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PERSPECTIVES ON TREATING DIABETIC MACULAR EDEMA IN PHAKIC PATIENTS

Experts discuss management strategies for patients receiving OZURDEX® (dexamethasone intravitreal implant)

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.

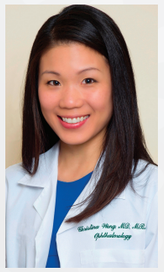
Please see additional Important Safety Information on the following pages.

FACULTY

MODERATOR
Nancy M. Holekamp, MD, is the director of Retina Services at the Pepose Vision Institute and a clinical professor of ophthalmology at the Washington University School of Medicine in St. Louis.

Seenu M. Hariprasad, MD, is the Shui-Chin Lee Professor of Ophthalmology and Visual Science, chief of the Vitreoretinal Service, director of Clinical Research, and director of Fellowships in Vitreoretinal Diseases and Surgery at the University of Chicago Medicine & Biological Sciences.

Eric D. Donnenfeld, MD, FACS, is a clinical professor in the Department of Ophthalmology at NYU. He is a cataract and refractive specialist.



Christina Y. Weng, MD, MBA, is an assistant professor in the Ophthalmology Department, Division of Vitreoretinal Diseases and Surgery, at the Baylor College of Medicine in Houston.

Roger A. Goldberg, MD, MBA, is in private practice with Bay Area Retina Associates in Walnut Creek, CA, and on the clinical faculty at the California Pacific Medical Center in San Francisco.

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.

PERSPECTIVES ON TREATING DIABETIC MACULAR EDEMA IN PHAKIC PATIENTS

Experts discuss management strategies for patients receiving OZURDEX® (dexamethasone intravitreal implant)

Please see the Administration instructions in the accompanying U.S. Prescribing Information, Section 2.2.

Nancy M. Holekamp, MD: Our discussion today focuses on the use of OZURDEX® (dexamethasone intravitreal implant; Allergan) to treat diabetic macular edema (DME) in phakic patients. We'll review the relationship between diabetic retinopathy and DME and cataract risk, and discuss progressive cataract formation with OZURDEX®. We'll also look at the 3-year findings from the MEAD clinical trial to understand the risk of cataract formation and progression with OZURDEX®, and we'll discuss treatment strategies for DME in phakic patients.

Dr. Donnenfeld, as the anterior segment specialist on the panel, you bring a unique perspective to this discussion. How do you manage lens opacities in patients who have DME?

Eric D. Donnenfeld, MD: The coexistence of cataract and diabetes is potentially sight-threatening, but, from my perspective, cataract surgery is a common procedure for diabetic patients.[1] Thus, I take a secondary position in the patient's treatment, while my retina colleagues address the diabetic maculopathy. Once the DME is under control, I assess the lens opacities and perform cataract surgery when the patient is ready.

"I address the DME first, and I treat it fairly aggressively. If the retina isn't functioning optimally, the patient won't see well, which is why this is my primary focus."
— ROGER A. GOLDBERG, MD, MBA

Dr. Holekamp: Dr. Goldberg, how does the lens opacity affect your treatment of DME?

Roger A. Goldberg, MD, MBA: I address the DME first, and I treat it fairly aggressively. If the retina isn't functioning optimally, the patient won't see well, which is why this is my primary focus. I work closely with referring cataract surgeons because cataract surgery may exacerbate DME.[1] It's important that I treat the DME and have it under control in the 1 to 2 weeks prior to cataract surgery.

Dr. Holekamp: Dr. Weng, do you determine the appropriate time for a patient who is being treated for DME to have cataract surgery?

Christina Y. Weng, MD, MBA: In a way, yes. We know that people with diabetes are more prone to developing cataracts in the first place, and that their cataracts progress with age.[2,3] If their DME treatment includes steroid, that may cause the cataracts to progress even more quickly.[4,5] I see these patients regularly, often monthly; therefore, I likely have the opportunity to detect cataract progression before their general ophthalmologists or cataract specialists.

Dr. Holekamp: When do you refer a patient for evaluation by a cataract surgeon?

Dr. Weng: I refer a patient when I feel a cataract is becoming visually significant, either to me in terms of being able to monitor the diabetic retinopathy — perhaps by attenuating the signal strength of the optical coherence tomography (OCT) — or to the patient, when it is affecting visual acuity. When a cataract becomes advanced, it can be

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.

Please see additional Important Safety Information on the following pages.

a confounding factor in the decision-making process, because we don't know if vision loss is from the DME or the cataract.

Dr. Holekamp: In addition to cataracts being more common in people with diabetes, they are also more common in patients who have diabetic retinopathy and DME.[6-8] Additional risk factors for cataracts in the diabetes population include age, poor glycemic control, smoking, and the degree of retinopathy.[2,3,9,10]

Dr. Hariprasad, what is your approach when a patient being treated for DME develops a cataract?

"Another consideration from an anterior segment perspective is the impact of macular edema on a patient's quality of vision and contrast sensitivity. These are areas where significant changes can occur."

— ERIC D. DONNENFELD, MD

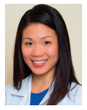
Seenu M. Hariprasad, MD: My mindset is similar to Dr. Donnenfeld's in terms of the importance of treating the retina before addressing the cataract.

Dr. Holekamp: Do the cataract surgeons at your institution wait for you to give the green light for surgery?

Dr. Hariprasad: Yes, we discuss the timing of treatments relative to cataract surgery, as well as follow-up after cataract surgery.

Dr. Holekamp: Dr. Donnenfeld, do you agree with our panelists' approaches?

Dr. Donnenfeld: I completely agree.



"I don't go into the details of whether they have a nuclear sclerotic cataract (NSC) versus cortical or posterior subcapsular cataract (PSC). ...However, I do think it's important to address the presence of a cataract before starting therapy."

— CHRISTINA Y. WENG, MD, MBA

Another consideration from an anterior segment perspective is the impact of macular edema on a patient's quality of vision and contrast sensitivity. These are areas where significant changes can occur. Once the edema has resolved, patients may feel their vision is not quite as good as it was before, even though their Snellen acuity may be good. With macular edema, rapid assessment and aggressive therapy are the hallmarks of good care.

Complications From DME Therapy: What Patients Need to Know

Dr. Holekamp: Dr. Hariprasad, what do you tell patients who are newly diagnosed with DME about other eye issues that may arise during treatment?

Dr. Hariprasad: It depends on the treatment I'm about to administer. If I will use a corticosteroid, I discuss, among other things, the cataract, the possibility of intraocular pressure (IOP) elevation, and the rare need for incisional surgery to manage increased IOP.

Dr. Holekamp: Do you tell patients what type of cataract they have?

Dr. Hariprasad: I note the type and degree of cataract in the patient record, but I simply tell the patient they have a cataract and whether or not I'm recommending cataract surgery. I don't think there is too much value in delving deeper into cataract nuances with patients.

Dr. Holekamp: Dr. Weng, do you discuss the type of cataract a patient has?

Dr. Weng: I don't go into the details of whether they have a nuclear sclerotic cataract (NSC) versus cortical or posterior subcapsular cataract (PSC). I suspect that's beyond what most patients want to know. However, I do think it's important to address the presence of a cataract before starting therapy. Unless someone has a completely clear lens, I use the term "cataract" early on, so they know it's there, they're familiar with the word, they start learning about it, and it doesn't come as a shock when the cataract progresses. Typically, I explain, "You have a small cataract now, and if we proceed with a corticosteroid, the cataract will likely progress, but we can address that when appropriate."

Dr. Holekamp: Dr. Donnenfeld, should retina specialists describe the type of cataract a patient has, or is it sufficient for us to explain that the lens in the eye is cloudy and may be interfering with vision?

Dr. Donnenfeld: Patients don't need to know what type of cataract they have. They need to know that it's affecting their vision and why. When you're planning to use OZURDEX® (dexamethasone intravitreal implant), discussing the possibility that a cataract may develop and explaining in general terms what a cataract is and how we treat it is good medicine. It's a short but important conversation that puts patients at ease.

Dr. Holekamp: Dr. Goldberg, do you mention cataract at a patient's initial visit and then again when it becomes visually significant, or do you discuss it at every visit?

Dr. Goldberg: I certainly mention cataract at the beginning of the process, but I'm communicating so much information about diabetes and DME that I don't like to overemphasize the other eye issues. I mention what I notice, whether it's dry eye or a cataract, but I spend most of the chair time discussing diabetic eye disease. I find that patients remember only about 10% of what we tell them at any one time, so I avoid inundating them with too much information.[11] I do bring up cataract periodically, but not at every visit.

Incidence of Cataract in Diabetes: NSC vs PSC

Dr. Holekamp: Two major population-based studies show the 5-year and 10-year incidence of cataract in patients with diabetes (Figure 1).[12,13] Both studies show that the incidence of NSC was highest, compared to cortical cataract (CC) or PSC. Dr. Donnenfeld, are you surprised at the low rate of PSC in these patients?

Dr. Donnenfeld: Yes. I would have expected more PSCs. PSCs are associated with diabetes, prolonged use of corticosteroids, and trauma, but those numbers are lower than I would have expected them to be. NSC is the classic cataract that we see predominantly.[14-16]

While it's interesting to consider the etiology of cataracts and where they occur in the lens, at the end of the day, the management is the same.[17]

Dr. Holekamp: Dr. Weng, at presentation, do your patients with diabetes have NSCs more often than PSCs?

Dr. Weng: In my practice, I see a higher prevalence of nuclear sclerosis, but, as Dr. Donnenfeld notes, we address cataracts the same way regardless of the type, so I don't dwell on this classification too much. While I do note a cataract's type and grade so I can track progression, I am confident that once it's removed, any vision loss attributable to the cataract will be reversed.

Dr. Holekamp: Dr. Goldberg, what was your reaction when you saw these data?

Dr. Goldberg: Frankly, I was surprised, because I think we all tend to expect PSCs more in patients with diabetes in general and in those who are treated with corticosteroids in particular. I think it has to do with the speed of progression in PSCs vs NSCs. NSCs are slow to develop, so we don't perceive the change as much. A PSC can develop quickly.[17,18]

Dr. Holekamp: I think most people are surprised by these data.

As someone who has done cataract research, I always comment on whether it's an NSC or a PSC because of expectations. An NSC will grow slowly, whereas a PSC will not only grow more quickly, but, if it is in the central visual axis, it will likely need surgical attention sooner rather than later.[17]

Multifocal Intraocular Lenses (IOLs) for Patients With DME

Dr. Holekamp: Dr. Donnenfeld, what is your approach to implanting multifocal IOLs in patients with DME?

Dr. Donnenfeld: The quality of

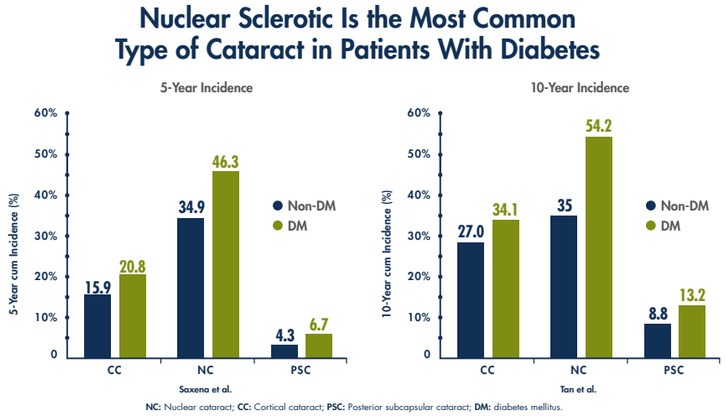


Figure 1. Studies have shown the incidence of NSC is higher than that of PSC in patients with diabetes.[12,13]

IMPORTANT SAFETY INFORMATION (continued)
Warnings and Precautions (continued)

Steroid-related Effects: Use of corticosteroids including OZURDEX® (dexamethasone intravitreal implant) 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 should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

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.

presbyopia-correcting IOLs has improved dramatically over the last several years. The introduction of low-add multifocal lenses that induce less glare and halo has been a game-changer, and the newest generation of extended depth-of-focus lenses is even better.[19-22]

As the issues of glare and halo have diminished greatly, I am comfortable implanting some of these lenses in patients who have relatively good macular function. I usually consult with my retina colleagues about the patient's prognosis, and I obtain an informed consent from the patient. I always tell patients who are diabetic that they have an added risk of visual sequelae with a presbyopia-correcting IOL, and the worst-case scenario — an IOL exchange — could become necessary.[23,24] I have scores of patients with diabetes who function well and are happy with multifocal IOLs.

Dr. Holekamp: Did these patients have no diabetic retinopathy, some diabetic retinopathy, as in mild to moderate nonproliferative diabetic retinopathy, or did they also have DME in some cases?

Dr. Donnenfeld: Generally, I don't consider patients who have proliferative retinopathy good candidates for presbyopia-correcting IOLs.[24-26] If patients have some macular thickening that I feel is reversible, however, I may be comfortable implanting presbyopia-correcting IOLs. Typically, I ask my retina colleagues to consider aggressive intervention before I perform cataract surgery to ensure that they have every opportunity to treat the diabetic maculopathy.

I view the management of diabetic maculopathy to be independent of whether a patient does or does not have cataract surgery. It doesn't change my decision-making and my support of patients undergoing aggressive therapy. This is totally in the hands of the retina specialist. The cataract progression is almost incidental to the patient's ocular health, and to me, aggressive therapy is the hallmark of good medical care for patients who have diabetes.

Dr. Holekamp: Dr. Weng, do you advise your cataract surgeon colleagues as to whether or not a standard IOL would be preferable for certain patients versus a presbyopia-correcting IOL?

Dr. Weng: I do not. I defer to the cataract surgeons as the experts. Similarly, they defer to me to determine the best time for cataract surgery in the context of the patient's diabetic eye disease. Most of my cataract surgeon colleagues prefer to use monofocal lenses in patients with DME because of the differences in visual quality that these patients can experience.

MEAD DME Study Population

	OZURDEX® (n = 328)	Sham (n = 328)
Mean age, years (range)	**62.8** (33–85)	**62.9** (26–88)
Gender (% male)	**62.8%**	**63.4%**
Race (%)		
White	**71.0%**	**70.1%**
Black	**4.9%**	**6.1%**
Asian	**16.5%**	**16.2%**
Hispanic	**4.3%**	**4.6%**
Other	**3.4%**	**3.0%**
Lens status (%)		
Pseudophakic	**25.0%**	**30.2%**
Phakic	**75.0%**	**69.8%**
Mean BCVA, letters (SD[a])	**55.7** (9.96)	**56.6** (8.77)
Median BCVA, letters (range)	**59.0** (34–95)	**58.0** (34–82)
Mean center subfield retinal thickness on OCT (SD)	**469.8** (156.99)	**468.7** (128.96)
Mean IOP, mm Hg (SD)	**15.3** (2.64)	**15.3** (3.09)
Mean diabetes duration, years (SD)	**16.5** (9.15)	**15.9** (9.26)

	OZURDEX® (n = 328)	Sham (n = 328)
Diabetes type (%)		
Type 1	**10.4%**	**8.5%**
Type 2	**88.7%**	**91.5%**
Mean HbA1c (SD)	**7.6** (1.15)	**7.5** (1.05)
≤ 8% (%)	**67.1%**	**71.6%**
Mean DME duration, months (SD)	**24.0** (25.92)	**26.3** (26.11)
DME subtype (%)		
None	**0.6%**	**0.6%**
Focal	**35.1%**	**39.9%**
Intermediate	**39.9%**	**35.7%**
Diffuse	**19.5%**	**20.7%**
Severity of diabetic retinopathy (%)		
Moderately severe or better nonproliferative diabetic retinopathy (NPDR)	**48.2%**	**49.7%**
Severe or worse NPDR	**43.6%**	**42.1%**
Prior DME treatment (%)		
Anti-VEGF[b]	**7.6%**	**7.9%**
Intravitreal steroid	**17.7%**	**18.3%**
Laser	**68.6%**	**72.3%**
None	**26.5%**	**22.3%**

[a]Standard deviation. [b]Vascular endothelial growth factor.

Figure 2. Baseline characteristics and demographics influence outcomes.[27,28]

OZURDEX® in Phakic Patients

Dr. Holekamp: We're going to shift gears to discuss the use of OZURDEX® (dexamethasone intravitreal implant) to treat DME in phakic patients. Specifically, we'll consider some relevant data from the MEAD study.[27] First, I want to focus on the baseline characteristics of the MEAD study population (Figure 2). The mean age of patients in this study was 62 to 63 years, and 75% of the OZURDEX® patients were phakic at the time of entry into the trial.[27,28] Dr. Donnenfeld, what's the average age of someone having cataract surgery these days?

Dr. Donnenfeld: I estimate the mean age for cataract surgery is about 70 years for a person in the general population.[29,30] The average age for cataract surgery for someone who is diabetic is probably 20 years younger than that.[1]

Dr. Holekamp: That makes sense because we know people with diabetes develop cataracts at an earlier age because of their multiple risk factors.[1]

Dr. Hariprasad, are most of your patients who have DME phakic?

Dr. Hariprasad: Yes. When I see them initially, many are phakic and have type 2 diabetes that is poorly managed. Often, they haven't seen a medical professional, and we're the first physicians to refer them for primary care services.

Dr. Holekamp: In the clinical trial, 67% of OZURDEX® (dexamethasone intravitreal implant) patients had hemoglobin A1c of 8 or better.[28] That may be unique to a clinical trial population. In our clinics, we may be managing patients who have worse control of their diabetes.

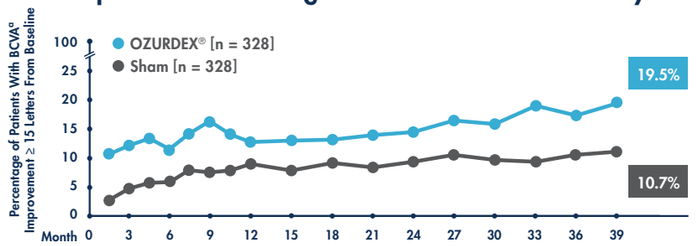
Dr. Hariprasad: I agree. In my patient population, I estimate fewer than 40% have good hemoglobin A1c levels — and we know that poor control is also a risk factor for cataract progression.[2,3,9]

Dr. Holekamp: In the MEAD trial, patients, regardless of lens status, treated with OZURDEX® showed sustained improvement through 3 years (Figure 3). 19.5% of OZURDEX® patients gained 15 or more letters in best corrected visual acuity (BCVA) at month 39, compared with 10.7% in the sham arm.[28] Breaking down the visual acuity results, 13.7% of patients receiving OZURDEX® lost 15 or more letters in BCVA at month 39, compared with 10.7% in the sham arm (estimated difference: 3%; 95% CI: -2%, 8.1%) (Figure 4).[28] Dr. Goldberg, what's your take on this statistic and the reason why patients treated with OZURDEX® lost more vision than those in the sham arm?

Dr. Goldberg: These results are predominantly reflected in the patients who were phakic, as shown in Figure 5.

In the proportion of the population that was pseudophakic at baseline, there was essentially a 2% difference in the percentage of 3-line losers in either arm of the trial [4 OZURDEX® patients (5%) vs 7 sham patients (7%)] (estimated difference: -2.2%; 95% CI: -9.1%, 4.7%). However, there was a 5% difference in the percentage of 3-line losers who

OZURDEX® Sustained Clinically Significant Vision Improvements Throughout the 3-Year MEAD Study



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).

[a]Best-corrected visual acuity.

▶ Patients who received escape therapy were withdrawn from the study

Figure 3. Patients treated with OZURDEX® showed sustained improvement through 3 years.[28]

Vision Improvements With OZURDEX® Were Clinically Significant at Month 39

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)	2.2 (15.88)	0.8 (12.72)	1.3 (-0.9, 3.4)

BCVA Baseline and Change From Baseline After 1 Treatment

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

Figure 4. Patients treated with OZURDEX® achieved clinically significant visual acuity improvement.[28]

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® (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.

Please see additional Important Safety Information on the following pages.

Clinical Outcomes Observed in Phakic and Pseudophakic Patients

Phakic Patients: Visual Acuity Outcomes at Month 39

Measurement	OZURDEX® (n = 246)	Sham (n = 229)	Estimated Difference (95% CI)
Patients gaining ≥ 15 letters (3 lines) in BCVA (n)	20% (48)	11% (24)	9.0% (2.7%, 15.4%)
Patients losing ≥ 15 letters in BCVA (n)	17% (41)	12% (28)	4.4% (-1.9%, 10.7%)
Mean change in BCVA (letters) (SD)	1.0 (16.9)	0.6 (12.9)	0.3 (-2.4, 3.0)

- 68% of phakic OZURDEX® (dexamethasone intravitreal implant) patients (n = 243) experienced a cataract versus 21% of sham patients (n = 230)
- The occurrence of cataracts impacted visual acuity during the study

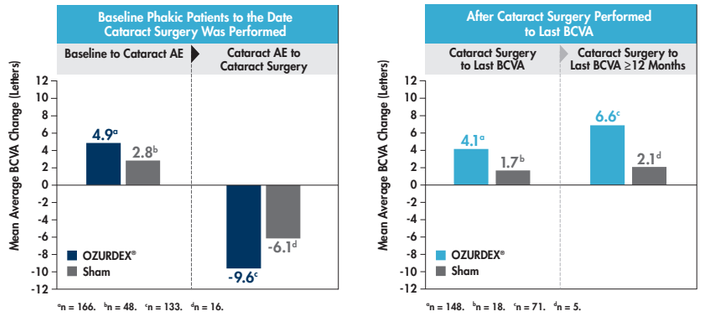
Pseudophakic Patients: Visual Acuity Outcomes at Month 39

Measurement	OZURDEX® (n = 82)	Sham (n = 99)	Estimated Difference (95% CI)
Patients gaining ≥ 15 letters (3 lines) in BCVA (n)	20% (16)	11% (11)	8.4% (-2.2%, 19.0%)
Patients losing ≥ 15 letters in BCVA (n)	5% (4)	7% (7)	-2.2% (-9.1%, 4.7%)
Mean change in BCVA (letters) (SD)	5.8 (11.6)	1.4 (12.3)	4.2 (0.8, 7.6)

Figure 5. There was a 2% difference in the percentage of 3-line losers in either arm of the trial in patients who were pseudophakic at baseline.[28,31]

Patients Who Were Phakic at Baseline: Mean Average Change in BCVA by Change in Lens Status

Post Hoc Analysis



Pooled results from 2 multicenter, masked, randomized, sham-controlled, 3-year trials in studies with DME. Subgroup for pooled data with LOCF. BCVA was measured using a standard ETDRS protocol.

Figure 6. Phakic patients had vision improvements until their cataract adverse effect; once the cataract was removed, their vision improved again.[28]

were phakic at baseline [41 OZURDEX® (dexamethasone intravitreal implant) patients (17%) vs 28 sham patients (12%)] (estimated difference: 4.4%; 95% CI: -1.9%, 10.7%). Patients who were pseudophakic at baseline also achieved greater mean BCVA change from baseline at the final study visit than phakic patients (Figure 5).[31]

Dr. Holekamp: Most phakic patients in the MEAD trial went on a journey that looks like the graphs in Figure 6. They were treated with OZURDEX®,

"Most phakic patients in the MEAD trial went on a journey that looks like the graphs in Figure 6. They were treated with OZURDEX®, and their vision improved until they had their cataract adverse event. Their vision deteriorated until they could be referred to a cataract surgeon. They had their cataract extraction, and then they seemed to do well again.[28]"

— NANCY M. HOLEKAMP, MD

and their vision improved until they had their cataract adverse event. Their vision deteriorated until they could be referred to a cataract surgeon. They had their cataract extraction, and then they seemed to do well again.[28]

Dr. Weng, is this consistent with your clinical experience?

Dr. Weng: Absolutely, and I think Figure 6 is a very important graphic from the MEAD trial, because while cataract progression in this study — in which the majority of patients were phakic — may have reduced vision in some of its subjects, after cataract surgery, vision improved.

Dr. Holekamp: Dr. Donnenfeld, in the MEAD trial, patients referred for cataract surgery had OZURDEX® (dexamethasone intravitreal implant) in the eye. How do you feel about operating on that eye?

Dr. Donnenfeld: Aggressive management of inflammation is the hallmark of modern cataract surgery.[32,33] With OZURDEX® on board, I can still achieve visual acuity improvement.

Risk-Benefit Ratio for OZURDEX®

Dr. Holekamp: Dr. Hariprasad, how do you decide when to use OZURDEX®?

Dr. Hariprasad: OZURDEX® can have quite a positive impact on the treatment of DME. I use OZURDEX® when I need a corticosteroid to treat inflammation. I use an anti-VEGF to address VEGF. In my experience, there are patients who can benefit from just one OZURDEX® injection.

As for cataract risk, with a single injection of OZURDEX®, I may see a cataract, since the OZURDEX® pivotal data show a 9.9% rate of cataract after one injection (month 6). I still believe the visual benefit can be significant.

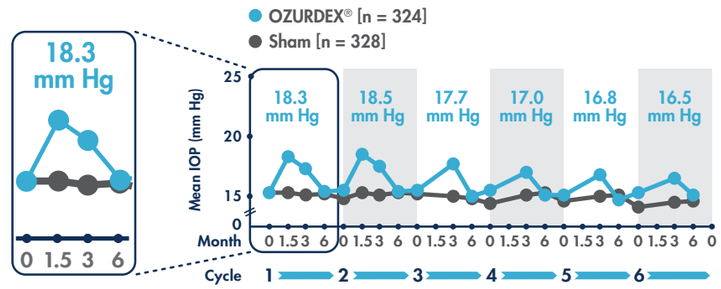
IOP may rise, but typically the increase is manageable with topical IOP-lowering drops.[27] I've implanted OZURDEX® numerous times.

In my opinion, one OZURDEX® injection may benefit patients whose DME has an inflammatory component.[28]

Dr. Holekamp: Dr. Weng, what do you tell patients about their first OZURDEX® injection?

Dr. Weng: It's important to discuss the main risks. I explain that steroid treatment carries an inherent risk that a cataract will progress or develop.

Mean IOP Generally Returned to Baseline Between Treatment Cycles



- 28% of OZURDEX® patients (91/324) experienced an IOP elevation ≥ 10 mm Hg from baseline versus 4% with sham (13/328) at any visit during the 3-year MEAD study
- 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)

Figure 7. Typically, IOP generally returns to baseline between treatment cycles.[28,31]

I also tell patients that we will monitor their IOP closely and if it increases, it can be managed with eye drops the majority of the time.[27]

"I use OZURDEX® when I need a corticosteroid to treat inflammation. I use an anti-VEGF to address VEGF. In my experience, there are patients who can benefit from just one OZURDEX® injection."

— SEENU M. HARIPRASAD, MD

Dr. Holekamp: We are fortunate to have clinical trial data to help us manage expectations regarding elevated IOP. From the MEAD trial, we know that after the first injection, we can identify more than half of patients who are likely to experience their first pressure increase of ≥ 10 mm Hg, and that the increase in mean IOP was seen with each treatment cycle.[28,31] Over time, the pressure generally returns to baseline between treatment cycles.[31] We also know that most pressures can be managed with topical medical therapy.[27]

Dr. Holekamp: Dr. Goldberg, are these results typical in your practice?

Dr. Goldberg: Most of us have used at least some anti-VEGF to determine if the DME is primarily a VEGF-mediated disease. If a disease is more inflammatory in nature, I also consider OZURDEX®. I'm always impressed with the result after just one injection, and, frankly, the patients are impressed when they see the improvement at their 6-week follow-up visit.

Dr. Holekamp: Does the risk profile for a cataract adverse event change if we're administering multiple OZURDEX® injections?

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.

"If a disease is more inflammatory in nature, I consider OZURDEX®. I'm always impressed with the result after just one injection, and, frankly, the patients are impressed when they see the improvement at their 6-week follow-up visit."

— ROGER A. GOLDBERG, MD

Dr. Goldberg: The risk of cataract with one OZURDEX® (dexamethasone intravitreal implant) was 9.9% in the MEAD trial. With repeated injections of OZURDEX®, there is an increased incidence of cataracts.[28] After up to 7 treatment cycles during the 39-month study, 68% of OZURDEX® patients vs 21% of sham-treated patients reported a cataract adverse event.[28] After that first injection, however, you see how the retinal anatomy responds, and how the vision and visual function respond. In addition, as we discussed, after that first OZURDEX® injection, you can also identify a large proportion of patients who have an IOP response. Thus, you learn a great deal that can help guide the further use of OZURDEX®.

Dr. Holekamp: Dr. Hariprasad, what has been your experience when administering multiple OZURDEX® injections?

Dr. Hariprasad: In some patients who have received multiple OZURDEX® injections, they may notice after several injections that their vision is hazy. It may be a cataract.

Since I told them about the possibility of cataract at their initial visit, they willingly undergo surgery. I very rarely have any pushback or hesitation about proceeding with cataract surgery, because they saw the benefit of this implant. They undergo cataract surgery, come back to our clinic, and continue with DME therapy.

Dr. Holekamp: So, after one injection, you can potentially assess the benefit.

Dr. Hariprasad: It is possible to see the benefit in terms of vision (vision improved after injection and got worse just before this visit — they are describing the recurrence of macular edema as OZURDEX® wears off).

Dr. Holekamp: The benefit is significant and that helps you calculate the risk with future OZURDEX® injections if required. That's an interesting concept.

A Closer Look at Cataract Formation

Dr. Holekamp: In the MEAD trial, about 68% of eyes treated with OZURDEX® had a cataract during the 39-month study compared with 21% in the sham group, which corresponds with our own clinical experiences.[28] As a reminder, these patients, on average, were about 62 or 63 years old, so they likely have more NSCs than we would normally associate with someone that age.

After one OZURDEX® injection, cataract was reported as an ocular adverse event in 9.9% of the OZURDEX® eyes and 7.8% of eyes in the sham arm. When we look at cataract surgery through the first 6 months after one OZURDEX® injection, the number is 3.7% vs 2.2% with sham.[28] After up to 7 treatment cycles during the 39-month study, 61% of OZURDEX® patients and 8% of sham-treated patients underwent cataract surgery.[31]

Dr. Weng, would you like to comment?

Dr. Weng: My experience matches the data in regard to the risk of cataract development.

Dr. Holekamp: The median time to cataract development was approximately 15 months in the OZURDEX® group compared with 12 months in the sham group.[31] Dr. Goldberg, in your experience, when are these patients developing visually significant cataracts?

Dr. Goldberg: It tends to be after 1 or even 2 years. In the MEAD trial, 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. I find it's difficult to predict which patients will develop a cataract more quickly.[31]

Dr. Holekamp: This is why we have clinical trial data, because we have to look at large groups of patients in a rigorous fashion to find out when the cataract forms after OZURDEX® injections. We find that it tends to be at a median of 15 months (Figure 8).[31]

As someone who pays attention to cataracts and has done cataract research, I find that my patients generally need a cataract procedure by their fifth OZURDEX® injection. In the MEAD trial, 61% of OZURDEX® subjects vs 8% of sham-controlled subjects underwent cataract surgery, generally between month 18 and month 39 of the studies (median: month 21 for OZURDEX® patients and month 20 for sham patients).[31]

Dr. Goldberg: In the MEAD trial, treatment was limited to one OZURDEX® (dexamethasone intravitreal implant) injection every 6 months. In clinical practice, I believe most of us are treating at a slightly higher rate or shorter intervals between treatments. That probably lands you somewhere in the second year of treatment.

Dr. Weng: When I discuss cataracts with patients, I compare it to gray hair. I tell them we can't predict when cataracts will occur or the rate they will progress — just as we can't predict if someone will go gray quickly or slowly. That explanation resonates with patients and helps them understand that we don't have a crystal ball to tell them when they're going to get their cataract.

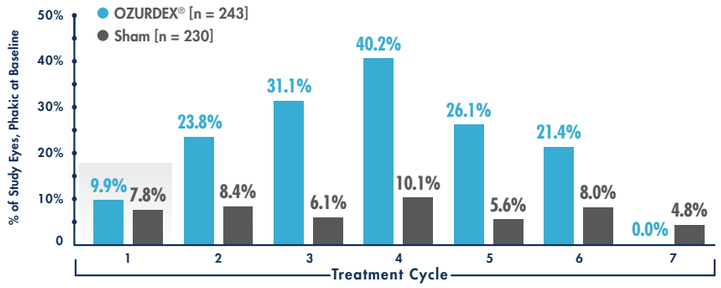
I advise patients that a cataract may occur after repeated treatment with OZURDEX®. If this occurs, I advise patients that their vision will decrease and they will need an operation to remove the cataract and restore their vision.[31]

Dr. Holekamp: Dr. Donnenfeld, what's the predominant type of cataract you're removing in patients who are diabetic?

Dr. Donnenfeld: Most patients have nuclear cataracts, but many have more than one type of cataract, and the presence of PSC with NSC is probably the most common combination that I see. Again, the type of cataract doesn't change my surgical technique in any way, and it doesn't change my surgical outcomes. My diabetic patients deserve therapy, and if they end up with cataracts, we'll take care of them.

Dr. Holekamp: I encourage my retina colleagues to take a close look at the lens status in patients undergoing successive OZURDEX® injections. I believe the cataract is predominantly nuclear sclerotic, and it is predictable after the fourth or fifth OZURDEX® injection. The MEAD clinical trial was our first clue to this pattern, and I think we'll see it in our clinical practices, as well.

Cataract Occurrence Peaked During Year 2 After 4 Treatment Cycles[28]



At month 6, the incidence of cataract surgery in phakic patients was 3.7% with OZURDEX® vs 2.2% with sham

Figure 8. The MEAD trial offers guidance as to when to expect cataract formation in patients treated with OZURDEX®.[28]

I feel comfortable that patients who have cataracts will let their surgeon know when they're ready for surgery.

Dr. Holekamp: I would like to conclude this discussion on OZURDEX® use in phakic patients by thanking all of the panelists for their insightful comments.

We have clear data from the MEAD clinical trial regarding OZURDEX® use in phakic patients, and we know that the progressive cataract can be managed. This resonates with our clinical practice. Retina specialists and cataract surgeons are aligned when it comes to prioritizing the DME with OZURDEX® and then proceeding with cataract extraction. A few interesting new points have arisen, including the predominance of

"As someone who pays attention to cataracts and has done cataract research, I find that my patients generally need a cataract procedure by their fifth OZURDEX® injection."

— NANCY M. HOLEKAMP, MD

Dr. Donnenfeld: Cataract is a disease in which the patients largely determine when they need surgery. In my experience, they tell us when they're ready. As retina specialists, you can refer patients for evaluation for cataract surgery, but the visual need and the visual disturbance and how it affects every patient is an individual idiosyncratic event. You can

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.

nuclear sclerotic cataract over posterior subcapsular cataract in our DME patients.

Another interesting point is the 9.9% risk of cataract progression associated with a single OZURDEX® (dexamethasone intravitreal implant) injection. I advise my patients that a cataract may occur after OZURDEX® treatments. During the 39-month MEAD trial after up to 7 treatment cycles, 68% of OZURDEX® patients vs 21% of sham-treated patients reported a cataract adverse event. Clinical trials, such as the MEAD study, and broad clinical experience, such as that shared by our panelists, help us manage both DME and our diabetic patients' expectations. ●

"I advise my patients that a cataract may occur after OZURDEX® treatments. Clinical trials, such as the MEAD study, and broad clinical experience, such as that shared by our panelists, help us manage both DME and our diabetic patients' expectations."

— NANCY M. HOLEKAMP, MD

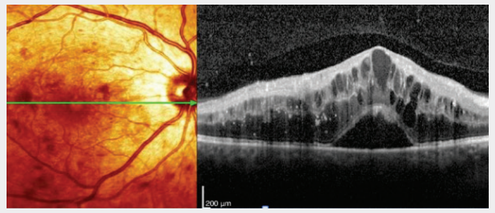
Introducing OZURDEX® (dexamethasone intravitreal implant) to Your Patients

- The swelling in your retina can be caused by several factors[34]
- OZURDEX® is a corticosteroid and works to help reduce the inflammation in your retina. OZURDEX® helps by improving visual acuity[31]
- 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[31]
- OZURDEX® is injected directly into the back of the eye, with minimal systemic absorption[35]
- 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[31]
- 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[31]
- In clinical studies, OZURDEX® improved vision in patients without the need for monthly injections[31]

CASE: Christina Y. Weng, MD

BACKGROUND

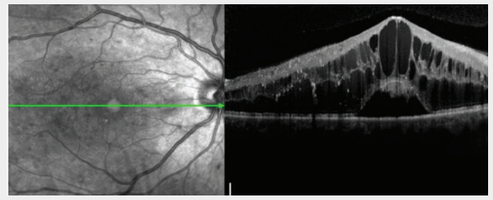
- 41-year-old man with non–insulin-dependent diabetes and DME with a chief complaint of blurry vision
- Taking some oral medications for his diabetes, but admitted he does not check his blood sugar regularly
- The patient, who is phakic, had never been to an eye doctor
- Today I focus on the right eye only
- At his initial visit, the patient's visual acuity was 20/50+1 OD. Central foveal thickness was 862 µm
- IOP was normal at 17 mm Hg, mild (+0.5) nuclear sclerosis was present, and funduscopic examination revealed severe nonproliferative diabetic retinopathy with DME



Physician notes:
- *Multiple previous treatments over 4 months*
- *Patient noted high visit frequency*
- *Patient is lost to follow-up for 3 months*

NEXT VISIT

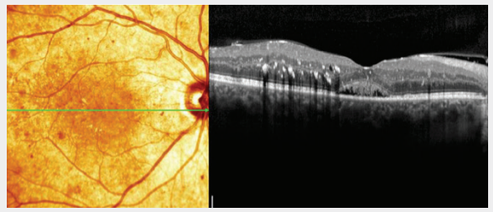
- Visual acuity in OD was 20/60 and his central foveal thickness was 913 µm
- Decided to proceed with OZURDEX® (dexamethasone intravitreal implant) OD



Physician notes:
- *Patient apologized for not returning for follow-up for 3 months*

6 WEEKS AFTER 1 OZURDEX® TREATMENT

- The patient had a 3-line improvement in visual acuity to 20/40+2, IOP was normal at 18 mm Hg, central foveal thickness had decreased to 332 µm



Physician notes:
- *Patient reported stable vision clarity*

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.

IMPORTANT SAFETY INFORMATION (continued)
Warnings and Precautions (continued)
Steroid-related Effects: Use of corticosteroids including OZURDEX® (dexamethasone intravitreal implant) may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

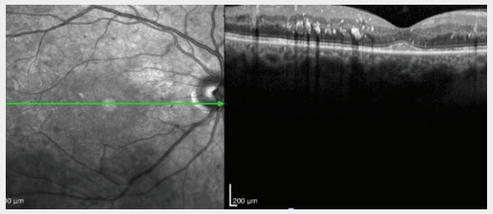
Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Please see additional Important Safety Information on the following pages.

CASE: Christina Y. Weng, MD (cont)

12 WEEKS AFTER 1 OZURDEX® (DEXAMETHASONE INTRAVITREAL IMPLANT) TREATMENT

- Visual acuity was improved to 20/25-1; central foveal thickness had decreased to 280 µm; IOP was 20 mm Hg, still within normal limits; and the nuclear sclerosis was exactly the same



Physician notes:

- *Patient noted improvement in vision*

18 WEEKS AFTER 1 OZURDEX® TREATMENT

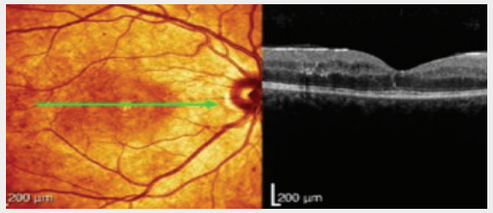
- Patient's visual acuity was 20/25-1 and his central foveal thickness was 277 µm. His IOP was 18 mm Hg, and the nuclear sclerosis was unchanged

Physician notes:

- *Patient reported stable vision; decided to hold off on treatment*

24 WEEKS AFTER 1 OZURDEX® TREATMENT

- Patient CRT was 302 µm and IOP was the same as the last visit
- Visual acuity was still 20/25-

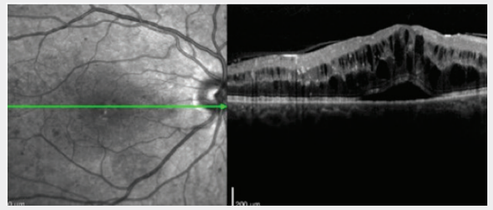


Physician notes:

- *Observed some recurrent trace cysts temporal to the foveal center*
- *Patient reported stable vision; decided to hold off on treatment*

30 WEEKS AFTER 1 OZURDEX® TREATMENT

- DME had reoccurred and visual acuity had dropped to 20/40 with a CRT of 675 µm. IOP was 16 mm Hg and nuclear sclerosis was unchanged.
- Second OZURDEX® administered OD



DISCUSSION:

- Patient's visual acuity went from 20/60 to 20/25-1, 18 weeks after 1 OZURDEX®
- The DME patient achieved efficacy without the need for monthly injections

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%).

CASE: Nancy M. Holekamp, MD

BACKGROUND:

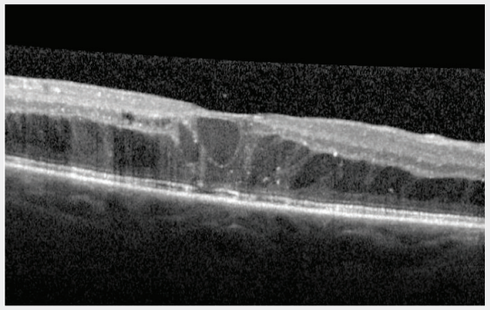
- 59-year-old woman had a 3-year history of non–insulin-dependent diabetes
- She had no health insurance. Probably had diabetes longer than 3 years
- She had been going to the university resident clinic for 2 years and received multiple treatments to both eyes
- She had moderately severe nonproliferative disease with DME, greater in the right eye than the left eye. Going forward, this presentation focuses on the right eye
- Patient's chief complaint was blurry vision
- Her visual acuity was 20/50 OD, OCT 442 µm, and IOP 14 mm Hg
- 1+ NS cataracts in both eyes with normal IOP

Physician notes:

- *Patient receives multiple treatments over 4 months*

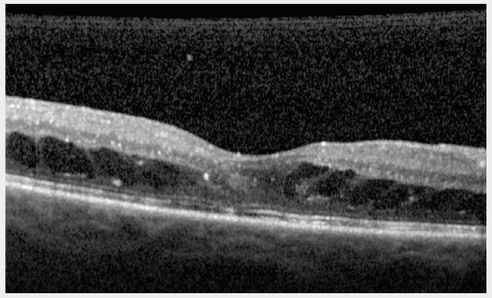
1 MONTH AFTER FIRST OZURDEX® (dexamethasone intravitreal implant)

- Patient returned for follow-up. Noted improvement in the right eye on OCT (359 µm), visual acuity improved to 20/25, and IOP was normal at 16 mm Hg



2 MONTHS AFTER FIRST OZURDEX®

- DME in the right eye, although not completely resolved, was certainly improved
- Visual acuity of 20/32 OD, OCT 331 µm, IOP was 11 mm Hg, and lens status remained the same
- Continued treating with OZURDEX®



DISCUSSION:

- I've been seeing this patient for 2 years and she has continued with OZURDEX®
- She comes in religiously for pressure checks, which have always been normal
- By the time I saw her initially, the right eye had permanent architectural damage, and I was never going to get it completely flat
- On OZURDEX®, her VA is 20/32 OD and the patient notes improvement with her vision and reduced treatment schedule

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. 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 page.

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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

