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Perspectives on Treatment With OZURDEX (dexamethasone intravitreal implant) 0.7 mg

Treatment of Diabetic Macular Edema (DME) and Macular Edema (ME) Following Retinal Vein Occlusion (RVO)* With a Discussion on Use in Pseudophakic Patients With DME

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[®] 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.

*Retinal vein occlusion: branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Perspectives on Treatment With OZURDEX (dexamethasone intravitreal implant) 0.7 mg

Treatment of Diabetic Macular Edema (DME) and Macular Edema (ME) Following Retinal Vein Occlusion (RVO) With a Discussion on Use in Pseudophakic Patients With DME

ecent studies have shown us that the inflammatory cascade is highly relevant in the development and persistence of ME and that interventions aimed at multiple inflammatory mediators help improve visual acuity.¹ Corticosteroids form the basis for such approaches in the clinic, although there is an appreciable risk of cataract progression and intraocular pressure (IOP) elevation associated with their use.^{1,2} In the following article, a panel of experts will discuss these risks, adding important clinical context about safety concerns. Additionally, this supplement will include a focus on patients with RVO and DME and discuss pseudophakic patients with DME. In particular, we will discuss whether patients with a pseudophakic lens require any special treatment considerations for DME. — Tarek S. Hassan, MD, Moderator



TAREK S. HASSAN, MD

- Professor of Ophthalmology, Oakland University William Beaumont School of Medicine, Auburn Hills, Michigan
- Partner and Vitreoretinal Surgery Fellowship Director at Associated Retinal Consultants, Royal Oak, Michigan
- Member of the Retina Today editorial advisory board
- tsahassan@yahoo.com
- Financial disclosure: Consultant (Alcon, Allergan, ArcticDx, Bayer, Broadspot, Genentech, Iconic, Katalyst, Novartis, Ocugenix, Oculus Surgical, Regeneron, Roche, Surgicube, Vitreq); Equity (Arctic Dx, Broadspot, Oculus Surgical)

BARUCH D. KUPPERMANN, MD, PhD

- Steinert Professor of Ophthalmology and Biomedical Engineering, Chair of the Department of Ophthalmology, and Director of the Gavin Herbert Eye Institute, University of California, Irvine, School of Medicine
- bdkupper@uci.edu
- Financial disclosure: Consultant (Aerpio, Alcon, Alimera, Allegro, Allergan, Ampio, Catalyst, Dose, Eleven Biotherapeutics, Genentech, Glaukos, Lumenis, Neurotech, Novartis, Ophthotech, Regeneron, SciFluor); Clinical Research (Alcon, Alimera, Allegro, Allergan, Apellis, Genentech, GSK, J-Cyte, Neurotech, Ohr, Ophthotech, Regeneron, ThromboGenics)

IMPORTANT SAFETY INFORMATION (continued) Contraindications (continued)

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

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

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

HOWARD F. FINE, MD, MHSc

- Associate Professor, Rutgers University, University of Medicine and Dentistry of New Jersey, New Brunswick
- NJ Retina, New Brunswick
- hfine@njretina.com
- Financial disclosure: Consultant/Speaker (Alimera Sciences, Allergan, Genentech, Regeneron, Spark Therapeutics, Inc.); Research (Alcon; Alimera; Allergan; Genentech; Ohr; Regeneron); Patent/Equity Holder (Auris Health)

ERIC D. NUDLEMAN, MD, PhD

- Assistant Professor, Shiley Eye Institute, University of California, San Diego
- eric.nudleman@gmail.com
- Financial disclosure: Consultant (Allergan and Visunex Medical Systems)

AMY C. SCHEFLER, MD, FACS

- Assistant Professor of Ophthalmology, University of Texas, Houston
- Partner, Retina Consultants of Houston, Texas
- acsmd@houstonretina.com
- Financial disclosure: Consultant (Allergan, Aura Biosciences, Castle Biosciences, Genentech); Clinical Research (Aura Biosciences, Castle Biosciences, Genentech, Regeneron)

THE ROLE AND RELEVANCE OF INFLAMMATION IN MACULAR EDEMA

Tarek S. Hassan, MD: ME is a feature of many commonly occurring eye diseases, including diabetic eye disease and RVO. ME is the most common cause of visual impairment in RVO.³ Corticosteroids, due to their anti-inflammatory properties, and anti-vascular endothelial growth factor (VEGF) therapy both play a prominent role in the therapy of ME.⁴ Yet, while inflammatory mediators and VEGF each drive ME pathophysiology, it appears that one or the other may predominate in a given clinical presentation.⁵

Baruch D. Kuppermann, MD, PhD: The relative contributions of VEGF and inflammatory mediators are individualized, and they also vary in different disease states. For example, while VEGF and inflammatory mediators are key drivers of ME in RVO and DME, VEGF may be slightly more important in RVO due to the potential for induced hypoxia. In diabetic retinopathy (DR), there is growing evidence regarding the role of inflammatory mediators in the disease process.⁶

What is common to DME, RVO, and uveitis with respect to ME, though, is that it is the result of a cascade of events caused by vascular disease that is facilitated by inflammatory cytokines that lead to vasodilation, leukostasis, diapedesis, increased vascular permeability, and the accumulation of various inflammatory proteins.⁷ Thus, while VEGF blockade is an important approach, we may need to address other clinical factors as well. Inflammation plays an important role, and this broader context should be considered.

Dr. Hassan: It has been proposed that the relative contributions of the inflammatory component and the VEGF might vary in DME.⁵ Is there any evidence of this?

Amy C. Schefler, MD, FACS: I have found that patients in my practice who have longer-term DME need a multifactorial approach. That would suggest to me that perhaps another mediator is active, and that inflammation can also play a critical role.⁵

IMPORTANT SAFETY INFORMATION (continued) Warnings and Precautions

Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX® (dexamethasone intravitreal implant), 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.

Please see additional Important Safety Information on the following pages.



Dr. Hassan: I wonder if the chronicity of the eye disease is the only factor.^{2,5,8} In some cases, it appears that the ME is driven by either VEGF or inflammation, whereas in others, both are factors.⁹

Eric D. Nudleman, MD. PhD: There are some interesting clinical trial data that are worth considering. In a subgroup analysis of the FAME trial, which was investigating the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera), patients who had chronic edema-defined as a 3-year duration or longer-had greater improvement on visual outcomes than those with DME less than 3 years.¹⁰ The reason is uncertain, but it was suggested that fluocinolone was more beneficial in eyes with inflammatory disease, indicated by longer duration of active edema.¹⁰

Dr. Kuppermann: Interestingly, a reanalysis of the FAME trial suggested that the median duration of DME was less than 2 years; this observed effect in patients with chronic DME started to occur after about 2 years of median disease duration. Delaying initiation of anti-VEGF may have consequences for visual ability.⁹ In the RISE/ RIDE trial, patients who were crossed over to ranibizumab (Lucentis, Genentech) at 24 months did not gain as much vision as patients initially treated with anti-VEGF.¹¹ Taken together, these data support what Dr. Hassan is suggesting, that steroids may have an important place in therapy because of the role of inflammation in the pathophysiology of ME. Also, because the inflammatory response is a cascade, it intensifies over time and becomes more active as the DME persists, which may explain why we may see an effect in more chronic ME.⁵

There is another piece of evidence that speaks to the relative contributions of VEGF and inflammation in ME. Dong et al showed that VEGF is elevated in aqueous samples taken from eyes with DR, but other inflammatory cytokines also appeared to be prominently elevated as well. This suggests to me that, while VEGF is certainly a key player, the presence of a variety of cytokines suggest that inflammation is also important and DME may also be responsive to treatment with steroids.¹²

Dr. Hassan: Are there any clinical trial data that might help us predict who will respond to anti-VEGF?

Howard F. Fine, MD, MHSc: The data from the EARLY trial was a post-hoc analysis of the Diabetic Retinopathy Clinical Research (DRCR) Network Protocol I data.¹³ That can be helpful when thinking about who will be a good responder, a medium responder, or a poor responder to anti-VEGF therapy. In my clinic, I look at this a little bit differently.

My endpoint for therapy is to gain improvement in visual acuity and to get a dry macula.

ADDRESSING INFLAMMATION IN RVO

Dr. Hassan: The classic thinking in RVO is that the VEGF mediators are much more influential in ME. However, there is evidence that corticosteroid therapy targeted at multiple inflammatory cytokines also may help reduce ME in eyes with RVO.⁴ The importance of treating inflammation is further supported by data from the GENEVA trial, in which 853 patients with central (CRVO) or branch (BRVO) RVO were randomized 1:1 to OZURDEX implant or sham. Time to achieve \geq 15 letters (3-line) improvement in best corrected visual acuity (BCVA) cumulative response rate curves was significantly faster with OZURDEX compared to sham (P < .01).¹⁴ Patients had a mean duration of ME of 157 days.¹³ Overall, the proportion of patients achieving at least a 15-letter improvement from baseline BCVA was significantly greater in the OZURDEX group than in the sham group from day 30 through day 90 (Figure 1).^{14,15} At 180 days, this difference was not statistically significant.14

Dr. Kuppermann:

The window of response from 30 to 90 days is actually pretty reflective of what we see in practice, with most patients responding early, by day 30, and the effect peaking by 60 days, then a continued clinical effect over the next month. I find the response to be quite predictable, and if there is a response to the first implant injection, I feel comfortable reusing it if needed.

Dr. Hassan: Is there a difference between BRVO and CRVO in how we should approach treatment?

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%).

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX[®] patients versus 4% of sham patients. 42% of the patients who received OZURDEX[®] were subsequently treated with IOPlowering medications during the study versus 10% of sham patients.

After 1 OZURDEX, More Patients Gained 3 Lines of Vision Significantly Faster vs Sham

Percentage of Patients With ≥ 15-Letter Gains From Baseline in BCVA



Figure 1. Percentage of patients with \geq 15-letter gains from baseline in BCVA.14,15

Dr. Fine: Anti-VEGF is likely the first consideration in both BRVO and CRVO, but the reasons for evaluating therapy typically differ. There is a worse prognosis associated with CRVO,^{3,9} so in many cases I start with anti-VEGF therapy, but I may also think about a dexamethasone implant to suppress the inflammation.¹⁶

Dr. Schefler: Certainly, the prognosis with treatment is better in BRVO compared to CRVO, and that is just the nature of these conditions. Still, as we saw in the GENEVA study data, the dexamethasone implant is effective for treating both BRVO and CRVO, with a peak effect around day 60 (Figure 2).14,15

Dr. Hassan: How long do you stick with a given treatment approach before escalating therapy?

Dr. Fine: It really depends. With OZURDEX, if there is a response, I will continue to use it. I will know pretty quickly if it works or not before moving on to other treatment strategies.

Dr. Schefler: Because inflammation is such an important part of RVO, I have a low threshold for considering OZURDEX.

Dr. Hassan: What factors might we consider regarding the timing of a repeat OZURDEX injection?

Dr. Fine: RVO is a highly time-dependent disease.¹⁷ I have found that there is a specific point at which the drug wears off and the edema can come back very guickly. That said, the acute nature of the ME also makes it a little forgiving, because even if the swelling recurs, repeat treatment is likely to improve the vision similar to how it did with the prior injections.¹⁸ The goal should be to time the retreatment so the effect of the implant remains continuous without losing efficacy.^{14,15}

OZURDEX IOP AND CATARACT SAFETY INFORMATION IN RVO AND POSTERIOR SEGMENT UVEITIS

Combined results from the OZURDEX phase 3 RVO and posterior segment uveitis studies showed:

- 25% of OZURDEX patients (n = 497) versus 2% of sham patients (n = 498) experienced increased IOP; increased IOP with OZURDEX peaked at approximately week 816
 - 1% of the patients who received OZURDEX (3/421) required surgical procedures for management of elevated IOP during the initial treatment period¹⁶
- 5% of OZURDEX patients versus 2% of sham patients experienced a cataract; following a second injection of OZURDEX in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year¹⁶

ME IN DME: MEAD TRIAL DATA IN CONTEXT

Dr. Hassan: The pivotal MEAD trial led the FDA to approve OZURDEX for treatment of DME based in part on the proportion of patients gaining \geq 15 letters in BCVA from baseline at the patient's final efficacy assessment (Table 1).¹⁵ The outcome was positive, yet I wonder if some of the

IMPORTANT SAFETY INFORMATION (continued) Adverse Reactions (continued)

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

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

Please see additional Important Safety Information on the following pages.



ment phase (A) and open-label extension (B). Results are also presented in CRVO patients (C and D).^{14,15}

TABLE 1. VISUAL ACUITY OUTCOMES AT 39 MONTHS IN THE MEAD TRIAL. ¹⁵			
All Randomized Patients: Visual Acuity Outcomes at Month 39			
Measurement	OZURDEX (n = 328)	Sham (n = 328)	Estimated Difference (95% Confidence Interval [CI])
Patients gaining \geq 15 letters (3 lines) in BCVA (n)	19.5% (64)	10.7% (35)	8.8% (3.4%, 14.3%)
Patients losing \geq 15 letters in BCVA (n)	13.7% (45)	10.7% (35)	3.0% (-2.0%, 8.1%)
Mean change in BCVA (letters) (SD ^a)	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 2.6 letters gained	in OZURDEX group in sham group

Pooled results of all DME randomized patients with last observation carried forward (LOCF) from two 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).^{15,19}

with DMF?

improvement in mean BCVA versus sham patients and the phakic

subset of patients (Tables 3 and 4 and Figures 4 and 5).^{16,19} Does that

suggest we should consider the lens status in the treatment of patients

Dr. Fine: I do not think we need to change our treatment endpoint

in a pseudophakic eye, but it might affect the approach. My treatment

endpoint is always to improve visual acuity and achieve a dry macula.

That is not always achievable, but pseudophakia might encourage me

Dr. Kuppermann: I attempt to treat until the macula is dry as well,

but there is also a balance. If the excess macular thickness is 50 µm or

less, and the vision is good after using anti-VEGF therapy, I would not

Dr. Hassan: What other endpoints are important? How do you

Dr. Schefler: In DME, I think it is important to not ignore vision.

All of the variables we use in the clinic add up in our evaluation, and

EVALUATING AND MANAGING IOP ELEVATION

well-known risks associated with use of corticosteroid therapy.

Dr. Hassan: Cataract progression and IOP elevation are two

to think about using OZURDEX to treat edema.

be inclined to add OZURDEX in my treatment of DME.

use OCT and/or vision to guide treatment decisions?

there may be other factors to consider as well.

^a Standard deviation.

baseline characteristics might be interesting to consider for context. For instance, the mean DME duration of the patients in the trial was 2 years, and I wonder if that may have influenced the results?

Dr. Fine: The cohort enrolled to MEAD would fit the profile of some of the tougher cases of DME that we would deal with in the clinic. In addition to the longer duration of DME, a majority had received other previous treatments, for example (Table 2).¹⁹ In my view, there appears to be a bit more advanced disease at baseline in the MEAD trial study population in terms of severity of nonproliferative diabetic retinopathy (NPDR).¹⁹

Dr. Hassan: I think the high percentage of phakic patients, 75%,^{15,19} might have had an impact on final acuity outcomes, as well (Figure 3). It is also important to acknowledge that there was a reinjection protocol of every 6 months with OZURDEX, based on physician's discretion after examination including OCT. In clinical practice, we may reinject at shorter intervals. These are variables that should be taken into consideration.

DME IN THE PSEUDOPHAKIC PATIENT

Dr. Hassan: Certain populations of patients appear to be particularly good candidates for earlier initiation of OZURDEX therapy. In MEAD, 20% of pseudophakic patients on OZURDEX gained 3 or more lines of BCVA at 39 months versus 11% of sham patients (estimated difference 8.4%; 95% Cl: -2.2%, 19.0%), and this pseudophakic subset had a greater

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.

	TABLE	2. MEAD DME	STUDY POPULATION. ¹⁵		
	OZURDEX (n = 328)	Sham (n = 328)		OZURDEX (n = 328)	Sham (n = 328)
Aean age, years range)	62.8 (33–85)	62.9 (26–88)	Diabetes type (%) Type 1	10.4%	8.5%
Gender (% male)	62.8%	63.4%	Type 2	88.7%	91.5%
tace (%) White	71.0% 70.1%	Mean HbA1c (SD) ≤ 8% (%)	7.6 (1.15) 67.1%	7.5 (1.05) 71.6%	
Black Asian Hispanic	4.9% 16.5% 4.3%	6.1% 16.2% 4.6%	Mean DME duration, months (SD)	24.0 (25.92)	26.3 (26.11)
Other	3.4%	3.0%	DME subtype (%)		
ens status (%) Pseudophakic Phakic	25.0% 75.0%	30.2% 69.8%	- None Focal Intermediate Diffuse	0.6% 35.1% 39.9% 19.5%	0.6% 39.9% 35.7% 20.7%
Aean BCVA, letters SD ^a)	55.7 (9.96)	56.6 (8.77)	Severity of diabetic retinopathy (%) Moderately severe or better nonproliferative diabetic retinopathy (NPDR) Severe or worse NPDR Prior DME treatment (%) Anti-VEGF ^b Intravitreal steroid Laser None		
Aedian BCVA, letters range)	59.0 (34–95)	58.0 (34–82)		48.2%	49.7 %
Aean center subfield etinal thickness on OCT	469.8 (156.99)	468.7 (128.96)		43.6%	42.1%
Nean IOP, mm Hg SD)	15.3 (2.64)	15.3 (3.09)		7.6% 17.7%	7.9% 18.3%
Aean diabetes duration, years SD)	16.5 (9.15)	15.9 (9.26)		68.6% 26.5%	72.3% 22.3%
Standard deviation	•				

Anti-vascular endothelial growth factor.

While pseudophakic lens status obviates the former, IOP elevation is something that should be carefully considered for all patients. How common is IOP elevation after an OZURDEX implant?

Dr. Nudleman: I think what we saw in the MEAD trial, over the course of the 3-year study after up to seven implants, where 28% in the implant group compared with 4% in the sham group had an IOP

IMPORTANT SAFETY INFORMATION Contraindications

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Glaucoma: OZURDEX[®] is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

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

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

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elevation of 10 mm Hg or greater, is a fair representation of actual experience.¹⁶ 15.7% experienced their first IOP elevation \geq 10 mm Hg from baseline during the first cycle of treatments with OZURDEX. In clinical trials, for elevated IOP in the study eye up to 30 mm Hg, the need for treatment was at the discretion of the investigator based on

the patient's risk factors for optic nerve damage. For IOP > 30 mm Hg, consultation with a glaucoma specialist was recommended.¹⁵

TABLE 3. PHAKIC PATIENTS: VISUAL ACUITY OUTCOMES AT MONTH 39. ¹⁶			
Measurement	OZURDEX (n = 246)	Sham (n = 229)	Estimated Difference (95% CI)
Patients gaining \geq 15 letters (3 lines) in BCVA (n)	20% (48)	11% (24)	9.0% (2.7%, 15.4%)
Patients losing \geq 15 letters in BCVA (n)	17% (41)	12% (28)	4.4% (-1.9%, 10.7%)
Mean change in BCVA (letters) (SD ^a)	1.0 (16.9)	0.6 (12.9)	0.3 (-2.4, 3.0)
^a Standard deviation.			

OZURDEX Sustained Clinically Significant Vision Improvements Throughout the 3-Year MEAD Study **Primary Endpoint: Percentage of All Patients** With ≥ 15-Letter (3-Line) Gains in BCVA From Baseline OZURDEX (n = 328) Sham (n = 328) 19.5% 15 L

12 15 18 21 24 27 30 33 36 Pooled results of all DME randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) from 2 multicenter, masked, randomized patients with last observation carried forward (LOCF) forward (LO Protect research of an other characteristic and source water than the strength of the strength Patients who received escape therapy were withdrawn from the study.

Figure 3. Percentage of patients with ≥ 15-letter (3-line) gains in BCVA from baseline in MEAD.¹⁵

Dr. Hassan: How do you manage those patients?

Dr. Nudleman: If there is elevation, I want to see the patient back in about a week, because I want to see elevation on two consecutive visits before considering starting topical therapy.

Dr. Hassan: Does anyone use a benchmark, for example a pressure greater than 25 mm Hg?

TABLE 4. PSEUDOPHAKIC PATIENTS: VISUAL ACUITY OUTCOMES AT MONTH 39.¹⁶

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



Figure 4. Pseudophakic patients: mean change in BCVA from baseline.¹⁵



Figure 5. Phakic patients: mean change in BCVA from baseline.¹⁵

IMPORTANT SAFETY INFORMATION (continued) Warnings and Precautions

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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.

Dr. Fine: You have to consider the whole picture, because in that same patient, the cup-to-disc ratio might be 0.5 and the optic nerve looks healthy. If there is cupping and a pressure above target, I might be more aggressive about treating the elevation. I typically use a beta-blocker.

Dr. Schefler: We should make a distinction here because elevated ocular pressure does not always equal glaucoma. We should assess the whole health of the eye first. In MEAD, throughout the 3-year study, 28% of patients had an IOP elevation \geq 10 mm Hg from baseline at some point during treatment compared with 4% of sham-treated patients. 42% of OZURDEX patients compared with 10% of sham patients needed any IOP-lowering medication during the study. Yet, over the course of the 3-year study, 0.3% of OZURDEX patients required incisional surgery for steroid-induced IOP increases, and 1.2% of OZURDEX patients needed any surgical intervention for elevated IOP as compared with 0.3% of sham-treated patients.¹⁶ The goal is to save vision, and that should be the high priority.

Dr. Nudleman: I agree completely.

Dr. Hassan:

Returning to the MEAD data, after the first injection, 15.7% of OZURDEX eyes exhibited an elevated IOP of \geq 10 mm Hg from baseline.^{15,16} The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles.^{15,16} I have noticed this same thing in clinical practice.

Dr. Fine: The nice thing about OZURDEX is that we have data to provide context for IOP elevations.

Dr. Hassan: Let us say that a patient experiences a rise in IOP to 30 mm Hg, and topical therapy is initiated. Once that pressure is back to target or something reasonable, will you reinject the implant?

Dr. Kuppermann: Yes. First, if I start topical therapy and lower

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%).

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

Please see additional Important Safety Information on the following pages.



Figure 6. Mean IOP by visit within treatment cycle.^{15,16}

the pressure to 20 or 25 mm Hg, I can start to taper because the pharmacokinetics of the implant suggest the steroid will not last long in the eye, with peak drug levels at 60 days post injection.²⁰ In clinical practice, it might be sufficient to observe patients, rather than use topical drops, in certain cases, to see if the IOP settles on its own.¹⁵ Elevated IOP on its own can be a little misleading, and this is seen even in the MEAD trial, where there was an increase in mean IOP after each injection of the implant, but mean IOP generally returned to baseline between treatment cycles (Figure 6). Based on that, I try to manage each patient on an individualized basis in regard to IOP elevation.

Dr. Schefler: I think you can use the implant as the primary mode of therapy even after an IOP elevation. If the IOP is still elevated after 60 days, I have a conversation with the patient regarding their longterm goals and the need to try and achieve a dry macula and improve visual acuity. Generally speaking, though, having a patient on topical therapy for IOP is not a contraindication for reinjecting OZURDEX. Patients with glaucoma who have cup to disc ratios of greater than 0.8 is one of the contraindications.

Dr. Hassan: How do you manage the patient who is going to be reinjected with OZURDEX who had a previous IOP spike?

(Continued on page 15)

Case 1: Finding the Injection Sweet Spot

Eric D. Nudleman, MD, PhD

CASE BACKGROUND

2011 to 2013

This is a case of a 49-year-old white female with a 20-year history of poorly controlled type 2 diabetes, metabolic syndrome, hypertension, and hyperlipidemia. The patient had a membrane peel and received previous treatment for diabetic macular edema (DME). She underwent cataract surgery in the right eye (OD) in March 2013. She presented with DME OD. I began treatment with dexamethasone intravitreal implant 0.7 mg (OZURDEX, Allergan).

Initial Visit



- tral retinal thickness (CRT) was 312 µm (A)
- Treated with OZURDEX OD

FIRST INJECTION

1 Month Post OZURDEX

• The patient's VA was 20/40+2, CRT was 251 µm, and IOP was 15 mm Hg (B)

3 Months Post OZURDEX

• The patient's VA was 20/40+3, CRT was 232 µm, and IOP was 12 mm Hg(C)

4.5 Months Post OZURDEX

- Some VA was lost by month 3 (VA was 20/50), CRT was
- $306 \,\mu\text{m}$, and IOP was $13 \,\text{mm}$ Hg (D)
- I administered a second treatment with OZURDEX OD

D

В

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions (continued)

Diabetic Macular Edema (continued)

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

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

SECOND INJECTION

- **1 Month Post Second OZURDEX**
- The patient's VA was 20/40+2, CRT was 231 µm, and IOP was 12 mm Hg (E)



3 Months Post Second OZURDEX

• The patient's VA was 20/40, CRT was 229 µm, and IOP was 17 mm Hg (F)



4.5 Months Post Second OZURDEX

• The patient's VA was 20/50, CRT was 274 µm, and IOP was 21 mm Hg (G)



I administered a third injection with OZURDEX, as there was reduced VA

THIRD INJECTION

1 Month Post Third OZURDEX

• The patient's VA was 20/40, CRT was 243 µm, and IOP was 14 mm Hg (H)



3 Months Post Third OZURDEX

• The patient's VA was 20/40, CRT was 226 µm, and IOP was 21 mm Hg



(Continued on next page)

4.5 Months Post Third OZURDEX

• The patient's VA was 20/50, CRT was 329 µm, and IOP was 18 mm Hg (J)



I administered a fourth injection with OZURDEX, as there was reduced VA

FOURTH INJECTION

- **1 Month Post Fourth OZURDEX**
- The patient's VA was 20/40+2, CRT was 237 µm, and IOP was 19 mm Hg (K)



3 Months Post Fourth OZURDEX

• The patient's VA was 20/40+3. CRT was 232 µm, and IOP was 20 mm Hg (L)



4.5 Months Post Fourth OZURDEX

 The patient's VA was 20/50, CRT was 259 µm, and IOP was 17 mm Hg (M)



• I administered a fifth injection of OZURDEX, as there was reduced VA

FIFTH INJECTION

1 Month Post Fifth OZURDEX

• The patient's VA was 20/40+2, CRT was 232 µm, and IOP was 20 mm Hg (N)



3 Months Post Fifth OZURDEX

• The patient's VA was 20/40, CRT was 240 µm, and IOP was 20 mm Hg (O)



IMPORTANT SAFETY INFORMATION (continued) Adverse Reactions (continued)

Retinal Vein Occlusion and Posterior Segment Uveitis

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

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

Please see additional Important Safety Information on the following pages.







4.5 Months Post Fifth OZURDEX

• The patient's VA was 20/50, P CRT was 283 µm, and IOP was 17 mm Hg (P)

SIXTH INJECTION

• The patient's VA was

 $16 \,\mathrm{mm}\,\mathrm{Hg}\,(\mathrm{Q})$

20/40, CRT was 228 µm,

and IOP was down to







1 Month Post Sixth OZURDEX

• The patient's VA was 20/40, CRT was 216 µm, and IOP was back up to 20 mm Hg (R)







• The patient's VA was 20/50, s CRT was 346 µm, and IOP was 17 mm Hg (S)

SEVENTH INJECTION



DISCUSSION

18 mm Hg (T)

20/40+2, CRT was

- Monotherapy with OZURDEX improved vision
- Her pattern was predictable—improved VA until month 4.5, when she required another OZURDEX injection
- The patient maintained improvements in VA for 2 years with OZURDEX every 4.5 months





Case 2: OZURDEX in a Case of DME

Baruch D. Kuppermann, MD, PhD

CASE BACKGROUND

This is a case of a 65-year-old female with diabetic macular edema (DME) OD.

FIRST INJECTION First Visit

- The patient's VA was 20/100, and CRT was 846 µm (A, B, C)
- · I administered the first injection of dexamethasone intravitreal implant 0.7 mg (OZURDEX, Allergan)

4 Weeks Post OZURDEX

• The patient's VA was 20/60, and CRT was 227 µm (D)

11 Weeks Post OZURDEX

• The patient's VA was 20/50. and CRT was 209 µm (E)

24 Weeks Post OZURDEX

- The patient's VA was 20/50, and CRT was 752 µm (F)
- A second OZURDEX injection was required (we

required insurance approval prior to administering the injection)

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[®] is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

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

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

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.

SECOND INJECTION

5 Weeks Post Second OZURDEX

• The patient's VA was 20/60, and CRT was 244 µm (G)

12 Weeks Post Second **OZURDEX**

• The patient's VA was 20/40, and CRT was 222 µm (H)

DISCUSSION

• I generally wind up using a









Amy C. Schefler, MD, FACS

CASE BACKGROUND

This is a case of a 68-year-old white female with a history of diabetes, hypertension, and hypercholesterolemia. She takes several prescription medications and presents with diabetic macular edema (DME) in the left eye (OS).

FIRST INJECTION First Visit

- The patient's VA was 20/80, CRT was 563 µm, and IOP was 11 mm Hg (A, B, C)
- · I administered the first injection of dexamethasone intravitreal implant 0.7 mg (OZURDEX, Allergan) OS



• The patient's VA was 20/50, CRT was 332 μ m, and IOP was 18 mm Hg (D)

3 Months Post OZURDEX

- The patient's VA was 20/40, CRT was 339 μm, and IOP was 13 mm Hg (E)
- No treatment needed at this time

4 Months Post OZURDEX

- The patient's VA was 20/40+1, CRT was 353 µm, and IOP was 13 mm Hg (F)
- No treatment needed at this time

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 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.

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® 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%).

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX[®] patients versus 4% of sham patients. 42% of the patients who received OZURDEX[®] were subsequently treated with IOPlowering medications during the study versus 10% of sham patients.

















6 Months Post OZURDEX

- The patient's VA was 20/30+1, CRT was 343 µm, and IOP was 15 mm Hg (G)
- No treatment needed at this time

7 Months Post First OZURDEX

- The patient's VA was 20/40. CRT was 348 µm, and IOP was 17 mm Hg (H)
- I administered a second injection of OZURDEX

SECOND INJECTION

- 2 Months Post Second OZURDEX • The patient's VA was 20/30-2, CRT was 330 µm, and IOP was 15 mm Hg (I)
- No treatment needed at this time

5 Months Post Second OZURDEX

- The patient's VA was 20/30+2. CRT was 339 μ m, and IOP was 15 mm Hg (J)
- No treatment needed at this time

8 Months Post Second OZURDEX

- The patient's VA was 20/40+1, CRT was 327 µm, and IOP was 15 mm Hg (K, L, M)
- No treatment needed at this time

DISCUSSION

- There was no new retinopathy
- This patient continues to hold steady today









Case 4: Improvement in DME Without Monthly Injections

Howard F. Fine, MD, MHSc

CASE BACKGROUND

This is a case of a 68-year-old southeast Asian female who presents with diabetic macular edema (DME) OS. She presented with pseudophakic OS postoperatively 2 years earlier. Her past medical history includes hypertension, hyperlipidemia, renal insufficiency, and coronary disease.

FIRST INJECTION

First Visit

- The patient's VA was 20/150, CRT was 745 μm, and IOP was 17 mm Hg (A)
- I administered the first injection of dexamethasone intravitreal implant 0.7 mg (OZURDEX, Allergan)

5 Weeks Post First OZURDEX

- The patient's VA was 20/70, CRT was 231 μ m, and IOP was 16 mm Hg (B)
- No treatment needed at this time

14 Weeks Post First OZURDEX

- The patient's VA was 20/60, CRT was 260 μ m, and IOP was 16 mm Hg (C)
- No treatment needed at this time

18 Weeks Post First OZURDEX

- The patient's VA was 20/100, CRT was 524 µm, and IOP was 18 mm Hg (D)
- I administered a second injection of OZURDEX



SECOND INJECTION

7 Weeks Post Second OZURDEX

- The patient's VA was 20/40, CRT was 191 μm, and IOP was 15 mm Hg (E)
- No treatment needed at this time

(Continued on next page)

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions (continued)

Diabetic Macular Edema (continued)

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

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

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® 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.

18 Weeks Post Second OZURDEX

- The patient's VA was 20/40, CRT was 215 μm, and IOP was 18 mm Hg (F)
- · I administered a third injection of OZURDEX

THIRD INJECTION

7 Weeks Post Third Injection OZURDEX

- The patient's VA was 20/30, CRT was 165 μ m, and IOP was 16 mm Hg (G)
- No treatment needed at this time

DISCUSSION

- OZURDEX improved VA: from 20/70 to 20/40 to 20/30
- The patient experienced improvement in her DME without the need for monthly injections

(Continued from page 9)

Dr. Fine: I will usually start that patient on an IOP-lo medication before I reinject, just to be cautious.

Dr. Kuppermann: I would consider the status of th it is healthy, there may not be a need for topical therap IOP is being controlled by some other measure, topica not be warranted.

Dr. Hassan: Is there a role for a topical steroid trial the implant?

Dr. Schefler: Unless there is compromise to the pos

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® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

contraindication for OZURDEX® use.

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

Please see Dosage and Administration on the following page.



owering	in which case there is potential for anterior segment migration, then no, I do not see any reason why you would not start with the dexamethasone implant.
e optic nerve. If oy. As well, if the I therapy might	Dr. Kuppermann: In most settings, I am most comfortable starting with OZURDEX, which is approved for intraocular use. ¹⁶
1, 0,	Dr. Fine: With the OZURDEX NOVADUR technology, you can be assured the patient is getting the exact dose inside the eye.
l before injecting	Dr. Kuppermann: I agree with that and would add that IOP
sterior capsule,	elevation, should it occur, is manageable after a dexamethasone implant. In the clinical trials, there was a 15.7% rate of first IOP

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 elevation \geq 10 mm Hg from baseline associated with the first injection of the implant.¹⁵ But if the IOP does elevate, topical drops can be effective management.¹⁶

Dr. Fine:

There is another reason to believe that outcomes of steroid challenges are not definitive. There are a number of genes that regulate steroid response, and they appear to be specific to specific types of steroids. For example, response to dexamethasone has different genes dictating the response than with triamcinolone.²¹ And so, a steroid challenge is not a guarantee that a patient will be a responder to one steroid versus another.

INTRODUCING THE IMPLANT TO PATIENTS

Dr. Hassan: There are a couple of key points to introduce when we discuss OZURDEX as a potential treatment for patients, namely that swelling can be caused by a number of factors, and that OZURDEX works to reduce inflammation in the retina and thereby improve visual acuity.²² I think it is also worthwhile to explain a little bit about the actual procedure, that we will be injecting the implant into the back of the eye, and that it will resorb on its own, and there is no need for a second procedure to remove the implant.²³ As far as safety concerns, I introduce the potential for cataract progression in phakic patients, especially after repeat injections, and elevated IOP \geq 10 mm Hg, which occurred in 28% of patients on OZURDEX in the 3-year MEAD trial and typically was first seen after the initial implant.¹⁶ In MEAD, the rate of IOP elevation greater than or equal to 10 mm Hg was 15.7% of patients on OZURDEX in the first treatment cycle.^{16,19}

Dr. Nudleman: In addition to that, I also tell patients that in clinical trials, OZURDEX improved visual acuity without need for monthly injections.¹⁹

Dr. Fine: As far as the actual procedure goes, I also tell patients they may hear a click when we inject the OZURDEX implant¹⁶ because I do not want them to be startled when that happens.

CONCLUSION

Dr. Hassan: OZURDEX is an effective treatment for DME, which as we have discussed, can be caused by a number of different pathologic entities.^{14,19} While IOP elevation is a concern, most cases are manageable with topical medication.^{14,16} As we have learned, it may be possible to observe some patients with IOP elevation off of medication if the optic nerve is healthy and there are no additional concerns.

INTRODUCING OZURDEX TO YOUR PATIENTS

- The swelling in your retina can be caused by several factors.²²
- OZURDEX is a corticosteroid and works to help reduce the inflammation in your retina. OZURDEX helps by improving visual acuity.¹⁶
- 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.¹⁶
- OZURDEX is injected directly into the back of the eye with minimal systemic absorption.²³
- 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.¹⁶
- 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.¹⁶
- In clinical studies, OZURDEX improved vision in patients without the need for monthly injections.¹⁶

Overall, the inflammatory cascade is highly relevant to the formation of edema in the macula, and OZURDEX offers us a mechanism to address this.^{7,16}

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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