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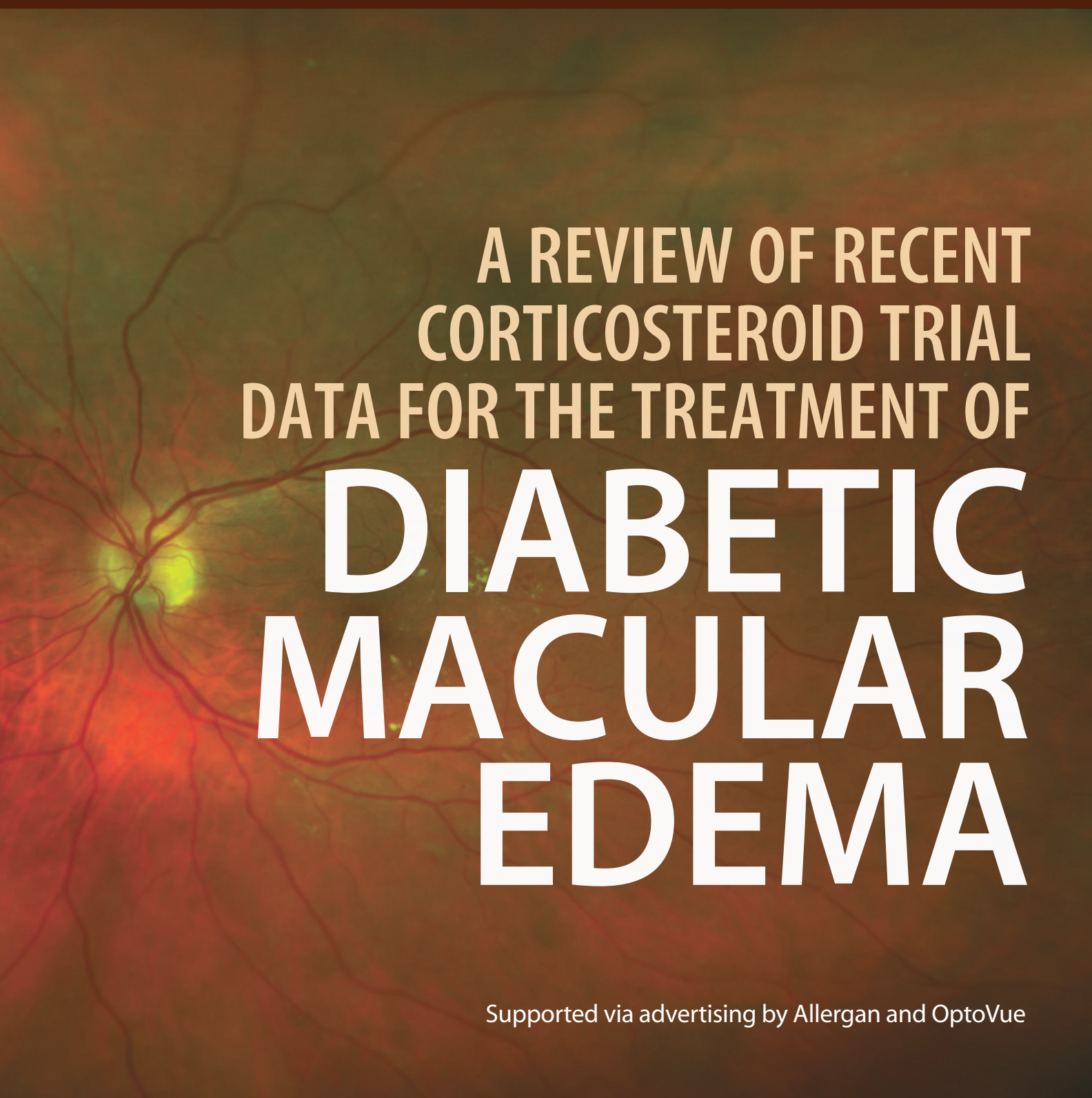

A REVIEW OF RECENT CORTICOSTEROID TRIAL DATA FOR THE TREATMENT OF DIABETIC MACULAR EDEMA

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A Review of Recent Corticosteroid Trial Data for the Treatment of Diabetic Macular Edema

Go to eyetube.net/series/corticosteroid-roundtable to watch videos of the participants sharing additional content related to this roundtable discussion.

Diabetic macular edema (DME) is a multifactorial disease that involves interleukins, adhesion molecules, and growth factors,[1,2] and involves excessive vascular permeability and inflammatory damage to blood vessels.[3] As such, targeting a single component is not necessarily the best approach. Even vitreous samples have shown that inflammatory cytokines are upregulated.[4] We may need a broad spectrum of treatments that can target all the inflammatory mediators.[2] It remains equally imperative to remember that vascular endothelial growth factor (VEGF) is part of the inflammatory pathway; there is nothing in the literature to suggest one is more important than the other. Since the introduction of the anti-VEGF compounds, the one question that has most confounded retina specialists relates to the optimal time we should be giving our patients before determining we have obtained the best response on one treatment modality. When can we safely switch therapies and know we are not leaving potential vision gains on the table? *Retina Today* gathered a group of leading retina physicians to discuss the current landscape of DME treatments.

—Victor Gonzalez, MD

Participants

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Dr. Gonzalez is the founder of Valley Research Institute in McAllen, Texas. He may be reached at maculadoc@aol.com. Dr. Gonzalez disclosed a financial relationship with Allergan, Eyetech, Genentech, Iconics, National Eye Institute, Pfizer, and Regeneron Pharmaceuticals.

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A Review of Recent Corticosteroid Trial Data for the Treatment of Diabetic Macular Edema

Protocol I data may have the potential to substantially impact clinical treatment and decision making.

Dr. Gonzalez: There is no doubt that the anti-VEGF compounds have had a major impact on how we manage diabetic retinopathy (DR), in particular how we manage diabetic macular edema (DME). The anti-VEGFs are the first nontissue-destructive way of reversing and sometimes improving the visual acuity losses that we have had with diabetes. What has the impact of the clinical trial data been in your clinics?

Dr. Kitchens: The real pivotal change in how I manage these patients has been the data from Protocol I.[5,6] Before Protocol I, we were without a cross-comparative trial. Protocol I looked at anti-VEGF versus lasers and steroids versus laser alone, and it showed such a difference in outcomes in the patients who were in the anti-VEGF arm at 1 and 2 years that that is when I started using anti-VEGFs as a first-line treatment.

Dr. Gonzalez: Are the outcomes from RISE and RIDE[7] and VIVID and VISTA[8] enough to make either ranibizumab (Lucentis; Genentech) or aflibercept (Eylea; Regeneron) the first-line therapy, regardless of patient presentation? Or do you begin to evaluate patients by visual acuity? Do you consider the optical coherence tomography (OCT)?

Dr. Wykoff: We have a tremendous amount of data from multiple large prospective, randomized trials showing that anti-VEGF therapies work well on average in eyes with center-involved DME with visual acuity loss. So for me, anti-VEGFs are the first-line treatment in that population: center-involved fluid with significant visual acuity loss. But that is on average. There are patients who are incomplete responders to the anti-VEGF pharmacologics, maybe even some nonresponders, where one needs to think more broadly beyond anti-VEGFs at a relatively early stage.

Dr. Gonzalez: How do you define nonresponders or poor responders?

Dr. Holekamp: We mainly concentrate on vision and OCT, and it is important not to choose one over the other, or become an "injecting machine" based solely on OCT. We need to continue to be thinking physicians and monitor our patients on a regular basis when they come in for injections. We would all like to see flat OCTs, and the anti-VEGFs have been a big step forward in achieving that, but not for every patient. Vision is what really matters to the patient, not their OCT. So we need to consider both the anatomic and functional endpoints as our main goal.

Dr. Gonzalez: Various trials—RESTORE, Protocol I, BOLT, RIDE/RISE, VIVID/VISTA[5-7, 9-11]—are showing us that 10-letter gainers are right around 42% to 63%, depending on which trial data you cite. But when you evaluate the percentage of patients who failed to achieve a 15-letter gain, the range is somewhere around 67% to 88%.[5-7, 9-11] These studies are reinforcing the fact that there is still a very significant number of patients where we are leaving vision on the table.

Dr. Holekamp: Those first statistics you quote were just for 10-letter gains, or 2 lines. There are substantial proportions of patients not even achieving 10-letter gains. There is an opportunity to do more for these patients.

TREATMENT PRESUMPTIONS AND REALITY

Dr. Gonzalez: There is no doubt that the anti-VEGFs have had an important impact on the prognosis of DME, and our clinical trials have demonstrated that monthly injections give superior visual and anatomic outcomes compared to laser alone. But I think we realize now that even in the most intensive, nonclinically applicable situations, monthly injections for 2 years as in our clinical trials, we are still leaving vision on the table. Dr. Holekamp, you have done some work on real-world utilization of anti-VEGFs in DME. What have you found?

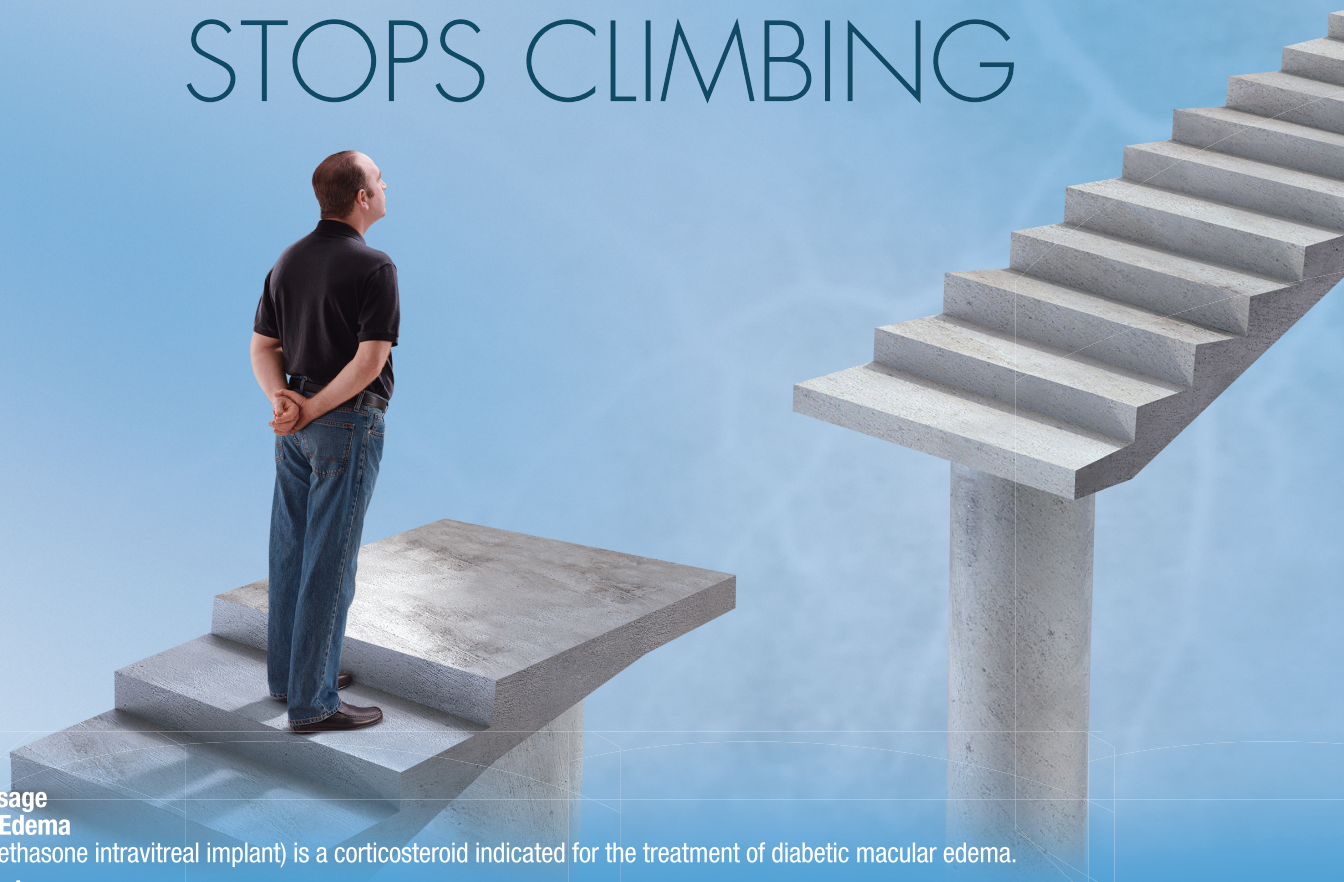
Dr. Holekamp: We have done a real-world analysis of anti-VEGF use in patients with DME. And we have looked at large Medicare databases. We have looked at closed health care systems, such as Geisinger or Kaiser Permanente. And we have even looked at a private practice consortium called Vestrum. What we find across the board is that diabetic patients in the first year of treatment are receiving less than 4 anti-VEGF injections for their DME. This is in stark contrast to all the randomized clinical trials.

RIDE and RISE were monthly injections for 2 years.[7] VIVID and VISTA were 5 monthly injections followed by an injection every 8 weeks.[8] Those are intensive treatment schedules. In the first year of treatment in Protocol T, patients averaged nine to 10 injections.[12]

In the real world, we are probably not achieving the same

In DME,* macular edema following RVO,† and noninfectious posterior segment uveitis,

WHEN VISUAL ACUITY STOPS CLIMBING



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

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

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

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

Glaucoma: OZURDEX® 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.

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

START EARLY

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg

Consider OZURDEX® early, for a pathway toward proven clinical results.

The OZURDEX® approach:

- Achieves clinically significant 3-line gains in BCVA[1,‡]
- Significantly reduces vitreous haze versus sham in noninfectious posterior segment uveitis[1]
- Suppresses inflammation by inhibiting multiple inflammatory cytokines[1]

*Diabetic macular edema. †Retinal vein occlusion. ‡Best-corrected visual acuity.

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® 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 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.

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.

Please see Brief Summary of full Prescribing Information on adjacent page.

1. OZURDEX® Prescribing Information.

Allergan

OZURDEX®

(dexamethasone intravitreal implant) 0.7 mg

Brief Summary—Please see the OZURDEX® package insert for full Prescribing Information.

INDICATIONS AND USAGE

Retinal Vein Occlusion: OZURDEX® (dexamethasone intravitreal implant) 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 non-infectious uveitis affecting the posterior segment of the eye.

Diabetic Macular Edema

OZURDEX® is indicated for the treatment of diabetic macular edema.

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 *[see Adverse Reactions]*.

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 *[see Patient Counseling Information]*.

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 *[see Adverse Reactions]*.

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

ADVERSE REACTIONS

Clinical Studies Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse reactions associated with ophthalmic steroids including OZURDEX® include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Retinal Vein Occlusion and Posterior Segment Uveitis

The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):

Adverse Reactions Reported by Greater than 2% of Patients

MedDRA Term	OZURDEX® N=497 (%)	Sham N=498 (%)
Intraocular pressure increased	125 (25%)	10 (2%)
Conjunctival hemorrhage	108 (22%)	79 (16%)
Eye pain	40 (8%)	26 (5%)
Conjunctival hyperemia	33 (7%)	27 (5%)
Ocular hypertension	23 (5%)	3 (1%)
Cataract	24 (5%)	10 (2%)
Vitreous detachment	12 (2%)	8 (2%)
Headache	19 (4%)	12 (2%)

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.

Following a second injection of OZURDEX® (dexamethasone intravitreal implant) in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

Diabetic Macular Edema

The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in the table below were 3% in the OZURDEX® group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are as follows:

Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients

MedDRA Term	OZURDEX® N=324 (%)	Sham N=328 (%)
Ocular		
Cataract[1]	166/243[2] (68%)	49/230 (21%)
Conjunctival hemorrhage	73 (23%)	44 (13%)
Visual acuity reduced	28 (9%)	13 (4%)
Conjunctivitis	19 (6%)	8 (2%)
Vitreous floaters	16 (5%)	6 (2%)
Conjunctival edema	15 (5%)	4 (1%)
Dry eye	15 (5%)	7 (2%)
Vitreous detachment	14 (4%)	8 (2%)
Vitreous opacities	11 (3%)	3 (1%)
Retinal aneurysm	10 (3%)	5 (2%)
Foreign body sensation	7 (2%)	4 (1%)
Corneal erosion	7 (2%)	3 (1%)
Keratitis	6 (2%)	3 (1%)
Anterior Chamber Inflammation	6 (2%)	0 (0%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)
Non-ocular		
Hypertension	41 (13%)	21 (6%)
Bronchitis	15 (5%)	8 (2%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

[2] 243 of the 324 OZURDEX® subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

	Treatment: N (%)	
IOP	**OZURDEX®** N=324	**Sham** N=328
IOP elevation ≥10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization,1 laser iridotomy, 1 surgical iridectomy
Sham: 1 laser iridotomy

Cataracts and Cataract Surgery

At baseline, 243 of the 324 OZURDEX® subjects were phakic; 230 of 328 sham-controlled subjects were phakic. 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 vs. 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.

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).

USE IN SPECIFIC POPULATIONS

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with OZURDEX® in pregnant women. Animal reproduction studies using topical ocular administration of dexamethasone were conducted in mice and rabbits. Cleft palate and embryofetal death in mice and malformations of the intestines and kidneys in rabbits were observed. OZURDEX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.375 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.375 mg/kg/day in the mouse is approximately 3 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.13 mg/kg/day, on gestational day 6 followed by 0.20 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m2 basis.

Nursing Mothers: Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of dexamethasone following intravitreal treatment with OZURDEX® is low. It is not known whether intravitreal treatment with OZURDEX® could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when OZURDEX® is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of OZURDEX® in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies in animals have been conducted to determine whether OZURDEX® (dexamethasone intravitreal implant) has the potential for carcinogenesis.

Although no adequate studies have been conducted to determine the mutagenic potential of OZURDEX®, dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells *in vitro* or in the *in vivo* mouse micronucleus test. Adequate fertility studies have not been conducted in animals.

PATIENT COUNSELING INFORMATION

Steroid-related Effects

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

Advise patients that they may develop increased intraocular pressure with OZURDEX® treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

Intravitreal Injection-related Effects

Advise patients that in the days following intravitreal injection of OZURDEX®, patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

When to Seek Physician Advice

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Driving and Using Machines

Inform patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

> "I do not think anyone believes we are undertreating our DME patients, until we look back over the first year and realize we did not give 9 or 10 injections."
>
> —John W. Kitchens, MD

visual gains as we saw in the clinical trials. We need to remember that anti-VEGF therapy requires a very intensive injection program.

Dr. Kitchens: I do not think anyone believes we are undertreating our DME patients, until we look back over the first year and realize we did not give nine or 10 injections. Many of us do not review our data on how we treat these patients. That really resonates with me when I see a patient and decide to skip the injection because the patient does not want it and they may be borderline on OCT. But I think to myself, "maybe I am undertreating and leaving vision on the table."

Dr. Holekamp: The American Society of Retina Specialists Preferences and Trends (PAT) survey asked that very question.[13] How many injections are your DME patients receiving in the first year of treatment? More than 55% of the retina specialists responded that they give seven or more injections. But the data show it is actually fewer than four injections. So there is a disconnect between what we think we are doing and what we are actually doing.

Dr. Gonzalez: That is very elucidating. We know the majority of retina specialists are believers in anti-VEGFs and therefore the treatment regimen recommended by the clinical trials. But what they believe and what is actually happening seems to suggest there are obstacles that are preventing them from maximizing the treatment we are delivering to our patients.

Dr. Wykoff: Compliance is a huge issue. Retina specialists probably are giving six to eight injections to the patients who they see regularly. But there are patients who get one, two, or three injections and then do not come back. Compliance, from a patient perspective, is a big deal. Our DME patients are often working and they can find it challenging to make all of their doctors' appointments, not just the ophthalmologist appointments. Anything that can be done to decrease treatment burden for the patient would be valuable so they have the best chance of achieving a dry retina and maximizing their visual potential.

Dr. Holekamp: As it is currently being administered, anti-VEGF therapy is a pulse therapy. We are administering randomly—or at least intermittently—in that portion of patients who do not come back regularly. We are really not sure that a pulsed/intermittent therapy is as effective as these intensive treatment regimens we saw in the clinical trials. And so again, this issue with compliance may actually favor a continuous form of therapy, like long-term drug delivery.

Dr. Kitchens: Dr. Holekamp had a great point about Protocol T and the intensive nature of the therapy. I had a patient in Protocol T that I injected, dried her eye completely, saw her and thought she was not going to need an injection. Then we ran the numbers and sure enough, the study coordinator said the patient did need an injection per the study protocol. So even with the great data from Protocol T, it does not reflect how many of us are treating in the real world.

ACHIEVING BETTER OUTCOMES

Dr. Gonzalez: Even in the most intensive of protocols, we are not able to achieve significant visual acuity gains in well over 50% of these patients. Why do you think that is?

Dr. Holekamp: Because it is not all about VEGF. I consider acute retinal vein occlusion to be the most directly mediated VEGF pathophysiology. But I am not surprised at all that DME is far more complex than just VEGF alone. There are other factors that need to be considered, such as the inflammatory cytokines. Anti-VEGF is not a miracle drug and does not do much beyond blocking VEGF. We have other targets that are not being addressed adequately with anti-VEGF therapy.

Dr. Gonzalez: What is the thought process you use to determine if it is a VEGF-driven DME or an inflammatory-driven DME? Are they exclusionary to one another?

Dr. Wykoff: Based on quantification of intraocular cytokine levels, there is evidence that the longer an eye has DME, the less VEGF-dependent the DME becomes.[14] Chronic DME appears to differ from less chronic forms, not only in cytokine levels but also in responsiveness to at least some pharmacologics. It seems the longer someone has had DME, the less acutely responsive they are to anti-VEGF treatments. But this is empiric, and the key is to treat with an anti-VEGF and watch early on to see how the eye responds anatomically. While we all want our patients to have improved vision, it is easier to objectively measure OCT responses. Use OCT to gauge how responsive an eye is to VEGF blockade. If you are not getting the results you want early on, you may want to consider adding alternative therapies.

Dr. Gonzalez: How long do you treat your patients with anti-VEGFs before you consider changing your therapy?

Dr. Kitchens: What has really helped with that is Protocol T, which clearly showed patients with worse visual acuity and worse macular edema at presentation did better with aflibercept.[12] So, rather than switch within the anti-VEGF class if I was not getting a response after three injections, now I start those patients on aflibercept. If I do not get at least a 20% response after those initial three injections, that is when I start thinking that it may be more inflammatory macular edema and consider switching to a steroid.

Dr. Holekamp: These anti-VEGF agents are so potent that they are not only therapeutic, they are diagnostic. If I give someone an anti-VEGF drug, and there is a response, I have just found out its VEGF-mediated DME. DME can be completely VEGF mediated, it can be partially VEGF mediated, or it can be a nonresponsive to VEGF. In the latter, I immediately have to go to some other class of agents.

Dr. Gonzalez: Based on the data from Protocol T, how do you handle a patient that does not appear to be responding to your initial anti-VEGF choice? Do you always switch within the same class agents or do you immediately move to alternative therapies?

Dr. Wykoff: A majority of retina specialists begin with bevacizumab for the treatment of DME for economic reasons, but Protocol T gave us evidence that aflibercept is a better drying agent. If you are already starting with aflibercept and not getting the full response you would like, there is very limited data to suggest that switching to another anti-VEGF would be of value before adding a different treatment.

Dr. Gonzalez: So if you start with aflibercept, and after three or four injections you are not seeing a response, you are considering alternative therapy to anti-VEGFs?

Dr. Wykoff: Yes. If I see a suboptimal response to isolated anti-VEGF therapy after three or four injections, I will typically consider using a steroid or supplementing with focal macular laser as was performed in Protocol T.

Dr. Gonzalez: How do you handle a patient that has been switched to aflibercept because of suboptimal response to bevacizumab or ranibizumab and has continued limited response both visually and anatomically after three injections. Would you consider trying another three to four injections of afilbercept?

Dr. Kitchens: If this is not a VEGF-mediated process, you have now delayed drying out that patient another 4 months down the road. And we know that if you look at RIDE and RISE, patients who were in the control arm who did not receive treatment in that first year never caught up.[7] So I think

> "We have good data from many trials supporting the use of steroids for the treatment of DME, and they can certainly be used as first-line treatments for DME."
> —Charles C. Wykoff, MD, PhD

"time to dryness" is really important. If I have a choice, I prefer to start with aflibercept to know if anti-VEGF therapy is going to work for that patient.

Dr. Wykoff: The idea that persistent, or undertreated, central DME may limit ultimate visual acuity gain is a critical concept. We have data to support this from the control arms of both the RIDE/RISE and VISTA/VIVID study programs, and we saw a similar phenomenon in both analyses. If center-involving DME causing visual acuity loss is allowed to persist and not treated with anti-VEGF injections for either 2 years (RIDE/RISE) or until the patient loses substantial visual acuity, you can catch up from an anatomic perspective when anti-VEGF treatments are initiated.[15,16] You can dry out the retinas just as well as you could by treating the eyes earlier. But from a visual acuity perspective, you do not achieve the same level of robust outcomes as you would have with earlier anti-VEGF treatment, reinforcing that persistent DME can be damaging to long-term visual outcomes.

Dr. Holekamp: To echo what Dr. Wykoff has said, we really do not have any evidence for switching. We do not have any switching clinical trials that tell us an extra 3 or 4 months is going to make a significant difference. We may just be delaying getting the macula dry and achieving that optimal visual acuity outcome for our patients.

Dr. Gonzalez: We do not know what the exact time frame is before we lose the ability to recover visual acuity in our DME poor responders. For that reason,if I have a patient that has not responded significantly after three injections, I consider changing my treatment approach so that I do not lose my ability to gain the maximum vision possible.

ALTERNATIVE THERAPIES

Dr. Gonzalez: Patients in my clinic fall into three buckets—those who immediately respond to anti-VEGFs (anti-VEGF responders), those who have absolutely no response (anti-VEGF nonresponders) no matter how quickly after an injection we are seeing them, and the ones who are in the middle (combined mechanism). These are the patients in whom DME is both VEGF and inflammatory mediator dependent. How do you treat DME in these three groups?

Dr. Holekamp: I have patients in the exactly the same three buckets. For those who respond well, we continue them on anti-VEGF therapy. The people who are nonresponders, we may switch; and the people who have a suboptimal response, we may add therapy. That is where we really start thinking about the corticosteroids. Right now we have two FDA-approved intravitreal corticosteroid injections for treating DME, and they are both in long-term drug delivery systems. Both the dexamethasone 0.7-mg (Ozurdex; Allergan) and the 0.19-mg fluocinolone acetonide intravitreal implants have level 1 evidence from two parallel, randomized Phase 3 clinical trials. The MEAD studies evaluated dexamethasone with a primary endpoint at 3 years.[17] It showed a statistically significant benefit for patients receiving the dexamethasone implant. The FAME studies evaluated 0.19-mg fluocinolone acetonide intravitreal implant, but with a primary endpoint at 2 years.[18,19] FAME also showed significant benefit to patients with DME over a heavily treated control arm. The interesting part is that these were both done before we had anti-VEGFs for DME, so the patients were not just anti-VEGF failures. The dexamethasone and fluocinolone implants can be used as first-line therapy. It is important to understand that they have approval for all DME patients, not just those who have failed anti-VEGF therapies. This may be a particularly important consideration for pseudophakic patients.

Dr. Gonzalez: I think people overlook or forget that MEAD and FAME were initiated before the anti-VEGF era. The efficacy results in those studies, particularly the MEAD study, is against a control group that did not require laser. The patients in the study that required laser were taken out of the study. The control group at the end was a nonlaser requiring control, a group that may have done well without any intervention.

Dr. Wykoff: That brings us back to where we started the conversation. Protocol I had a steroid arm—triamcinolone acetonide. While the specific formulation used in Protocol I is not currently commercially available, the results may be applicable to other steroid formulations. In pseudophakic eyes within Protocol I at the 1-year timepoint, visual outcomes with steroid treatment were comparable to the anti-VEGF arms, with a much reduced treatment burden among steroid-treated eyes.[5] We have good data from many trials supporting the use of steroids for the treatment of DME, and they can certainly be used as first-line treatments for DME.

Dr. Kitchens: If you analyze the data from the pseudophakic patients in Protocol I, they did just as well as the anti-VEGF patients but only received three injections in the first year.[5] When you review the visual acuity gains during the first 6 months, patients were keeping up with the anti-VEGF therapy. It is only once those patients developed a cataract that we saw a drop off in the response. Also remember these patients were getting laser therapy. We know from the anti-VEGF arms that those patients who received prompt laser treatment never did as well as the patients who had deferred laser. So it is possible that we do some harm with prompt laser treatments, and we may have inadvertently put the steroid-treated patients into a worse outcome potential in Protocol I.

Dr. Holekamp: This concept that focal laser for DME may be harmful is an interesting one because it was required in the FAME clinical trial, that everyone have at least one laser treatment.[18,19] And that may have biased the visual acuity results.

Dr. Wykoff: We need to be cautious about over-interpreting these results. There may still be a role for focal macular laser in certain populations with center-involving DME with visual acuity loss. For example, Protocol T was not solely an anti-VEGF trial. It was really a combination trial using anti-VEGF therapy and focal macular laser that was applied when prespecified criteria were met; between 37% and 56% of eyes in Protocol T received focal laser when their DME was incompletely treated by anti-VEGF injections.[12] Additionally, 5-year follow-up of eyes in Protocol I suggested that focal macular laser may decrease treatment burden.[6]

Dr. Gonzalez: There are still a lot of unanswered questions about lasers. The Protocol I[5] data seem to suggest that this type of laser therapy may have a long-term toxic effect on macular function. Clinical trials currently in the planning stages will address the safety and efficacy of traditional laser and tissue-sparing lasers and their role in the management of DME.

During the past 5 years, the role of inflammation in DME has taken center stage—we realize that to better treat our patients we need to classify them based on cytokine and chemokine levels. Patients with DME have much higher levels of inflammatory cytokines and chemokines than diabetics who do not have DME. Many of us probably believe that the factor that correlates best with diabetic retinopathy severity on the ETDRS scale was vitreous VEGF levels. The best correlation of retinopathy severity is actually vitreous levels of inflammatory cytokines.[4] This is not to say that VEGF is not important in DME, I highlight this fact to help one understand why anti-VEGFs do not work for all patients and to point out that we need to make sure we treat the inflammatory component of the disease. So anti-VEGFs will address the VEGF component and the steroids will address the inflammation. There is experimental evidence that steroids may have an anti-VEGF effect on PDR. Dr. Wykoff, you have presented on the effect steroids have on both inflammation and VEGF levels. Can you summarize?

TABLE 1. PERCENTAGE OF PATIENTS: TIME TO PDR PROGRESSION

Month 24	
*0.5 µg/d	12%
†0.2 µg/d	13%
‡ Sham control	26%
Month 36	
*0.5 µg/d	18%
†0.2 µg/d	17%
‡ Sham control	31%

Data taken from FAME A and B[18,19] trials;
FAc, fluocinolone acetonide.
*n = 395;1.4 treatments (mean)
†n = 376; 1.3 treatments (mean)
‡n = 185;1.4 treatments (mean)

Dr. Wykoff: Absolutely. There is now data to show that steroids can slow the progression to proliferative diabetic retinopathy (PDR) with similar efficacy as that obtained with anti-VEGFs. The best data we have is from the prospective, randomized phase 3 FAME A and B studies, in which a mean of 1.3-1.4 intravitreal injections of fluocinolone were given over 3 years for the treatment of DME incompletely responsive to focal macular laser.[18,19] In the complete data set, through the primary endpoint of 2-years and then 3-years, 26% and 31% of sham-controlled eyes progressed to PDR; fluocinolone treatment significantly reduced the rate of progression to PDR with 12% to 13% and 17% to 18% of treated patients progressing to PDR at 2 and 3 years[20] (Table 1). The magnitude of this blunted progression to PDR is similar to that observed with monthly anti-VEGF therapy.[21] Demonstrating one can slow progression to PDR with steroids with a substantially reduced treatment burden is potentially powerful.

Dr. Kitchens: What we are not seeing with the steroids is the improvement in retinopathy we have seen with the anti-VEGFs. The two-step improvements in VIVID/VISTA and RISE/RIDE are really impressive, especially for those patients with the worst retinopathy. Those anti-VEGF studies showed us 60% to 70% of patients with very severe PDR (level 53 or worse) can have a two-step improvement.[7,8] You just do not see that with the steroids.

Dr. Wykoff: It is interesting that steroids, not anti-VEGF medications, were the first therapy to demonstrate improvements

Using Steroids in Practice

Dr. Gonzalez: The evidence seems to suggest steroids can have a very beneficial effect, whether as a first-line or adjunctive therapy, and that they can address both the VEGF and inflammation aspects of DME. So why have they not been readily embraced?

Dr. Holekamp: It is interesting that the retina community has embraced multimodal imaging, but not multimodal therapy. Multimodal imaging gives us so much more detail about the disease, yet we have not fully explored multimodal therapy.

We are still in the honeymoon phase with anti-VEGFs because they do work so well for the vast majority of our patients. They are safe. They are a very low-risk. Conversely, the steroids carry a risk of both cataract and glaucoma. We really need to wrap our heads around the issues of cataract and glaucoma.

Dr. Gonzalez: So let us discuss the MEAD trial and what we found relating to intraocular pressure (IOP).

Dr. Wykoff: Before the anti-VEGFs, we were using a lot of triamcinolone intravitreally. We saw substantial IOP responses in unpredictable ways. But the dexamethasone and fluocinolone implants appear much more predictable in their IOP effects and because of this, the clinical use of steroids for DME is increasing. What we found in MEAD was that about a third of patients will need topical drops to manage their pressure over time due to the effect of steroids.[17] But we also found that if after three injections the patient has not been an IOP responder, the chances of them subsequently becoming an IOP responder with ongoing steroid treatments are less than 15%.[17]

Dr. Gonzalez: An issue for the retina community is that we do not separate between a steroid-induced elevation of pressure and glaucoma. In the MEAD studies, there was less than a 1% rate of incisional surgery, and fewer than 6% developed a pressure spike over 30 mmHg.[17] But the members of the retina community seem surprised when we start talking about those numbers.

Dr. Holekamp: Therein lies the beauty of clinical trials—we can be reassured by the data that even patients who had an elevated pressure did well visually, and that it was not to their detriment if they needed drops or had incisional surgery. We can be reassured the rate of incisional surgery was very low in MEAD. In the pre-anti-VEGF era we were really shooting from the hip with triamcinolone—we did not have the kind of solid data we do today about complications and risks. If you were enrolled in MEAD as a phakic patient and developed cataract, your visual outcomes were just as good as those who were pseudophakic at baseline. If you were enrolled in MEAD and developed elevated pressure, you did just as well after the pressure was managed.

in diabetic retinopathy severity levels. Pearson and colleagues termed this, "reversal of NPDR severity," with fluocinolone treatment.[22] The effects on diabetic retinopathy severity improvements with steroids appear less impressive than with regular anti-VEGF therapy. But many of our steroid trials have underdosed the steroid arms. For example, in the MEAD trial we were not giving enough injections over time to maintain therapeutic levels of intraocular steroids.[17] The dexamethasone implant is a slow-release implant, but if you do not give it enough and the steroid levels drop below a therapeutic level, we may not be able to see the maximal benefit on retinopathy severity over time. We need more data evaluating if meaningful improvements in DRSS levels can be achieved with steroids.

Dr. Kitchens: The best study for that, in my mind, is Protocol B, which did not show the same kind of results as MEAD.[23]

Dr. Holekamp: People should be reassured that we now have signals finding corticosteroids can actually prevent progression of DR, and people's desire to continue with anti-VEGFs because they do not want to lose the effect on DR is not going to be lost if they switch. Dr. Wykoff's analysis of the FAME trial is hypothesis generating, and needs to be pursued.[20] We are starting to see some signals that clinicians do not have to abandon that protective effect 100% if they move away from anti-VEGFs because steroids offer some of that effect. But we do not know exactly how much yet.

Dr. Wykoff: In the open-label extension study of RIDE and RISE (OLE), much of the benefit on retinopathy severity achieved with monthly ranibizumab was maintained with PRN re-treatment in which substantially less frequent dosing was used.[24] This tells me that intensive anti-VEGF therapy initially inducing retinopathy improvements may be sustained even if one switches to a steroid to quell the edema.

PREDICTABLE RESPONSES

Dr. Kitchens: That is a nice aspect of the MEAD study—the steroid response IOP rise is fairly predictable.[17] If the patient's pressure spiked to 30 mmHg with the first injection, it will typically only go to 30 mmHg with the next one. It is not likely to spike higher, whereas when we were using triamcinolone there was almost a stepwise increase.

One pearl about using the dexamethasone implant—if you pretreat with pressure-lowering drops you will encounter even fewer patients with increased pressure, even after

> "There has been a bit of a hesitation in performing cataract surgery on patients with active DME, but using a dexamethasone implant can mitigate that risk."
>
> —Nancy Holekamp, MD

addtional steroid injections. So I will use a combination agent like brimonidine tartrate/timolol maleate ophthalmic solution (Combigan; Allergan) and once the pressure comes down, we will stop the drop. Then before the next injection 4 months later, I will have them start the drops 2 weeks before and stay on them for a month or so after the injection.

Dr. Gonzalez: There is now enough clinical evidence to suggest that using steroids will add to our ability to treat these patients without exposing our patients to unmanageable side effects. In the appropriate patient under the appropriate surveillance, I feel comfortable treating my patient's visually threatening DME with steroids.

Dr. Holekamp: It is interesting to get the perspective of our glaucoma colleagues. They have said if corticosteroids are what will help this patient see, they can handle the pressure issues if any arise.

Dr. Kitchens: I blatantly tell my patients they will develop a cataract with the treatment but without it and without being able to get that edema under control, they will lose sight. Let us not forget many of these patients are at an age where they have mild cataracts to start. We can improve the edema, we can remove the cataract, and often patients are going to see better than when they first started treatment for DME, simply because you have taken care of the cataract in addition to treating the macular edema.

Dr. Holekamp: Another aspect I like about the continuous delivery of corticosteroids is that once the patient has gone through cataract surgery, he or she tends to do very well because the steroid is already in place. There has been a bit of a hesitation in performing cataract surgery on patients with active DME, but using a dexamethasone implant can mitigate that risk.

Dr. Kitchens: And our cataract colleagues do not have to prescribe steroid drops; they will just need antibiotics postsurgery.

CHANGING CLINICAL PRACTICE PATTERNS

Dr. Gonzalez: To summarize what we have discussed: the majority of retina specialists will start with an anti-VEGF therapy as first-line treatment for DME. There is no set determination for when we should consider an alternative therapy, but in some patients it will be warranted. The data suggests steroids address the inflammatory side of the equation. There is enough clinical evidence at this point that the side effects can be addressed without major loss of vision. So, with the body of evidence we now have, how do you approach your diabetic patient?

Dr. Wykoff: We are now beginning to reanalyze the Protocol I data to determine if there is a signal that can predict long-term outcomes from the initial anti-VEGF response. This was presented for the first time at the 2015 American Academy of Ophthalmology meeting.[25] That data is important and may have the potential to impact clinical treatment and decision making substantially. Dr. Dugel reported that in patients treated with ranibizumab monthly for 3 months, the week 12 responses correlated well with the ultimate 1-, 2-, and 3-year responses. Patients who gained more than 10 letters were likely to hold on to that over the course of the following years. Conversely, patients who gained less than 5 letters were unlikely to gain significant vision subsequently. We now have a clinical time-point at which we may be able to identify incomplete responders earlier and therefore add those multimodal treatments Dr. Holekamp was discussing.

Dr. Kitchens: The correlation with OCT improvement is the same. If you see a less than 20% improvement in your OCT after the first 3 injections, you are going to stay in that same category and still have the thickened OCT at 1 year. I treat more based on OCT because in my office we do not do the ETDRS on routine patients who the clinical studies use. If I see a dry OCT, even though the vision may have decreased, I feel like we are having an effect on that patient and I will continue them on anti-VEGF therapy. But if I see that OCT not improving after those first three injections, I start to think about switching them.

Dr. Holekamp: Dr. Dugel challenged us into returning to thinking physicians again instead of injection clinics. He reiterated that we really should be closely monitoring our patients' response to vision and OCT because those two parameters can be predictive. In the past, we have always focused on who got better in these studies. Dr. Dugel challenged us to re-identify those who do not fare well and determine who they are early enough to switch to a different therapy or add a separate therapy to give these patients a greater chance at optimal visual benefit.

Dr. Gonzalez: What we are really saying here is that every patient with DME is unique and needs to have their treatments

individualized. We may be coming to the end of the era where we give every patient 12 injections over the course of the first year and hope we are doing our best. We can be more effective with our treatments by targeting them more precisely earlier on.

There are still many who will argue that we need 6 to 9 injections before we can determine who is responding. What are your thoughts on this approach?

Dr. Wykoff: It is easy clinically to just keep injecting anti-VEGFs in eyes with persistent edema, especially if there is continued anatomic improvement. This is the case even in eyes with DME that are responding gradually, maybe 5% or 10% each time. And a proportion of such eyes will eventually sustain substantial improvements, a group of late responders. But I cannot predict who those patients are. We do not really understand the biology behind the patients who show late or delayed improvements. We need to be looking hard at our patients where we do have accumulating data—leaving fluid is probably limiting ultimate visual gains. Having data that suggests you can reliably predict how much vision people will gain at 1 year after only 3 injections—it is powerful.

Dr. Holekamp: Dr. Wykoff made an excellent point about continued anti-VEGF therapy that can create "late responders." In Protocol I, it was about 29%.[5] But those were patients who received eight to nine injections in the first year. In the real world, that is probably not happening.

Dr. Kitchens: We need to consider the business aspects. If you are going to switch that patient after the third injection, you need to start thinking about that when they come for their third injection because we have to get prior authorizations. You will have the prior authorization already in place for the anti-VEGF, but you need to consider it for steroids.

Dr. Holekamp: There were signals discussed in the Protocol I analysis, even at 2 months. It just encourages us to look at our patients as early as 1 month, and re-evaluate after the second and third injections. Maybe consider a corticosteroid challenge before injecting the steroid. But bear in mind we may need to pull the trigger at 3 months because that is the inflection point.

DELIVERY METHODS

Dr. Wykoff: While we have discussed many attributes of the FDA-approved steroid options, the delivery method for the dexamethasone and fluocinolone implants may be disconcerting to some who have not used the devices clinically. Some may be hesitant to try the larger-gauge injectable devices because they are used to injecting with 30-gauge or smaller needles. In reality, using the steroid implants is very straightforward and can be performed similarly to a standard intravitreal injection for many of us using a beveled approach.

CONCOMITANT THERAPY

Dr. Kitchens: What are your thoughts on fluocinolone? After about 10 patients, I have seen some pressure problems, but nothing untreatable. What I have noticed, however, is an initial anatomic response and then regression (about 50% regression after 3 or 4 months). So I have had to give them anti-VEGF therapy on top of the implant. Granted, these are the hard-to-treat patients, but I just gave them a very expensive implant and did not see the kind of sustained anatomical response I see with repeated dexamethasone implants.

Dr. Holekamp: You almost want that pulse because it is much, much higher dose with dexamethasone, whereas the fluocinolone implant is low-dose across the board.

Dr. Gonzalez: What do you do when you do switch a patient? Do you completely stop anti-VEGF? Do you add a steroid and move the anti-VEGF to a treat-and-extend or as needed? How do you approach those patients?

Dr. Kitchens: I will make a class switch because I want to see how they respond to this new class of medicine. Once the patient's not responding after the first 3 injections, I have them come back to switch them to intravitreal dexamethasone, and I will see them about 6 weeks later. And if they have a significant anatomical improvement, then I will keep them on the intravitreal steroid and treat on an as-needed basis with continued monitoring for any edema recurrence. If they have a partial response, then I will add the anti-VEGF therapy to see if we can get some additional improvement.

Dr. Wykoff: I take a similar approach. If I am going to add or switch to a steroid, I like to see what the steroid can do before I make it more complicated through a combination approach. I will see how long the pharmacologic effect will last—could be 3, 4, or 5 months—before I give a second injection. That is when I consider a switch to combination therapy and add the anti-VEGF back into the treatment regimen.

Let us say Mrs. Jones is a 4-month responder with dexamethasone. If she is still dry at 2 or 3 months, but at month 4 there is some recurrence of DME, I will bring her back at 3-3.5 months after the second injection and give her an anti-VEGF and see how long I can keep her dry using a combination approach.

Dr. Holekamp: I start with anti-VEGF. If I feel that I have a suboptimal response, I generally switch. And then I follow them and see. And if they are flat with intravitreal corticosteroid, then I never have to do anything again. But if there is some persistent

> "I will start with an anti-VEGF and will, after 2 to 3 injections, switch to a steroid if there is no visual or anatomical response."
>
> —Victor Gonzalez, MD

fluid on their OCT, I go back and I add an anti-VEGF agent. So I have flipped the usual paradigm on its head.

Dr. Gonzalez: I agree with you. I will start with an anti-VEGF and will after two to three injections switch to a steroid if there is no visual or anatomical response. In these patients, I will treat them with a steroid as monotherapy. If the anti-VEGF is working, I will continue injections and will add a steroid only if the central macular thickness is abnormal and not improving after at least three anti-VEGFs. I continue the anti-VEGF along with the steroid and will consider stopping the anti-VEGF if the visual acuity stops improving and the central macular thickness normalizes.

Dr. Kitchens: And these patients are typically nonresponders. We may be selecting out for the toughest-to-treat patients in some ways. It always astounds me how well steroids work in those patients.

FINAL THOUGHTS

Dr. Wykoff: There is one upcoming study—the DRCR.net's Protocol U—that incorporates both ranibizumab and dexamethasone. That may give us some guidelines.

Dr. Holekamp: It is equally important to note that Dr. Dugel looked at all the data—2-, 4-, 5- and 6-month data, but it was the 3-month data that had the best predictive value. He did not present the OCT data—OCT predicts OCT, but not vision. That is not to say month 3 is the magic number, but it was the earliest time period with the best predictive value of long-term visual outcomes.

Dr. Wykoff: The on-label treatment for fluocinolone includes patients who have not had a previous IOP response to steroids. So what is your steroid challenge?

Dr. Kitchens: My challenge is always these patients. I challenge them with dexamethasone, usually multiple injections because, first, I want to see an anatomical improvement with steroids, and then that they do not have the pressure rise. And I think it is hard to predict after one injection.

Dr. Holekamp: I do exactly the same thing. But they also have to demonstrate to me they need long-term corticosteroid therapy. Because if I am going to put a 3-year drug delivery system into someone's eye, they have to demonstrate to me that they need long-term continuous therapy. And that really requires several dexamethasone injections first.

Dr. Gonzalez: I think that Dr. Holekamp brings up an important point. Just like not all patients will need prolonged anti-VEGF treatment, some patients will need only a short exposure to corticosteroids. Some of our patients are going to be well served with just one dexamethasone application. When you have demonstrated the efficacy and the safety of the corticoidsteroid in a patient that needs continued applications of the device, a 3-year delivery system may be considered.

Dr. Wykoff: The FAME data supports that.[26] Patients who appeared to receive the most benefit from the fluocinolone implant were the ones with chronic DME—the patients I define in my clinic as those necessitating ongoing therapy. The eyes with less chronic DME probably do not need that duration of steroid.

Dr. Gonzalez: How do you manage your DME in postvitrectomized patients?

Dr. Holekamp: The pharmacokinetics of these drug delivery systems are essentially the same, even in the vitrectomized eye. And we know that is just not the case for the anti-VEGF injections. You really need durability.

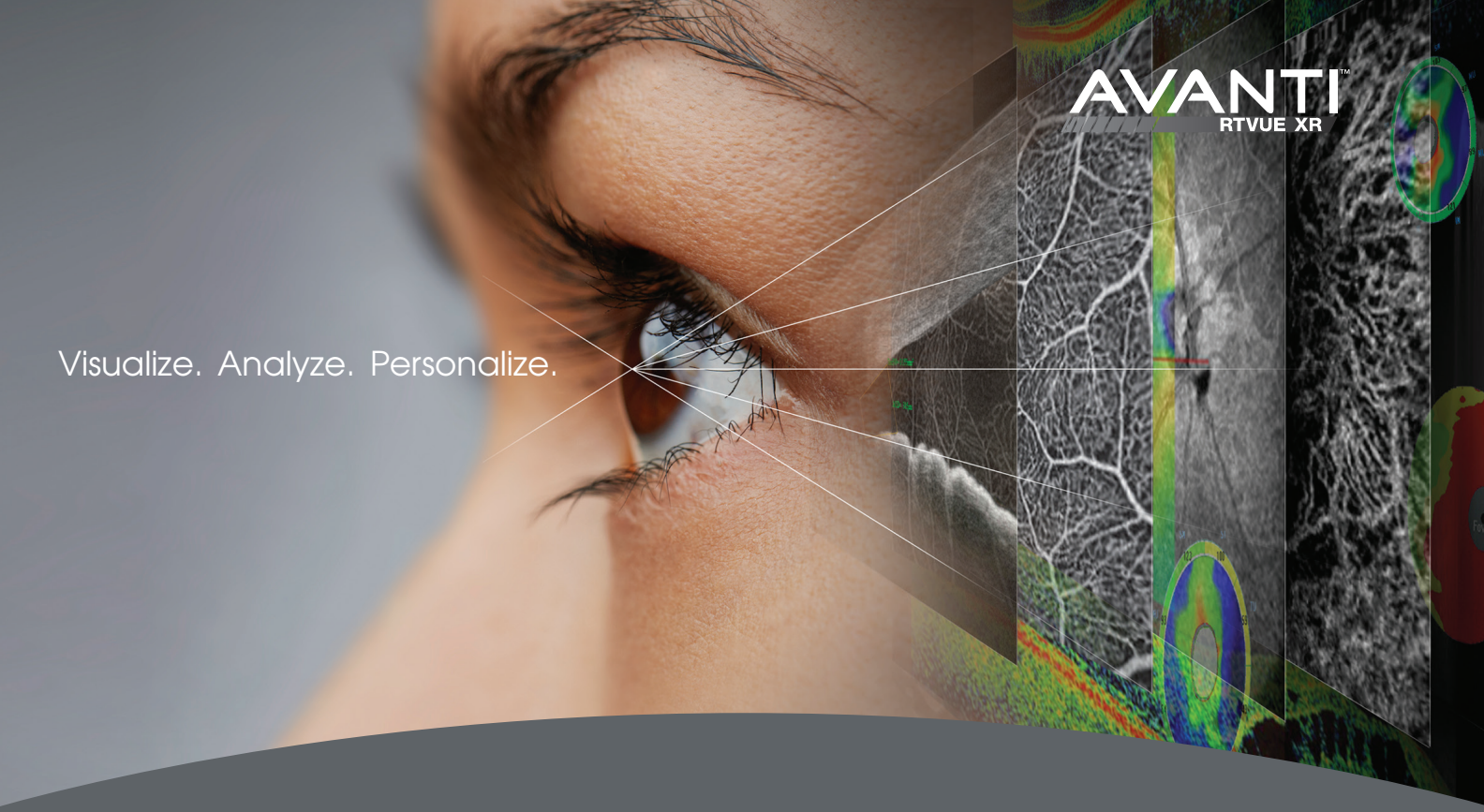
Dr. Kitchens: I think that is a big role for these extended-release devices, because anti-VEGFs just do not last as long in those eyes. I will use dexamethasone in patients who have had postvitrectomy residual edema.

Dr. Wykoff: It is a fascinating question. There is limited data from a small subset of Protocol I patients who underwent vitrectomy. In these postvitrectomy eyes, anti-VEGF therapy with ranibizumab did appear to have a good effect.[27] Often I try anti-VEGF agents first in postvitrectomy eyes, but in most cases I find exactly what you are both pointing out—that there is not the same durability of action as I observe in eyes that have not had a vitrectomy. In such cases, I tend to prefer to use a slow-release steroid implant.

Dr. Holekamp: You raise a good point—there were only 25 eyes and it was a post-hoc subanalysis. [27] But it was provocative. ■

1. Augustin A, Loewenstein A, Kuppermann BD. Macular edema. General pathophysiology. *Dev Ophthalmol.* 2010;47:10-26.
2. Adamis AP, Berman AJ. Immunological mechanisms in the pathogenesis of diabetic retinopathy. *Semin Immunopathol.* 2008;30(2):65-84.
3. Lee WJ, Kang MH, Seong M, Cho HY. Comparison of aqueous concentrations of angiogenic and inflammatory cytokines in diabetic macular oedema and macular oedema due to branch retinal vein occlusion. *Br J Ophthalmol.* 2012;96(11):1426-3140.
4. H Funatsu, H Yamashita, H Noma, et al. Aqueous humor levels of cytokines are related to vitreous levels and progression of diabetic retinopathy in diabetic patients. *Graefes Arch Clin Exp Ophthalmol.* 2005;243(1):3-8.
5. Diabetic Retinopathy Clinical Research Network, Elman MJ, Qin H, et al. Intravitreal ranibizumab for diabetic macular edema

with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology*. 2012;119(11):2312-2318.
6. Elman MJ, Ayala A, Bressler NM, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. *Ophthalmology*. 2015;122(2):375-381.
7. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119(4):789-801.
8. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macularedema. *Ophthalmology*. 2014;21(11):2247-2254.
9. Korobelnik J-F. Intravitreal aflibercept for diabetic macular edema: long-term outcomes from the VIVID-DME and VISTA-DME studies. Presented at: 15th EURETINA; September 18, 2015; Nice, France.
10. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology*. 2010;117(6):1078-1086 e2.
11. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011;118(4):615-625.
12. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193-1203.
13. American Society of Retina Specialists, Stone TW. ASRS 2015 Preferences and Trends Membership Survey. Chicago, IL: American Society of Retina Specialists, 2015.
14. Dong N, Xu B, Wang B, Chu L. Study of 27 aqueous humor cytokines in patients with type 2 diabetes with or without retinopathy. *Mol Vis*. 2013;19:1734-1746.
15. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120(10):2013-2022.
16. Wykoff CC. Rescue intravitreal aflibercept in patients receiving laser for DME. Presented at: American Society of Retina Specialists. July 11-14, 2015; Vienna, Austria.
17. Boyer DS, Yoon YH, Belfort R, Jr., et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121(10):1904-1914.
18. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119(10):2125-2132.
19. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118(4):626-635 e2.
20. Wykoff C. Analysis of diabetic retinopathy progression in patients treated with 0.2 mg/day fluocinolone acetonide over 36 months. Presented at: Retina 2015: Upping the Ante. American Academy of Ophthalmology Subspecialty Day; November 13-14: Las Vegas.
21. Ip MS, Domalpally A, Sun JK, Ehrlich JS. Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. *Ophthalmology*. 2015;122(2):367-374.
22. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. *Ophthalmology*. 2011;118(8):1580-1587.
23. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology*. 2008;115(9):1447-1449, 9 e1-10.
24. Boyer DS, Nguyen QD, Brown DM, et al. Outcomes with as-needed ranibizumab after initial monthly therapy: long-term outcomes of the phase III RIDE and RISE trials. *Ophthalmology*. 2015;122(12):2504-2513.e1.
25. Dugel P. Long-term response to anti-VEGF therapy for diabetic macular edema can be predicted after 3 injections: An analysis of Protocol I data. Presented at: Retina 2015: Upping the Ante. American Academy of Ophthalmology Subspecialty Day; November 13-14, 2015: Las Vegas.
26. Cunha-Vaz J, Ashton P, Iezzi R, et al. Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema. *Ophthalmology*. 2014;121(10):1892-1903.
27. Bressler SB, Melia M, Glassman AR, et al. Ranibizumab plus prompt or deferred laser for diabetic macular edema in eyes with vitrectomy before anti-vascular endothelial growth factor therapy. *Retina*. 2015;35(12):2516-2528.



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