Retinal PHYSICIAN

NOVEMBER/DECEMBER

Identifying Appropriate Patients Who Can Benefit From OZURDEX® (dexamethasone intravitreal implant) Treatment

A Roundtable Discussion and Case Series

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 and accompanying full Prescribing Information.

Identifying Appropriate Patients Who Can Benefit From OZURDEX® (dexamethasone intravitreal implant) Treatment

A Roundtable Discussion and Case Series

With FDA-approved indications for diabetic macular edema (DME), macular edema following retinal vein occlusion (RVO), and noninfectious posterior segment uveitis, the dexamethasone intravitreal implant (OZURDEX®, Allergan, an AbbVie company) is a treatment option for appropriate patients under the care of retina specialists. The following discussion and case presentations center on how to identify appropriate patients who can benefit from integration of OZURDEX® into their care plan.

Using OZURDEX® for DME

▸ **Caroline Baumal, MD: Dr. Ip, you have extensive experience treating patients with DME. How can we evolve the care we provide for them?**

Michael Ip, MD: In the current standard of care, anti–vascular endothelial growth factor (anti-VEGF) injections are used as initial therapy and are effective.[1,2] However, a proportion of patients are refractory to this initial therapy.[3,4]

It has been well known for many years that DME has a multifactorial etiology (**Figure 1**). It is not only VEGF driven; inflammatory mediators are also involved in DME pathogenesis.[5-7] This can create a need for a treatment that helps address the inflammatory pathway beyond the VEGF mechanisms. OZURDEX® has a role in therapy for eyes with DME because corticosteroid therapy can modulate the inflammatory mediators.[8,9] Dexamethasone has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines, resulting in reduction of edema, fibrin deposition, capillary leakage, and migration of inflammatory cells.[10]

▸ **MODERATOR:**
CAROLINE BAUMAL, MD

Dr. Baumal is a professor and retina specialist with the Tufts University School of Medicine at the New England Eye Center in Boston. She specializes in vitreoretinal surgery, medical retina, retinal imaging, macular degeneration, diabetic eye disease, and pediatric retina.

BRIAN DO, MD

Dr. Do is a vitreoretinal surgeon and uveitis specialist with The Retina Group of Washington, which serves patients in Washington, DC; Maryland; and Virginia. He is active in medical education and clinical research, and holds a faculty appointment as an assistant professor of ophthalmology at the Georgetown University School of Medicine.

MICHAEL IP, MD

Dr. Ip is a professor of ophthalmology and a retina and macular disease specialist and surgeon with UCLA Doheny Eye Institute in Los Angeles. He is principal investigator or co-principal investigator for multiple clinical trials investigating treatments for diabetic retinopathy, age-related macular degeneration, retinal venous occlusive disease, and other retina diseases.

▸ **Dr. Baumal: Dr. Do, when you treat patients with DME, how do you decide whether they have completely responded to initial therapy? What parameters do you use?**

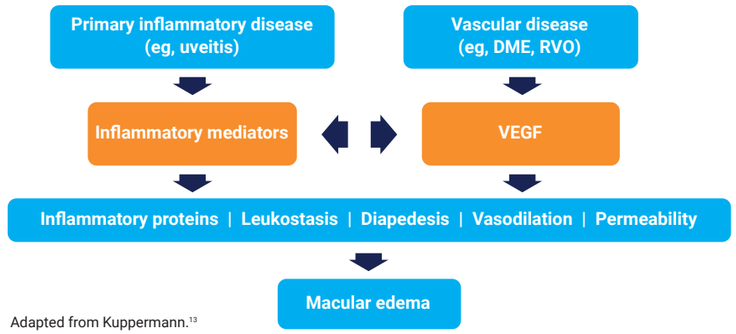
Brian Do, MD: Like most retina specialists, I use best-corrected visual acuity (BCVA) and optical coherence tomography (OCT) to guide my treatment decisions. I want to see resolution of intraretinal fluid as well as subretinal fluid when it's present. I also pay attention to whether intraretinal hyperreflective foci and cystoid spaces are improving on OCT.

Dr. Baumal: There has been some interesting research into whether specific OCT findings, such as hyperreflective dots as you mentioned, can potentially serve as biomarkers of an inflammatory process with potential to identify eyes that may be more responsive to steroid anti-inflammatory therapies.[11]

Keeping in mind that OZURDEX® (dexamethasone intravitreal implant) works by inhibiting multiple inflammatory cytokines,[10] let's review key data from the phase 3 MEAD trial.[10] MEAD consisted of 2 multicenter, masked, randomized, sham-controlled studies that evaluated the safety and efficacy of OZURDEX® (n = 328) compared with sham (n = 328) for the treatment of patients with DME over 3 years.[10]

After 1 treatment (3-month visit), the mean change in BCVA from baseline was 6.0 letters gained in the OZURDEX® group vs 2.6 letters in the sham group.[12] Also, the initial delta between the OZURDEX® arm and the sham arm was maintained over the long term out to 3 years (39-month visit). At 3 years, 19.5% of OZURDEX® patients gained ≥ 15 letters vs 10.7% with sham.[12] Only 14% of the study patients completed the month 39 visit (16.8% from OZURDEX® and 12.2% from sham).[10]

Diabetic Macular Edema Is Multifactorial [8,10,13]



Adapted from Kuppermann.[13]

Help address DME due to inflammation with treatments that target multiple inflammatory cytokines

FIGURE 1. The pathophysiology of macular edema involves an inflammatory response in the microvessels of the retina that may not respond adequately to initial therapy.

▸ **Dr. Baumal: As Dr. Do mentioned, we primarily monitor our DME patients with BCVA and OCT. What did the MEAD trial show with regard to retinal thickness?**

Dr. Ip: The trial wasn't designed to determine the significance of the retinal thickness secondary endpoint, but after 1 treatment (3-month visit), the mean change from the study baseline of 469.8 µm in central retinal thickness (CRT) was -160.4 µm with OZURDEX® vs -18.2 µm from 468.7 µm in the sham group.[12] At 3 years (39-month visit), the mean change from the study baseline thickness of 469.8 µm in CRT was -118.1 µm with OZURDEX® vs -64.5 µm from 468.7 µm with sham.[12]

With OZURDEX® there is a risk of intraocular pressure (IOP) elevation and cataract formation, which was observed during clinical trials.[14-16] The incidence of cataract formation was higher in phakic OZURDEX® treated patients with DME, RVO, and uveitis in the clinical trials compared with sham.[14-16] In MEAD, the incidence of cataract development was higher in the OZURDEX® group (68%) vs sham (21%).[10] Among these patients, 61% of OZURDEX® subjects vs 8% of sham-controlled subjects underwent cataract surgery.[10] In GENEVA and HURON, the incidence of cataract was 5% with OZURDEX® vs 2% with sham.[10] In a 2-year observational study, among patients who received > 2 injections, the most frequent adverse reaction was cataract 54% (n = 96 out of 178 phakic eyes at baseline).[10]

Identifying Patients

▸ **Dr. Baumal: What characteristics prompt you to use OZURDEX® (dexamethasone intravitreal implant) in a patient with DME?**

Dr. Do: Given the milieu of inflammatory cytokines that have been shown to be present in the vitreous of DME patients, I personally think about the appropriate patients who could benefit from OZURDEX®. I do whatever I can to dampen the negative impact the inflammatory molecules are having on the retina and retinal function. After 1 or 2 initial treatments, if I am not seeing an adequate response, I am quick to consider corticosteroid treatment with OZURDEX®.

Dr. Baumal: The following cases give us an opportunity to discuss how to identify patients who can benefit from OZURDEX® in their treatment regimens.

CASE 1: OZURDEX® in a Phakic Patient With DME and Previous Treatment

▸ **Dr. Baumal:** The first case I want to discuss with you is of a 68-year-old female **(Figure 2)**. She represents a common profile for patients of her age with diabetes. Her history included chronic renal failure, but she was not on dialysis nor insulin-dependent. She was unsure of her HbA1C level, but thought it might have been in the "9 or 10" range. She was also hypertensive, myopic, and phakic. She had previously received multiple intravitreal injections.

Based on the results of retinal imaging with FA and OCT (**Figure 2**), with the latter showing CRT of 655 µm, multiple intraretinal cystic spaces, and subretinal fluid, initial therapy was administered. The patient had limited ability to return for follow-up, but within the next 6 months she returned for another injection. At the visit following that injection, some improvement was noted. Visual acuity improved from 20/160 to 20/80-2. CRT improved to 550 µm, and FA showed less extensive leakage. However, anatomic appearance on OCT was not ideal (**Figure 2**). At this time, OZURDEX® (dexamethasone intravitreal implant) was given.

When the patient returned 14 weeks later, she was pleased with the results. Her vision had improved to 20/50-2, and CRT measured 300 µm (**Figure 3**).

Dr. Do: This is the kind of response I like to see with OZURDEX® in patients with DME. That said, I suspect the visual acuity reaching only 20/50-2 is due to the patchy disruption of the ellipsoid zone and outer retinal laminations visible on OCT (**Figure 3**). Those changes could be caused by long-standing DME and subretinal fluid, given the patient's difficulty with follow-up. This type of case points us toward the usefulness of introducing steroid earlier.

Dr. Ip: The angiogram shows the significant cystic macular edema, which is a characteristic that responds well to corticosteroid therapy.

▸ **Dr. Baumal: Would you have incorporated OZURDEX® sooner in this patient? How many treatments of initial therapy do you give before you consider OZURDEX®?**

Dr. Do: I give up to 3 administrations of initial-class therapy before deciding whether to use steroid. I often use branded agents, and if quite a bit of edema remains 1 month after the first injection, I start discussions with the patient about the possibility of using steroid. Of course, we want to minimize the likelihood of adverse effects from the treatments we provide, but we potentially do a disservice to patients by tolerating significant amounts of intraretinal and subretinal fluid for sustained periods of time.

OZURDEX® for RVO

Dr. Ip: As in DME, macular edema following RVO is not solely VEGF driven. Inflammatory mediators play an important role.[7,17] The GENEVA studies were 2 identical registration studies evaluating the efficacy and safety of OZURDEX® compared with sham injection in eyes with macular edema secondary to branch (BRVO) or central retinal vein occlusion (CRVO). From the GENEVA trials, OZURDEX® is effective in treating macular edema following both branch and central RVO.[14]

In GENEVA, at 30, 60, and 90 days after 1 OZURDEX® injection, there were statistically significant differences in BCVA between the patients treated with OZURDEX® and the sham-treated patients. The differences between OZURDEX® vs sham emerged as early as day 30, peaked at day 60, and remained statistically significant at day 90.[10] At day 60, 29.3% of patients treated with OZURDEX® gained 3 or more lines of BCVA vs 11.3% (48/426) treated with sham.[12] Within 1 to 2 months, 20% to 30% of OZURDEX® patients had gained 3 lines compared with 7% to 12% of sham patients.[10] The duration of effect persists approximately 1 to 3 months after onset.[10] CRT was first assessed at day 90. Mean decrease from baseline in CRT was significantly greater with OZURDEX® (208 µm ± 201) vs sham (85 µm ± 173) at day 90, but not at day 180.[14]

Dr. Baumal, do you approach using OZURDEX® for RVO patients differently than for DME patients?

Dr. Baumal: My patients with macular edema due to RVO respond well to OZURDEX®, and it remains an excellent option for patients who do not completely respond to other therapies or who want a therapy without the need for monthly injections. While development of cataract may be a concern in non-elderly patients, many of my elderly patients have already had cataract surgery when presenting with RVO. If I do not see the response I want after 3 injections, I move on to OZURDEX®. I may do so sooner than I would in a diabetic patient because I want to reduce the edema.

In GENEVA, some patients developed a cataract: 5% in the OZURDEX® arm vs 2% with the sham arm.[14] Following a second injection of OZURDEX® in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.[10]

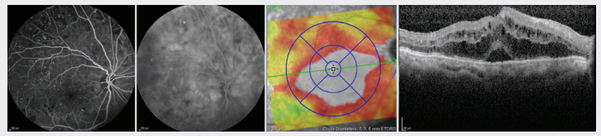
CASE 2: OZURDEX® in a Phakic CRVO Patient With Multiple Previous Treatments

Dr. Ip: Speaking of younger patients, I can share a case of mine involving a 53-year-old phakic male diagnosed with CRVO. He had concurrent diabetes and hypertension. He reported having 1 week of vision loss in the right eye. His visual acuity was 20/300 in that eye.

After a course of initial therapy, the patient noticed some improvement, but remained symptomatic. Visual acuity was 20/70. In addition, OCT showed significant retinal thickening and intraretinal cystic edema (**Figure 4**). At that time, I injected OZURDEX®. A month later, vision improved to 20/40 and CRT

CASE 1: OZURDEX® in a Phakic Patient With DME & Previous Treatment

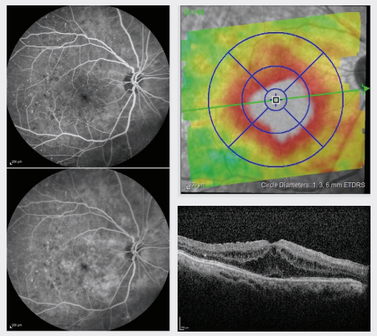
Initial Presentation



VA: 20/160 OD CRT: 655 µm

Treatment decision: First-line treatment initiated

Presentation After 6 Treatments With 2 Agents Over 6 Months

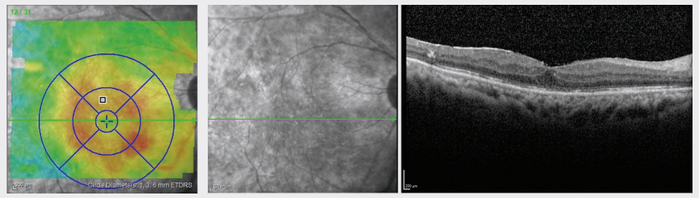


	OD
VA	20/80-2
CRT	550 µm
IOP	16 mm Hg

Treatment decision: OZURDEX® administered OD

FIGURE 2. Based on the results of FA and OCT in this patient with DME, initial therapy was administered. The patient had previously received alternate initial therapy as well. After multiple injections of initial therapy over time, improvement in the retinal anatomy of this DME patient was unsatisfactory. At this visit, the decision was made to administer OZURDEX® OD.

14 Weeks After 1 OZURDEX®



	OD
VA	20/50-2
CRT	300 µm
IOP	18 mm Hg

PHYSICIAN NOTES:

- IOP remained within normal limits and no topical drops were needed

FIGURE 3. Resolution of intraretinal and subretinal fluid following 1 OZURDEX® injection in a patient with DME who had previously undergone multiple injections of initial therapy with lackluster results.

CASE 2: OZURDEX® in a Phakic CRVO Patient With Previous Treatments

Summary: Before and After Treatment with 2 OZURDEX® Injections

Before OZURDEX®

	OD
VA	20/70
CRT	375 µm
IOP	15 mm Hg

After 2 OZURDEX®

	OD
VA	20/30
CRT	250 µm
IOP	20 mm Hg

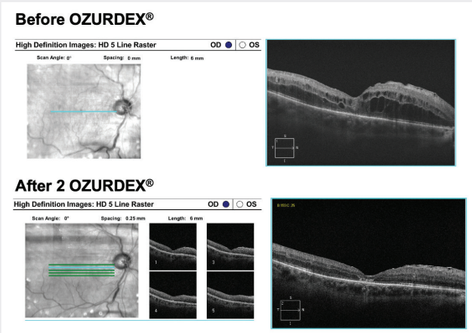


FIGURE 4. OZURDEX® (dexamethasone intravitreal implant) treatment was initiated for this patient when, after a course of initial therapy, OCT showed remaining retinal thickening and intraretinal cystic edema. After 2 injections of OZURDEX®, retinal anatomy and visual acuity improved. IOP remained within normal limits and no topical drops were needed.

decreased from 375 µm to 250 µm.

Four months after the first administration of OZURDEX®, the patient's visual acuity was stable, but retinal thickening began to return. I was confident that if we waited another month, the retinal anatomy would likely regress close to presteroid status. Therefore, I treated the patient with a second OZURDEX® injection. At 2 months after the second treatment, we had achieved a visual acuity of 20/30 (**Figure 4**).

Dr. Baumal, does this mirror your experience with OZURDEX® for RVO cases refractory to initial therapy?

Dr. Baumal: Absolutely. Some RVO patients do not respond completely, and some do not respond at all to initial therapy. They are ideal candidates for sustained-release intraocular steroid. The age of the patient in this case is notable as well. In younger patients, we should consider the possibility of an inflammatory component to RVO that is different than the typical vasculopathic component we see in other patients.

Dr. Ip: In this case, the patient was phakic. What is your level of comfort with OZURDEX® in a phakic patient?

Dr. Do: Lens status is less of a consideration for me when it comes to my patients with complicated posterior segment disease, including RVO and DME—but especially posterior segment uveitis, a potentially blinding disease when not properly controlled. Because we are past the era of intracapsular cataract surgery when we might expect significant complications, I have a very high comfort level injecting steroid in somebody who is phakic. If the choice is saving the retina or developing cataract, I will choose saving the retina every time.

Patient-Centered Considerations for Choosing OZURDEX®

Retina specialists providing care for DME, macular edema following retinal vein occlusion, and noninfectious posterior segment uveitis may choose the dexamethasone intravitreal implant (OZURDEX®, Allergan, an AbbVie company) as first-line or second-line therapy. In many cases, OZURDEX® can be introduced into a treatment regimen for patients who have an unsatisfactory response to initial treatment.

OZURDEX® for Noninfectious Posterior Segment Uveitis

Dr. Do: The safety and effectiveness of OZURDEX® for the treatment of noninfectious posterior segment uveitis has also been evaluated in a controlled clinical trial. In the 26-week HURON trial, eyes with noninfectious posterior segment uveitis were randomized to a single treatment with OZURDEX® 0.7 mg (n = 77), dexamethasone 0.35 mg (n = 76), or sham injection (n = 76).[15] The primary outcome measure was the proportion of eyes with a vitreous haze score of 0 at week 8.[15]

The results reported for noninfectious posterior segment uveitis in the 0.7 mg arm showed that after a single injection, at week 8 the percentage of patients reaching a vitreous haze score of 0 was statistically significantly greater for patients receiving OZURDEX® (47%) compared with patients receiving sham (12%).[10] Also, after a single injection, the percentage of patients with at least a 2-grade reduction in vitreous haze was statistically significantly greater for patients in the OZURDEX® (dexamethasone intravitreal implant) arm at week 8. The difference between the 2 study arms decreased after week 8 up to week 26.[15]

HURON also assessed visual acuity. At week 8, 43% of the OZURDEX® group gained ≥ 15 letters from baseline BCVA compared with 7% of the sham group.[10] Also at week 8, after a single injection, the mean change in BCVA from baseline was statistically significantly greater for patients receiving OZURDEX® vs patients receiving sham.[15] With regard to CRT, at week 8 the data showed a marked difference in mean change. In the OZURDEX® arm, the mean change was -99.4 µm (from baseline mean 344 µm). In the sham arm, the mean change was -12.4 µm (from baseline mean 324.6 µm).[15]

Dr. Baumal: In my opinion, the benefit of OZURDEX® in uveitis patients is clear, especially when disease is unilateral and would otherwise require prolonged oral steroid dosing. In my clinical experience, the effect of intravitreal OZURDEX® for uveitis may last up to 6 months.[15] Also, some patients really do not want to take oral steroid therapy, and OZURDEX® is a good option for patients who do not require or cannot tolerate systemic corticosteroid therapy.

Dr. Ip: I personally treat a limited number of uveitis patients because we have several uveitis specialists on our faculty, but for the patients I have treated, OZURDEX® has been effective. It is clear that corticosteroids are very effective for inflammation secondary to uveitis.

Dr. Do: I have found that OZURDEX® works well for noninfectious posterior segment uveitis. An advantageous aspect of OZURDEX® is its duration of effect. I know that 10 to 12 weeks post injection, I can expect the effect to begin wearing off and immunosuppression to have begun kicking in. If I then begin to see signs of recurrent inflammation, I know that additional adjustments have to be made to the medication regimen. I use OZURDEX® for all appropriate posterior segment uveitis, especially in adult patients.

CASE 3: OZURDEX® for Management of Chronic Noninfectious Posterior Segment Uveitis

Dr. Do: A good example of the effectiveness of OZURDEX® in uveitis is a case provided by Emmett Cunningham, MD, PhD. The case involved a 40-year-old man with a 6-year history of recurrent noninfectious posterior segment uveitis in the right eye. The patient also had a biopsy-proven diagnosis of sarcoidosis. At presentation, he was phakic. His vitreous haze score was +1.5, and OCT showed subretinal and intraretinal fluid and inner and outer plexiform layer cysts that had separated. Visual acuity was reduced to 20/60. En face Henle fiber layer imaging showed the extent of the cystoid changes and revealed anatomically moderate macular edema (**Figure 5**). Based on the exam findings, OZURDEX® treatment was provided.

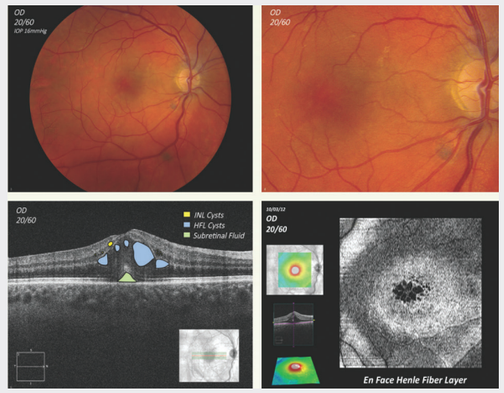
At 8 weeks after the injection, OCT showed improvement of the intraretinal and subretinal fluid (**Figure 6**). Vitreous haze also resolved, and visual acuity improved to 20/32. The decision was made to continue to monitor the patient.

Is this how you would have managed this patient?

Dr. Baumal: Yes. Based on the details provided, this patient appears to have uveitis related to sarcoid, with findings localized to the eye. I have similar patients in my practice who

CASE 3: OZURDEX® for Management of Chronic Noninfectious Posterior Segment Uveitis

Exam Findings and Treatment



	OD
VA	20/60
IOP	16 mm Hg
Vitreous haze	+1.5

Treatment decision: OZURDEX® administered OD

FIGURE 5. Imaging from the right eye of a 40-year-old patient with a 6-year history of recurrent posterior noninfectious uveitis. OZURDEX® was the chosen treatment at this visit.

Case 3 continued on page 8 ►

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).

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 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. 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.

Please see additional Important Safety Information on the following pages and accompanying full Prescribing Information.

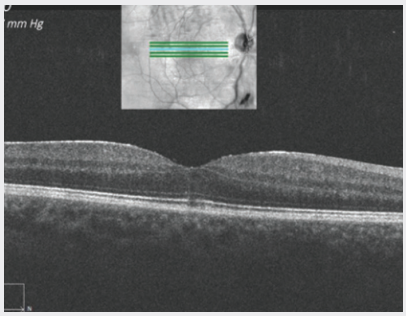
have solely ocular activity related to systemic sarcoidosis. These patients tend to have recurrence every few years, and OZURDEX® (dexamethasone intravitreal implant) is an excellent treatment providing a sustained-release corticosteroid in a biodegradable form for resolution of uveitis. I may try topical therapy briefly in a very mild case of uveitis, but otherwise I go right to OZURDEX®.

Dr. Do: I agree, especially in unilateral disease. It is easy to rationalize recommending localized therapy and sparing the rest of the body the negative effects of systemic treatment. I would have managed the case similarly, introducing OZURDEX® from the start.

Dr. Baumal: Uveitis differs from DME and RVO in that we typically go right to steroid therapy. Topical steroids have minimal utility in established posterior uveitis. In contrast, OZURDEX® is a very effective way to use steroids for the treatment of uveitis that involves the posterior segment, as was illustrated by this case. ■

CASE 3: OZURDEX® for Management of Chronic Noninfectious Posterior Segment Uveitis *(continued)*

Exam 8 Weeks Post OZURDEX® Treatment



	OD
VA	20/32
IOP	17 mm Hg
Vitreous haze	0
Spectral-domain OCT	ME resolved

No further treatment given

FIGURE 6. Eight weeks after 1 OZURDEX® injection for this patient with a history of recurrent posterior noninfectious uveitis, intraretinal fluid and subretinal fluid improved, vitreous haze resolved, and visual acuity was 20/32.

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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%).

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

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