 6 to 8 weeks, I will use OZURDEX®. For significant inflammation or a suspected chronic condition, I will recommend OZURDEX® as a first-line management.

Figure 5. Percentage of Patients With Vitreous Haze Score of Zero[8,14]



Results from an 8-week, multicenter, masked, randomized trial (with an 18-week masked extension) in patients with noninfectious uveitis affecting the posterior segment of the eye. Seventy-seven patients received OZURDEX® 0.7 mg and 76 received sham injections. Investigator-graded vitreous haze was measured on a scale of 0 to 4. Primary endpoint was week 8.[8-14]

Figure 6. Mean Change From Baseline BCVA (Letters Gained)[8]



Results from an 8-week, multicenter, masked, randomized trial (with an 18-week masked extension) in patients with noninfectious uveitis affecting the posterior segment of the eye. Seventy-seven patients received OZURDEX® 0.7 mg and 76 received sham injections. BCVA was measured using a standard ETDRS protocol. Primary endpoint was week 8.[8,14]

CATARACTS AND PSEUDOPHAKIA

Dr. Singer presented some background on pseudophakia. He noted that cataract surgery is the most commonly performed operation worldwide, with an estimated 2 million procedures performed in the United States per year.[15] Pseudophakia is highly prevalent and growing in the United States; as of 2000, an estimated 6.1 million Americans older than 40 years of age had pseudophakia or aphakia, and that number is expected to grow to 9.5 million by 2020.[16] According to 103 Retina Specialists responding to a 2014 online market research survey, almost half (45%) of patients they typically see are pseudophakic.[8]

DISCUSSION: SPEAKING WITH PATIENTS ABOUT THE RISK OF ELEVATED IOP AND CATARACTS WITH OZURDEX®

Dr. Singer: Do you have any hesitancy using OZURDEX® in patients with glaucoma?

Dr. Coney: For patients with glaucoma, I'm comfortable in using OZURDEX®, especially if they're well maintained with 1 or 2 topical drops with an IOP less than 20 mm Hg. If the glaucoma is advanced with a cup-to-disc ratio greater than 0.8, OZURDEX® is contraindicated in these patients. One great thing about OZURDEX® is that we have clinical trial data to help manage expectations regarding elevated IOP. Elevated IOP is typically seen within the first two cycles (Figure 7), well managed with topical eye drops, and rarely requires incisional surgery.

Dr. Singer: Usually, I can predict when the pressure increase is going to occur in the cycle, around 6 to 8 weeks after OZURDEX® implantation.[8,12] Also, the more cycles without an IOP spike, the lower likelihood that it will occur.[12]

Dr. Blinder: I am a little conservative using OZURDEX® in patients with preexisting glaucoma, but I still use it when it is not contraindicated and have them follow up with their glaucoma specialist.

Dr. Sanders: I separate out the risk of an injection versus the side effects of the medicine. Often patients who are given OZURDEX® have already experienced an injection, so I reiterate the risks. Then I explain that with OZURDEX®, there is the risk of cataract and elevated IOP. I will mention that to manage IOP elevations, we may need to add some drops or have them see a glaucoma specialist.

Dr. Coney: With one OZURDEX® injection, you are still trying to determine how the person responds; you likely won't see a clinical change in their lens status, although it is possible. Clinical changes in lens status, if they occur, usually take time.[7,8]

Dr. Blinder: It usually takes a year to a year and a half before you start seeing lens changes that might require surgery.[7]

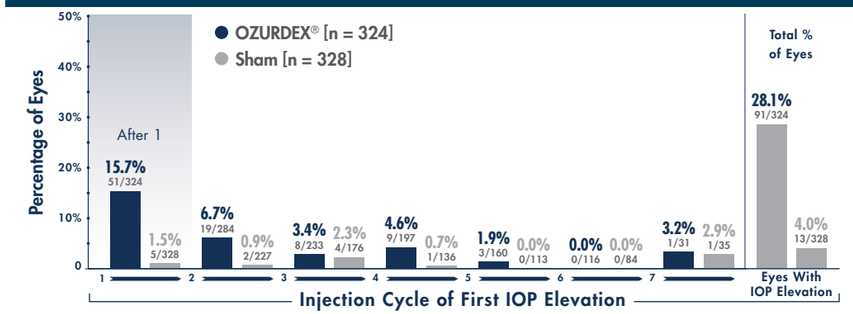
Dr. Coney: In my experience, cataract formation rate after 1 injection is low. After several injections, I do see patients with previously clear lenses start to have some changes in their clarity, even if the vision is still 20/20.[7,12] You want to have the discussion with them about cataract risk up front. Individuals with diabetes will likely develop cataracts earlier; especially as the disease progression is accelerated.[17,18] I tell patients if they have small changes consistent with cataracts before their first treatment, with the anticipation they will eventually need cataract surgery.

Dr. Sanders: I say, "People can have small cataracts in their 40s and 50s, but it does not usually impact vision until after age 60. At that time, a person will need surgery. However, in diabetic patients, the risk of cataracts is elevated and more frequent, so you may have the cataract surgery sooner.[17,19]

Dr. Blinder: I'm always surprised when I tell patients that there is a risk of cataracts with OZURDEX® and they respond with, "Well, doctor, isn't that treatable?" We are usually the ones to inform the patients that if a cataract develops, their lens can be replaced with an intraocular lens (IOL), but some of the patients are already aware that cataracts are commonly treated with surgical intervention.

Dr. Singer: As more and more people undergo cataract surgery, the surgical procedures are optimized. It is often considered a routine surgery.

Figure 7. First IOP Elevation by Treatment Cycle With IOP Increase ≥ 10 mm Hg Over Baseline[7,a]



[a] For patients who experienced repeated IOP elevations across multiple cycles, the patient is counted only once and is included in the respective cycle where the first IOP elevation was reported.

DISCUSSION: OVERALL APPROACH TO THE TREATMENT OF DME AND RVO

Dr. Coney: Based on my experience, it appears that eyes don't do well if you don't treat them aggressively. There is also a different response in each patient, and the most important thing is to try to understand what is driving their disease and then customize treatment accordingly. I use steroids a lot earlier to address the inflammatory component, and I've found that earlier treatment has a profound effect by improving vision and getting the retina drier, more quickly.

Dr. Sanders: There is nothing more powerful than clinical experience. To that point, in a disease that has myriad causes, presents with diabetes or vein occlusions, and has myriad treatments, clinical experience reveals which paths work and which ones do not work. Although our practice is guided by clinical studies, it is helpful to share our collective experience and have the opportunity to talk to each other and share our experience.

Dr. Blinder: In the past, we waited a certain amount of time before starting treatment, thinking that the patient would somehow improve on their own. We have learned a lot since then and now agree that we may need to treat DME and RVO patients more aggressively, and we have treatment options available to us. I think earlier steroid use can be effective, and if one treatment modality doesn't work, you have to quickly adapt and use another.

Dr. Singer: Treating patients earlier is the key. The risk-benefit profile of OZURDEX® is favorable, and as long as patients understand what is involved and how OCT is used to track their response, I would start treatment earlier to improve visual acuity.

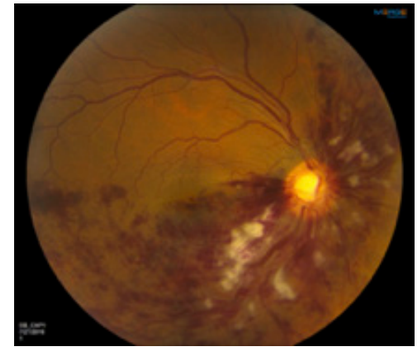
Introducing OZURDEX® to Your Patients

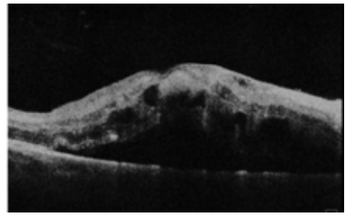
- The swelling in your retina can be caused by several factors[20]
- OZURDEX® is a corticosteroid and works to help reduce the inflammation in your retina. OZURDEX® helps by improving visual acuity[7]
- OZURDEX® is a tiny implant that slowly releases medication over time, without monthly injections. It will dissolve over months and will not need to be removed[7]
- OZURDEX® is injected directly into the back of the eye, with minimal systemic absorption[21]
- 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[7]
- 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[7]
- In clinical studies, OZURDEX® improved vision in patients without the need for monthly injections[7]

CASE 1: FIRST-LINE OZURDEX® IN A PATIENT WITH CENTRAL RETINAL VEIN OCCLUSION (CRVO) AND ME

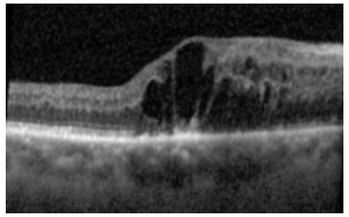
PRESENTED BY REGINALD J. SANDERS, MD

- 56-year-old male presented with abrupt loss of vision OD
- Controlled hypertension for 10 years
- Counting-fingers vision OD, 20/20 OS
- IOP normal
- Posterior chamber intraocular lens OU
- Diagnosed with hemicentral RVO with ME OD

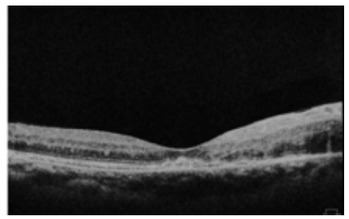




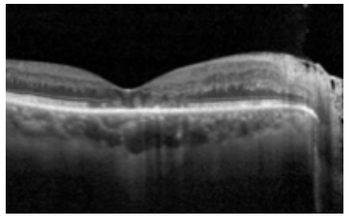
The patient wanted treatment without the need for monthly injections, and agreed to try an OZURDEX® implant OD as the first-line treatment.



6-month follow-up after OZURDEX® injection: Vision again worsened to counting fingers at 2 feet, and a second OZURDEX® was inserted OD.



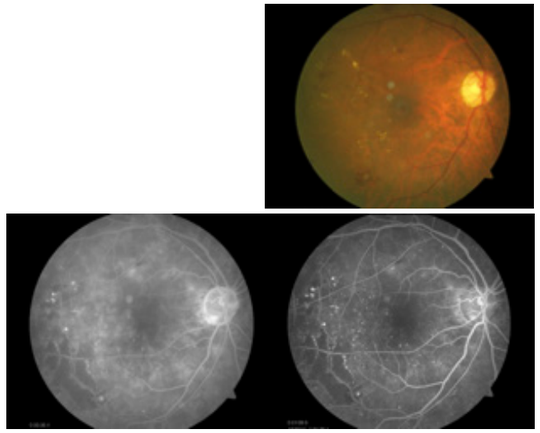
1-month follow-up after OZURDEX® injection: Vision improved to 20/70 OD after treatment.



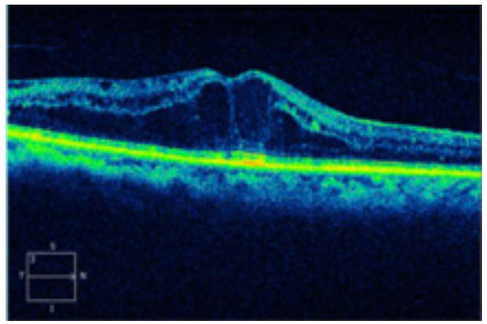
Vision again improved to 20/40 OD and has remained stable for the last 2 years.

PRESENTED BY MICHAEL A. SINGER, MD

- 67-year-old female complained of worsening vision OD
- Type 2 diabetes mellitus (T2DM) with ME OU
- Experienced a stroke 1 month prior, nonsmoker
- Taking insulin, metformin, losartan, metoprolol, amitriptyline, and aspirin
- Father was diagnosed with T2DM
- 20/70 OD, 20/40 OS
- Pupils equal, round, and reactive to light (PERRL)
- IOP 17 mm Hg OU
- Full confrontation visual field and intact extraocular muscle OU
- Slit lamp exam normal, pseudophakia OU

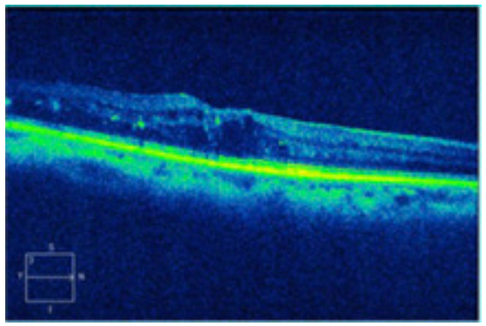


The dilated fundus exam revealed DME OU and microaneurysms with hard exudate and late leakage OD.

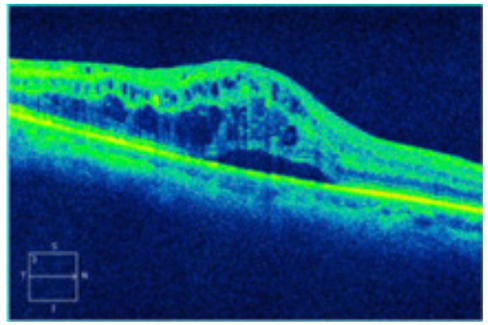


The patient received an OZURDEX® implant OD.

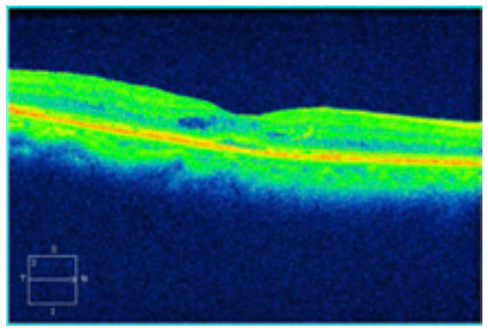
She returned for a follow-up 6 weeks later and her vision was 20/60 OD with an IOP of 18 mm Hg. No OCT was performed, and she was instructed to return in another 6 weeks.



Three months after receiving OZURDEX®, her vision was 20/50 OD and IOP 17 mm Hg.



After an additional 2 months, her vision was 20/50 OD and her IOP increased to 20 mm Hg. She was given a second OZURDEX® implant.



One month after the second implant, vision was 20/30 OD with an IOP of 22 mm Hg.

CASE 2: DISCUSSION

Dr. Singer: This patient certainly gave me pause with whether to use an anti-VEGF or try OZURDEX® earlier, particularly given her medical history and persistent edema.

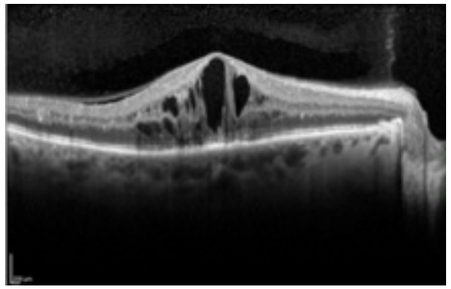
Dr. Sanders: I think this is an example of when OZURDEX® could be used earlier in the treatment course. I still struggle with this in certain patients.

Dr. Coney: I agree. My drug of choice for this patient is the steroid for branch retinal vein occlusion (BRVO).

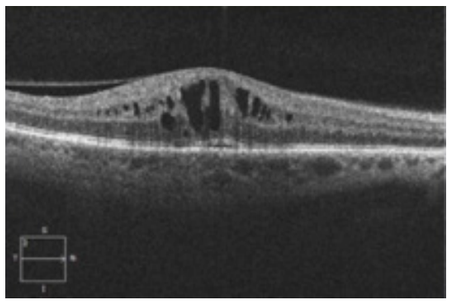
Dr. Blinder: Yes. These are sick patients and you certainly want to carefully consider your treatment options.

PRESENTED BY JOSEPH M. CONEY, MD

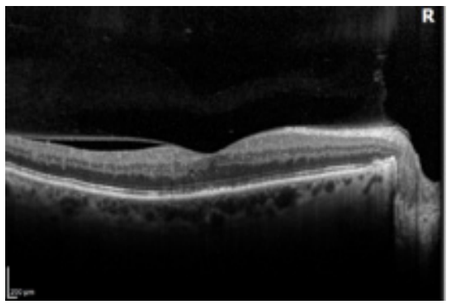
- 71-year-old phakic male with T2DM
- OD showed moderate NPDR and clinically significant macular edema (CSME)
- CST 605 µm
- 20/60 OD
- IOP 20 mm Hg OD
- Previously treated for persistent swelling



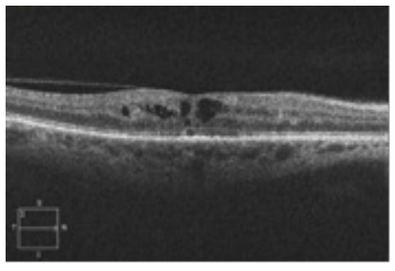
OCT at initial presentation.

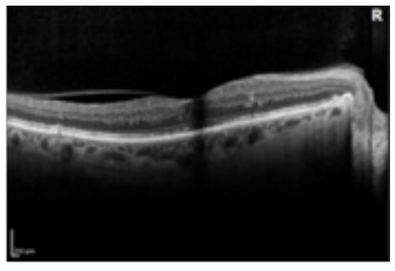


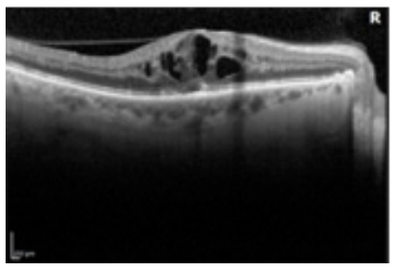
At the follow-up visit, the patient was counseled to try OZURDEX® but was hesitant about having something implanted in his eye. He was suspicious of doctors and had "fired" 4 before coming to our clinic.

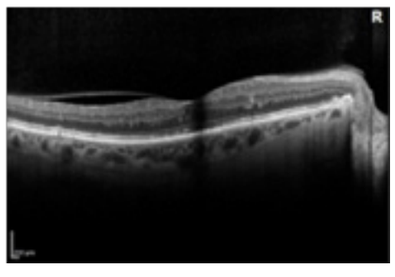


The patient received an initial OZURDEX® treatment and a month later showed improvement, with central subfield thickness (CST) dropping from 535 µm to 291 µm and vision at 20/40.



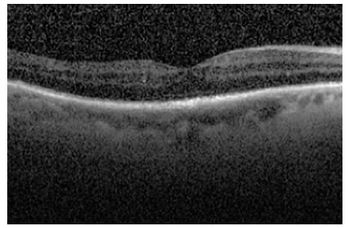




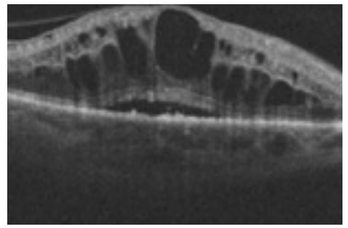


He returned for 2 additional OZURDEX® implantations, approximately every 5 months, with improvement seen 1 month after each treatment **(top images)**, CST decreased from 359 µm to 285 µm and VA was 20/30 **(bottom images)**, CST decreased from 488 µm to 284 µm after OZURDEX® implantation. VA went from 20/50 to 20/60. No swelling was seen for 2 years.

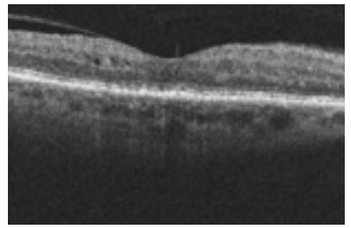
IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
Diabetic Macular Edema (continued)
Cataracts and Cataract Surgery: The incidence of cataract development in patients who had a phakic study eye was higher in the



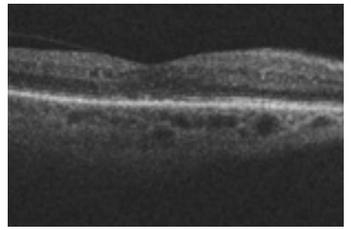
During this time, his cataract worsened (visual acuity declined from 20/30 to 4/200), and he was referred for cataract surgery.



He returned with severe swelling (CST 683 µm) and decreased visual acuity.



The patient was given OZURDEX® later, and CST decreased to 266 µm. Visual acuity was 20/40.



CST remained at 280 µm with 20/25 vision 3 months after treatment.

CASE 3: DISCUSSION

Dr. Coney: There were many things I observed and learned from this case. First, it is important to determine the main driver of the disease; is it VEGF or inflammatory mediated or a combination? Second, persistent fluid can limit potential vision. This patient achieved his best vision when all the fluid was resolved. Third, cataracts are a risk with OZURDEX® but can be treated, and vision can return to baseline after surgery. Finally, OZURDEX® can be used to treat recurring swelling even in eyes that have been stable for many years.

Dr. Blinder: Right. It's almost like a switch in some of these patients with diabetes. When the switch is on, you can't get rid of the edema, despite all efforts. Then suddenly, the switch goes off and the edema responds to therapy.

Dr. Coney: I've seen this before in patients with previous retinal surgery for epiretinal membranes and macular holes. They are stable for many years and later develop macular edema. There was no reason for me to give this patient an additional OZURDEX® treatment if there was no swelling for two years.

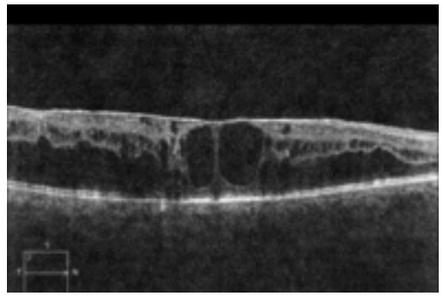
Dr. Sanders: Even if a patient has no edema for a long period of time, if they have a history of edema, the swelling could come back and then OZURDEX® would be a consideration.

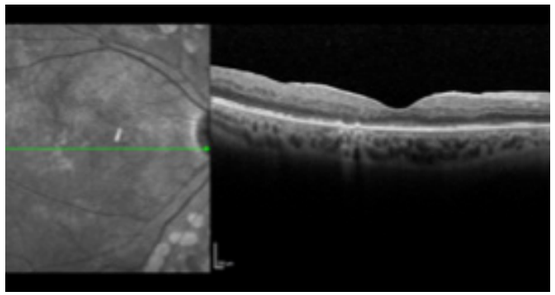
IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
Diabetic Macular Edema (continued)
Cataracts and Cataract Surgery (continued): OZURDEX® (dexamethasone intravitreal implant) group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group.

Please see additional Important Safety Information on the following pages.

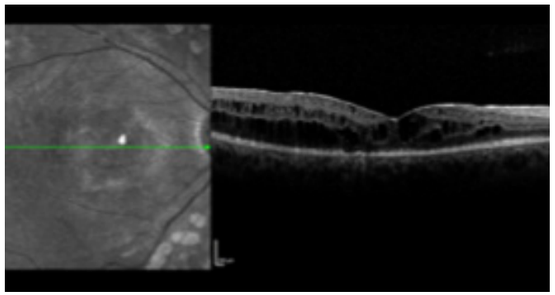
PRESENTED BY KEVIN J. BLINDER, MD

- 45-year-old female presented with DME OU
- History of bilateral vitrectomies for PDR with vitreous hemorrhage (VH)
- History of cataract surgery OD post vitrectomy
- Developed DME and received multiple prior treatments
- 20/50 OD
- IOP 21 mm Hg OD
- CRT on OCT 436 µm OD

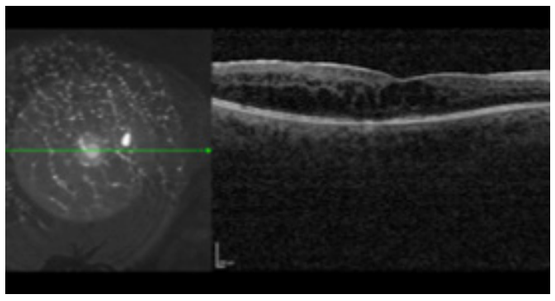




The patient was offered OZURDEX® and received her first implant in the right eye. After 2 months, thickness improved to 244 µm with visual acuity of 20/40-2 and IOP of 28 mm Hg. She was given latanoprost glaucoma drops.



One month later, visual acuity was 20/40-2 in the right eye. IOP was improved to 17 mm Hg. OCT showed that thickness was starting to increase in the right eye, to 344 µm.



After approximately 4 injections (over 2 years since starting OZURDEX®), she experienced vitreous hemorrhage in the right eye that resolved within a few weeks. She continues with OZURDEX® treatment.

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
Diabetic Macular Edema (continued)
Cataracts and Cataract Surgery (continued): Among these patients, 61% of OZURDEX® (dexamethasone intravitreal implant) 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.

CASE 4: DISCUSSION

Dr. Sanders: I noticed that her vision didn't change much after the injections.

Dr. Blinder: Correct. Even though we don't see much of a change in the Snellen acuity, the edema resolved and the patient was satisfied.

Dr. Singer: We examine visual acuity in an artificial room with black letters on a white background, but we use a questionnaire to ask what the patient can actually see.

Dr. Sanders: Patients with RVO and DME will tell me they need an injection before I see them because their vision is starting to get "fuzzy."

Dr. Singer: In this patient, would you consider anti-VEGF? Does the fact that she is vitrectomized change your treatment approach?

Dr. Blinder: The postvitrectomy patient is a good patient type for OZURDEX®, particularly with DME. I am not as concerned about neovascular glaucoma in these patients. Certainly, if I saw a change I would offer something else.

Dr. Blinder: In this case, she is doing well, and continues with OZURDEX® treatment.

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.

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

REFERENCES

1. Ascaso FJ, Huerva V, Grzybowski A. The role of inflammation in the pathogenesis of macular edema secondary to retinal vascular diseases. *Mediators Inflamm*. 2014;2014:432685.
2. Daruich A, Matet A, Moulin A, et al. Mechanisms of macular edema: Beyond the surface. *Prog Retin Eye Res*. 2018;63:20-68.
3. Lattanzio R, Torres Gimeno A, Battaglia Parodi M, Bandello F. Retinal vein occlusion: current treatment. *Ophthalmologica*. 2011;225(3):135-143.
4. Whitcup SM, Cidlowski JA, Csaky KG, Ambati J. Pharmacology of corticosteroids for diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2018;59(1):1-12.
5. Ho M, Liu DT, Lam DS, Jonas JB. Retinal vein occlusions, from basics to the latest treatment. *Retina*. 2016;36(3): 432-448.
6. Deobhakta A, Chang LK. Inflammation in retinal vein occlusion. *Int J Inflam*. 2013;2013:438412.
7. OZURDEX® Prescribing Information.
8. Data on file, Allergan.
9. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group; Maguire MG, Martin DF, Ying GS, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the Comparison of Age-related Macular Degeneration Treatments Trials. *Ophthalmology*. 2016;123(8):1751-1761.
10. Jansen ME, Krambeer CJ, Kermany DS, et al; Compliance Study Group. Appointment compliance in patients with diabetic macular edema and exudative macular degeneration. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49(3):186-190.
11. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology*. 1991;98(5 suppl):823-833.
12. Boyer DS, Yoon YH, Belfort R Jr, et al; OZURDEX® MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121(10): 1904-1914.
13. Haller JA, Bandello F, Belfort R Jr, et al; for OZURDEX® GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010;117(6):1134-1146.
14. Lowder C, Belfort R Jr, Lightman S, et al; for OZURDEX® HURON Study Group. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol*. 2011;129(5):545-553.
15. Sutter FK, Menghini M, Barthelmes D, et al. Is pseudophakia a risk factor for neovascular age-related macular degeneration? *Invest Ophthalmol Vis Sci*. 2007;48(4):1472-1475.
16. Congdon N, Vingerling JR, Klein BE, et al; Eye Diseases Prevalence Research Group. Prevalence of cataract and pseudophakia/aphakia among adults in the United States. *Arch Ophthalmol*. 2004;122(4):487-494.
17. Li L, Wan XH, Zhao GH. Meta-analysis of the risk of cataract in type 2 diabetes. *BMC Ophthalmol*. 2014;14:94.
18. Pollreisz A, Schmidt-Erfurth U. Diabetic cataract—pathogenesis, epidemiology and treatment. *J Ophthalmol*. 2010;2010:608751.
19. National Eye Institute. Facts about cataracts. National Eye Institute website. https://nei.nih.gov/health/cataract/cataract_facts. Reviewed September 2015. Accessed May 8, 2019.
20. Singh A, Stewart JM. Pathophysiology of diabetic macular edema. *Int Ophthalmol Clin*. 2009;49(2):1-11.
21. Moisseiev E, Goldstein M, Waisbourd M, Barak A, Loewenstein A. Long-term evaluation of patients treated with dexamethasone intravitreal implant for macular edema due to retinal vein occlusion. *Eye*. 2013;27(1):65-71.