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CME ACTIVITY

New Paradigms in the Management and Treatment of Diabetic Macular Edema

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New Paradigms in the Management and Treatment of Diabetic Macular Edema

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a series of three live webinars held during 2015.

METHOD OF INSTRUCTION

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ACTIVITY DESCRIPTION

Diabetes mellitus (diabetes) is a growing worldwide epidemic, affecting largely a working age population. By 2035, it is estimated to affect nearly 600 million people worldwide will be living with diabetes, a marked increase from the 382 million in 2013. Patients with diabetes are at an increased risk of several morbid and chronic conditions, among them acute coronary syndrome, hypertension, and retinopathy.

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TARGET AUDIENCE

This certified CME activity is designed for retina specialists and general ophthalmologists involved in the management of patients with retinal disease.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Describe the current epidemiology of diabetic macular edema and diabetic retinopathy
- Educate patients on the ophthalmic implications of systemic diabetes management
- Assess clinical studies involving new approaches to treat DME
- Use expert case examples to differentiate between clinical study dosing protocols and alternative dosing schedules
- Evaluate treatment options and develop a treatment regimen that can reduce patient burden and practice capacity
- Explain the early warning signs of elevated IOP
- Identify effective management strategies for patients requiring intervention

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New Treatment Strategies in Diabetic Macular Edema

Exploring anti-VEGF therapy in the real-world setting.

By Pravin U. Dugel, MD

The incidence of diabetes is increasing rapidly, not only in the United States, but around the world, particularly in emerging markets. We are experiencing an epidemic that has the capacity to become the leading cause of blindness in the next 20 years.[1] However, we are fortunate to have several options available to us to treat diabetic macular edema (DME), a leading cause of blindness in people with diabetes.

ANTI-VEGF THERAPY: STUDIES VS REAL WORLD

In most cases, our first-line treatment for DME is anti-VEGF monotherapy. We have excellent data demonstrating that patients who improve continue to do well for a long period.[2] In addition, for some patients in this group, anti-VEGF monotherapy seems to modify the disease, as the number of injections decreases dramatically after the first year of treatment (Figure 1).[3] Another line of evidence has shown that both ranibizumab and aflibercept appear to stabilize and even improve diabetic retinopathy in patients with DME.[4,5] In addition, the RESTORE study[6] found that anti-VEGF therapy not only improved anatomy and visual acuity but also improved patients' quality of life.

In light of this evidence, my colleagues and I performed a study to determine what percentage of patients were "cured" with anti-VEGF monotherapy. We examined a 5% sample of Medicare fee-for-service beneficiaries for the 3 years spanning 2007 to 2009. Because this is a coding database and not an outcomes database, the only way to determine if a case of DME was "cured" was to see if anti-VEGF injections were also coded for DME over those years. If the coding for DME ceased, we considered that a "cure." We also had a 1-year look-back period to confirm that patients had not been treated previously with anti-VEGF therapy.

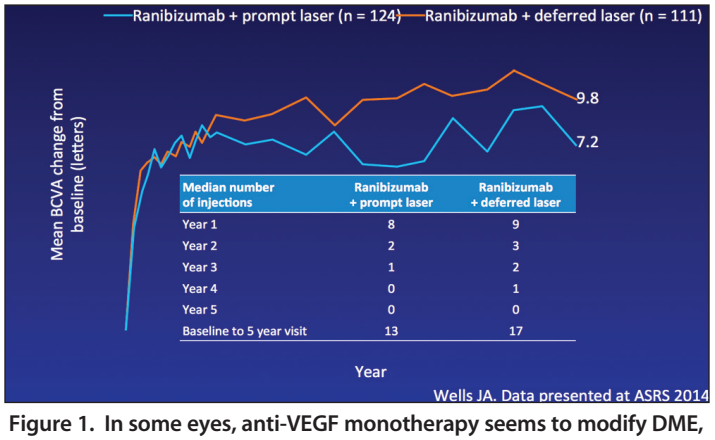

Figure 1. In some eyes, anti-VEGF monotherapy seems to modify DME, as the number of injections decreases dramatically after the first year of treatment.

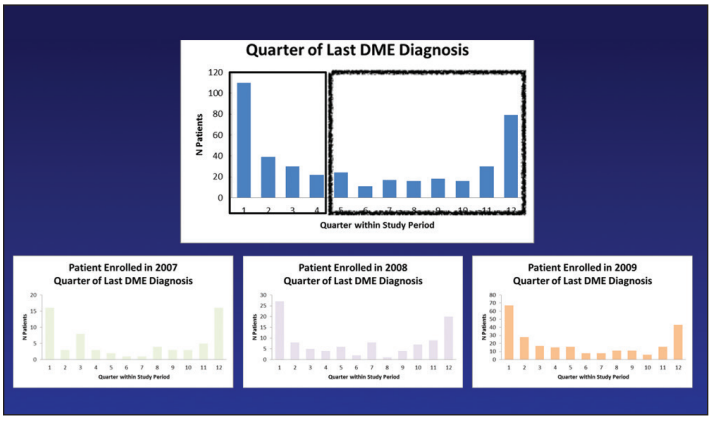

Figure 2. About 50% of eyes appeared to have been "cured" with anti-VEGF monotherapy; the other 50% had persistent DME.

What impressed me immediately was the low number of visits and injections these patients had, indicating a significant disconnect between what we are doing in real life and what the clinical trials tell us to do. Intuitively, one would think our real-world results may not be as good as the results in the clinical trials.

Figure 2 summarizes the diagnosis data. The similarities among the three smaller bar graphs, which represent each of the 3 years, indicate our findings were consistent from year to year. About 50% of eyes appeared to have been "cured" with anti-VEGF monotherapy, while the other 50% had persistent DME, requiring more than anti-VEGF monotherapy. This 50% number seems to resonate throughout many studies.

For confirmatory data, we can look at a subanalysis of the Diabetic Retinopathy Clinical Research (DRCR) Network's Protocol I study.[7] Patients were seen every 4 weeks and treated frequently, more than they would be in real life. Despite this motivated, biased patient population, almost 26% were deemed nonresponders. What's more, although 50% of patients were treated and "cured," the other 50% did not improve significantly and required more than anti-VEGF monotherapy. Consider, too, that eyes that improved the most had the lowest number of injections, while those that improved the least had the highest number of injections. "Curing" DME, therefore, is not related directly to the number of injections delivered.

Results in the two patient populations that emerged from the CMS data analysis appear to confirm the Protocol I subanalysis, and the 50% number seems to resonate. Is there something about this disease that is driving these results?

In the RISE and RIDE trials,[8] eyes from the sham group were allowed to cross over after 24 months to receive treatment. Those eyes improved but never caught up with those that started with anti-VEGF monotherapy. On the other hand, in the RESTORE study,[9] the crossover was allowed after 12 months, and those eyes did catch up with those that were originally treated with anti-VEGF monotherapy.

INFLAMMATION AND DME

Is there a window of time between 1 and 2 or 3 years when DME becomes resistant to anti-VEGF monotherapy and requires something in addition? Could that change be multifactorial? Could DME change from being primarily mediated by VEGF to a disease that is primarily mediated by inflammation?

Anti-VEGF agents inhibit only VEGF, which is a small component of DME. Inflammation has a strong role in diabetes, and the severity of diabetic retinopathy is directly related to the amount of cytokines in the eye.[10,11] Inflammatory cytokines are expressed at a higher level in eyes with DME, and eyes with more severe DME have an increased amount of cytokines, indicating a direct correlation with severity.[12]

Clinically, we see a disease that progresses from early focal leakage to diffuse leakage to fibrosis, followed by pigmentary changes, loss of photoreceptor cells, and loss of vision. Undoubtedly, vascular permeability is important throughout the natural course of the disease, but I believe that early in the disease, it is driven primarily by VEGF-mediated vascular permeability changes and later it is driven primarily by inflammation-related permeability mechanisms. At some point, perhaps between 1 and 3 years, DME changes from being primarily a monofactorial disease to primarily a multifactorial disease. When this happens, more than anti-VEGF monotherapy is required. When DME is mediated by multiple cytokines, steroids provide an effective therapeutic option.

STEROID DELIVERY

If inflammation is an important component of DME, why not simply deliver a bolus injection of a steroid? The pharmacokinetics (PK) of a bolus injection produces an immediate rise and a rapid decline in concentration. This PK will maximize the side effects and minimize the efficacy, exactly the opposite of the desired effect.

We now have two FDA-approved, sustained-release, intravitreal steroid implants: dexamethasone 0.7 mg and fluocinolone 0.19 mg. After the dexamethasone implant is injected, cavitations develop that increase its surface area. Initial burst patterns cause an immediate rise in the PK, followed by a gradual decline.[13] I believe this is more desirable than the rapid increase and rapid decrease of a bolus.

The fluocinolone implant is nonbioerodible and has one exposed tip. The PK of this device simulates a near zero order kinetics, so that a small amount of drug is released steadily over 3 years.[14] In eyes with DME that require control over the long term, I feel that this PK is more beneficial than that of a bolus injection.

PIVOTAL TRIALS

The MEAD study[15] was a pivotal phase 3 trial that compared two different doses of the dexamethasone intravitreal implant to sham. Both doses produced a statistically significant improvement in visual acuity over sham (Figure 3).

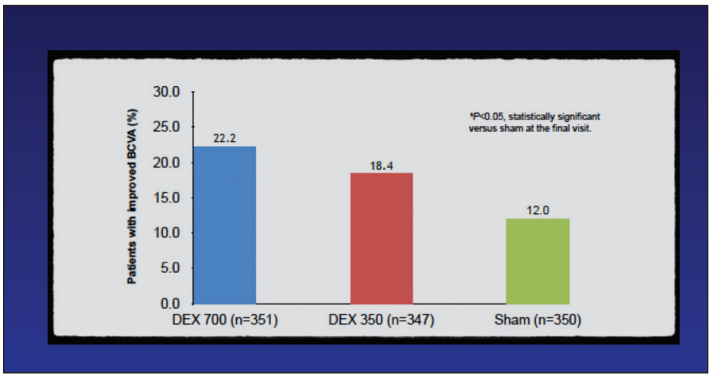

Figure 3. Both doses of the dexamethasone intravitreal implant produced a statistically significant improvement in visual acuity over sham in the MEAD trial.[15]

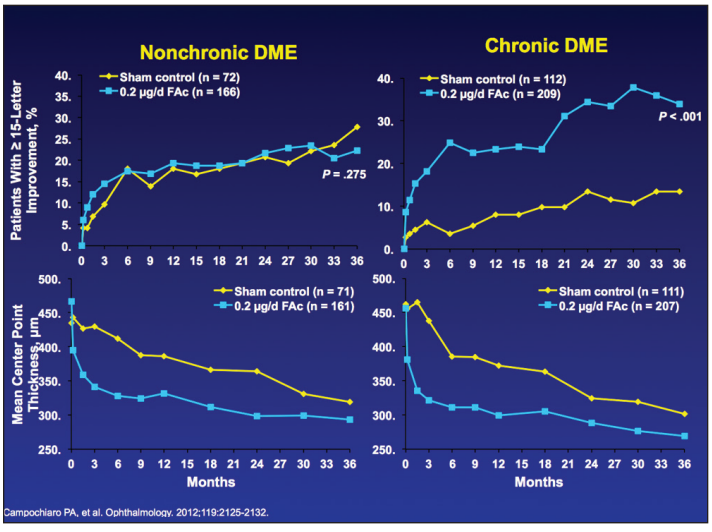

Figure 4. In eyes with chronic DME, there was a significant difference between results for treated eyes versus results for eyes in the sham group.[16]

The FAME-A and FAME-B trials[16] compared two different doses of the fluocinolone intravitreal implant to sham. In both trials, the primary endpoint was reached by the total patient population. Researchers performed a subanalysis of outcomes for eyes with chronic DME versus non-chronic DME at a 3-year threshold. In eyes with chronic DME, there was a significant difference between results for treated eyes versus results for eyes in the sham group; however, the difference was not as marked for eyes with non-chronic DME (Figure 4). Interestingly, these differences were not reflected in central retinal thickness on optical coherence tomography (OCT). This OCT-visual acuity disconnect suggests that while OCT is a good barometer for VEGF levels, it may not be a good barometer for other factors, such as inflammation.

As with any intraocular steroid, some adverse effects were associated with both the dexamethasone implant and the fluocinolone implant, ie, cataract formation and increased intraocular pressure (IOP).[16] In my opinion, cataract formation is not always a major deterrent, because DME is a blinding disease. In addition, the outcomes

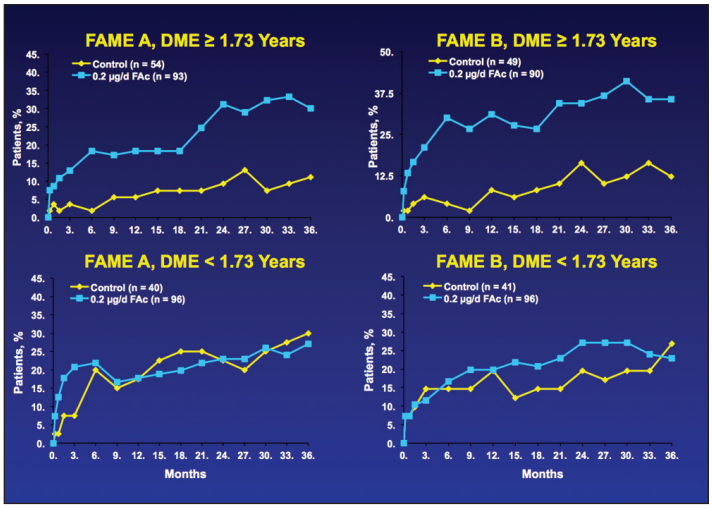

Figure 5. A secondary algorithm, requested by the FDA, resulted in a median duration of 1.73 years. These graphs looked almost exactly the same as the 3-year threshold graphs.

following cataract surgery with a steroid delivery device on board are generally excellent. Regarding IOP-related events, it is important to remember there is a difference between increased IOP and glaucoma. In both the MEAD study[15] and the FAME trials,[16] the percentage of eyes that required incisional pressure-lowering surgery was quite low. For most eyes treated with these implants, increased IOPs are well controlled by topical glaucoma medications.

TIMING THE MULTIFACTORIAL SWITCH: AN ALGORITHM

The FAME phase 3 trials[16] provide insight into the different therapeutic needs associated with DME as it transitions over time, ie, the 3-year threshold when the disease may be differentiated as chronic or non-chronic. How was that 3-year threshold identified?

The 3-year threshold was determined as follows: (year of randomization) minus (year of diagnosis) plus 1. The plus-1 in the formula was included to ensure that no eyes had a duration of zero years; however, it may have influenced the precision of the calculation. A secondary algorithm, requested by the FDA [(dd/mm/yyyy of randomization) minus (dd/mm/yyyy of diagnosis)], resulted in a median duration of 1.73 years. When these data were computed, the graphs (Figure 5) looked almost exactly the same as the 3-year threshold graphs (Figure 4).

This may be another set of data that confirm or at least support a multifactorial switch occurring between 1 and 3 years. The 3-year threshold as well as the 1.73-year threshold appear to show two distinct patient populations: one driven by a monofactorial cause and one driven by a multifactorial cause.

These data confirm that a transition occurs in the disease process of DME in some patients. This transition occurs on a continuum and may be unique for each patient. Clinical trial data support that the period between 1 and 3 years is an important inflection point for this patient population as a whole. Results from multiple phase 3 clinical trials support the observation of a differential need for therapy in patients with chronic or multifactorial DME.

CONCLUSIONS

Approximately 50% of patients with DME will require more than anti-VEGF monotherapy. During the natural history of DME, the disease appears to undergo a change from a primarily VEGF-mediated vascular permeability disease to one that is mediated primarily by inflammation. As a result of this multifactorial switch being turned on—sometime between 1 and 3 years—the therapeutic requirements of DME are drastically changed.

As we look to the future of our DME therapies, another consideration is our current inability to stage this disease. In oncology, for example, cancers are identified by type and severity to help guide physicians to the most appropriate therapies for specific patients. We do not have that granularity in our nomenclature for DME. Once we are able to refine our terminology and stage this disease, I believe we will be able to refine our diagnoses and glean more precise data from clinical trials, enabling us to better focus our therapeutics. ■

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Comparison of Outcomes From Diabetic Macular Edema Trials: Risk vs Benefit

We now have steroid delivery systems that are injected less frequently than anti-VEGF agents and have comparable efficacy.

By Baruch D. Kuppermann, MD, PhD

Anti-VEGF therapy is the acknowledged standard of care for treating diabetic macular edema (DME) in the United States. Based on clinical trials, the best results are observed with monthly injections, administered indefinitely.[1-10] A general rule of thumb, as seen in the RISE and RIDE[1] trials of ranibizumab, is that we can expect a 1-letter gain in visual acuity per anti-VEGF injection in the first year of monthly treatments. Many physicians have noted that maintaining this regimen is not realistic in clinical practice, and thus the real-world results do not match those of the trials. In addition, chronic DME appears to have a limited response to anti-VEGF therapy.[1]

Therapeutic safety is a concern when treating people with diabetes, as they have a high degree of underlying morbidity and a high risk of cardiovascular and cerebrovascular problems. Intravitreal anti-VEGF therapy is associated with an increased risk of death, stroke, and wound-healing problems. This has been shown with ranibizumab and is implicitly true for the other anti-VEGF agents, as well, as this is a class action for this group of compounds.

Steroids appear to be effective for both chronic and treatment-naïve, recent-onset DME, as shown in the FAME trials[2] of the fluocinolone acetonide 0.19-mg implant, as well as in real world trials with the 0.7-mg dexamethasone implant.[3] Evidence also suggests that intravitreal steroids lower many of the cytokines responsible for the cascade of events leading to DME.[4]

The down side of intraocular steroids is the ocular side profile—the increased risk of cataracts and elevated intraocular pressure (IOP). Although cataracts are common in people with diabetes,[5] we need to be concerned about this side effect and factor it into our treatment algorithm when deciding which therapeutic option to employ.

INFLAMMATION AND DME

Hyperglycemia leads to inflammation, vascular abnormalities, leakage of the blood-retinal barrier, edema, and thickening of the retina. Chronic hyperglycemia causes oxidative stress that initiates a local inflammatory reaction. Francine Behar-Cohen has shown that activation of microglial cells, dysfunction of Müller cells, and early release of inflammatory mediators, cytokines, and chemokines leads to chronic inflammation and neurodegeneration. Subsequently, retinal capillary damage and disruption of blood-retinal barrier vascular leakage occurs, leading to DME.[6]

Exploring the relationship between aqueous cytokine expression levels and severity of retinopathy, researchers have found a relative sensitivity to cytokine levels in patients who have diabetic retinopathy (Figure 1).[7] For example, MCP-1 levels are relatively low with mild retinopathy, and they increase with retinopathy severity. Conversely, VEGF is elevated but seems insensitive to the level of retinopathy.

ETDRS Retinopathy Severity	N	Cytokine Concentration (pg/mL)					
		VEGF	IL-1β	IL-6	IL-8	MCP-1	IP-10
10	28	967.0	10.0	32.1	22.8	252.2	2.1
20	23	952.8	11.0	33.5	20.6	303.6	2.5
35	26	956.4	9.2	33.1	22.7	339.5	5.6
43	18	1084.7	10.7	33.2	24.4	468.8	5.5
47	13	1172.6	18.8	56.6	29.2	645.2	9.5
53	8	1177.3	22.7	106.7	49.4	921.2	22.3
65	7	1142.7	23.7	116.8	51.0	1215.1	31.3
75	8	1051.4	27.6	147.0	75.7	1286.6	34.3
81	5	1165.4	45.8	188.6	74.4	1630.8	29.2
P-value		.733	.003	<.001	.001	<.001	<.001

- Disease severity-related increases in cytokines other than VEGF are orders of magnitude higher

Dong N *et al. Molecular Vision* 2013, 19:1734-1746

Figure 1. There is a relative sensitivity to cytokine levels in patients who have diabetic retinopathy.

In a study of 11 patients with bilateral DME, Sohn and colleagues treated one eye with triamcinolone and the other eye with bevacizumab.[4] In the triamcinolone-treated eyes, the steroid reduced the levels of most of the cytokines and also lowered VEGF levels by 80%. In the bevacizumab-treated eyes, VEGF levels were lowered by 99%; however, all of the other cytokines that were measured appeared unaffected by the reduced VEGF levels. This suggests that some eyes with DME are particularly sensitive to VEGF while others are not; therefore, anti-VEGF therapy will not alter their DME because the other inflammatory cytokines may be playing an important role in their disease.

In summary, in eyes with DME, VEGF levels are high throughout the entire cascade of events leading to VEGF-mediated vascular permeability, while inflammation appears to mount over time as noted by the increased levels of cytokines with progressive retinopathy. In other words, some eyes are mostly influenced by VEGF while others are more influenced by non-VEGF mediators, suggesting two patient populations: those who respond to anti-VEGF therapy, and those who do not. Steroids are effective in treating both types of patients.

CLINICAL TRIAL DATA

The Diabetic Retinopathy Clinical Research Network's Protocol I[7] study was the most important of the early DME clinical trials, because it looked at ranibizumab with prompt or deferred laser, compared with triamcinolone plus prompt laser and sham plus prompt laser.[8] At

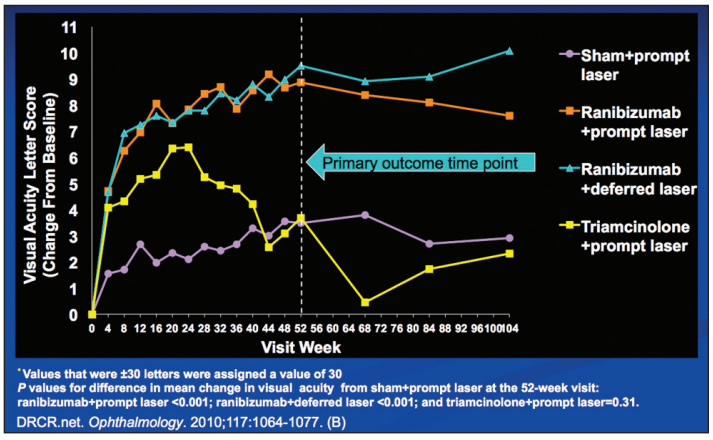

Figure 2. Eyes in the ranibizumab arms achieved significantly improved visual acuity at 1 year.[8]

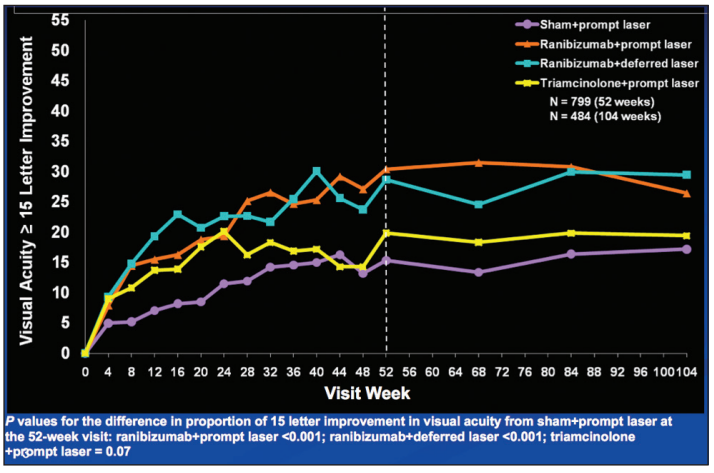

Figure 3. At 52 weeks, about 28% of eyes in the ranibizumab arms gained 3 lines of visual acuity.[8]

1 year, eyes in the ranibizumab arms achieved significantly improved visual acuity (Figure 2).

Protocol I[9] was a real-world trial, during which patients received fewer injections than in either the RISE and RIDE trials or the VIVID and VISTA trials of aflibercept.[1,9] In this setting, they gained approximately 8 letters of visual acuity in the first year. The eyes receiving triamcinolone improved initially but declined because of the development of cataracts.

We can learn another lesson from Protocol I in terms of real-world outcomes and creating a hypothesis or a unified concept of how patients are performing in relative clinical trials. At 52 weeks, about 28% of eyes in the ranibizumab arms gained 3 lines of visual acuity (Figure 3). This is an important number to keep in mind, as the real-world trials tend to be associated with about 7 to 8 letters gained and 28% to 30% 3-line gainers. I believe steroids are also capable of achieving those same thresholds.

In a subset of eyes that were pseudophakic at baseline in Protocol I, outcomes in the ranibizumab-treated eyes and the triamcinolone-treated eyes were similar, and eyes treated with triamcinolone received fewer injections. In the first year, eyes receiving triamcinolone had three injections versus eight or nine for eyes receiving anti-VEGF therapy. Again, the rule of thumb comes into play, as eyes that received eight anti-VEGF injections gained about 8 letters. Keep in mind, however, this rule of thumb applies only to anti-VEGF therapy.

With intraocular steroids, risks for IOP elevation and cataract formation exist, and these adverse events were seen in the triamcinolone-treated eyes in Protocol I (Figure 4). Cataracts tend to develop in the second year of treatment; therefore, in steroid trials, it is important to not look at the 1-year data only. By 24 months, we can usually get a sense of cataract rates, and that was observed with triamcinolone in the Protocol I study.

Elevated intraocular pressure	Sham +Prompt Laser n=293	Ranibizumab +Prompt Laser n=187	Ranibizumab +Deferred Laser n=188	Triamcinolone +Prompt Laser n=186
Increase ≥10 mm Hg from baseline	8%	9%	6%	42%
IOP ≥30 mm Hg	3%	2%	3%	27%
Initiation of IOP-lowering meds at any visit*	5%	5%	3%	28%
Number of eyes meeting ≥1 of the above	11%	11%	7%	50%
Glaucoma surgery**	<1%	1%	0	1%

*Excludes eyes with IOP-lowering medications at baseline.
**Includes 2 filter and 2 cilliary body destruction.
DRCR.net. Ophthalmology. 2010;117:1064-1077. (B)

Figure 4. With intraocular steroids, risks for IOP elevation and cataract formation exist.[8]

STEROID DELIVERY SYSTEM: FLUOCINOLONE

Two steroid delivery systems are FDA-approved for treating DME: fluocinolone acetonide 0.19 mg and dexamethasone 0.7 mg.

The fluocinolone non-bioerodible implant delivers drug over a 3-year period. It is injected into the eye through a self-sealing wound using a 25-gauge inserter. When the drug is fully eluted, an empty husk is left behind.

In the FAME trials[2] of fluocinolone for DME, 29% of eyes in the treatment groups gained 3 lines of visual acuity. After 6 weeks, eyes in the sham group were allowed to receive laser treatments, and these eyes showed a benefit but not nearly as much as the eyes that were initially treated with the fluocinolone implant.

In contrast, in the RISE and RIDE trials,[1] the control group received sham injections for 24 months and then were offered ranibizumab 0.5 mg. Patients who opted to receive treatment gained a little more than 2 letters (Figure 5). Ironically, this group appears similar to the group that had chronic DME in the FAME trials,[2] and those eyes had the most robust response. The fact that the steroid produced a robust response in chronic DME and anti-VEGF had a muted response is consistent with the cytokine data. Progressive retinopathy over time, is sensitive to cytokine levels, whereas VEGF levels are high but are not sensitive to the level of retinopathy.

RESTORE[10] was a real-world trial, in which ranibizumab injections were given less frequently. In the first year, ranibizumab-treated eyes achieved visual acuity gains of 7 to 8 letters, which I believe is a new benchmark for real-world trials (Figure 6). Importantly, little improvement was seen in the control group, and those patients were offered anti-VEGF therapy 1 year into the trial. Those eyes had a slow, delayed

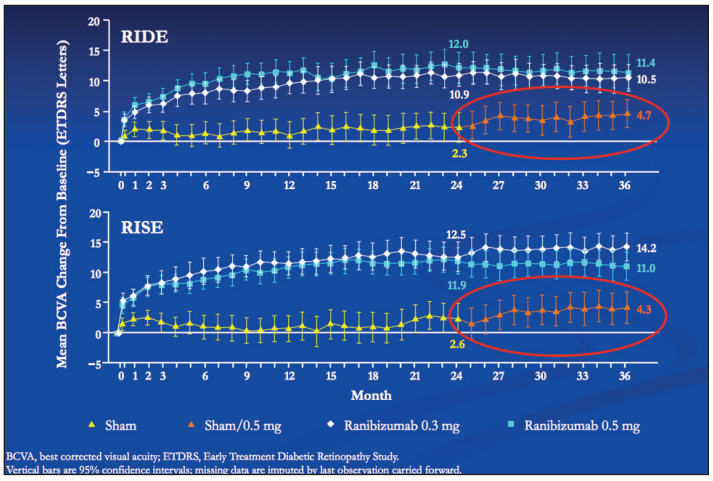

Figure 5. After about 2 years of no therapy, patients were offered ranibizumab 0.5 mg, and they gained a little over 2 letters.

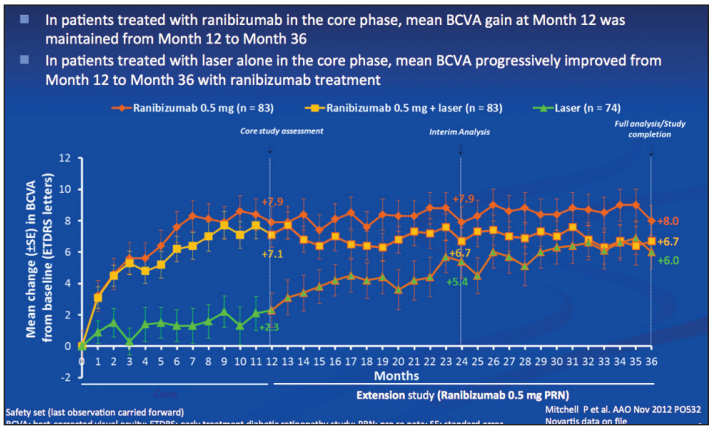

Figure 6. In the first year, ranibizumab-treated eyes achieved visual acuity gains of 7 to 8 letters.

response, and they eventually caught up with the eyes that were treated from the beginning of the study. Eyes that received early anti-VEGF therapy had a robust response. In the 1- to 2-year period, when a transition to chronic DME is occurring, there is a response but it is somewhat muted and slower. These results are significantly better than the blunt responses after 2 years in the RISE and RIDE trials.[1]

The FAME data show an 80% risk of cataract with fluocinolone treatment, and patients who are phakic must be informed that they will likely need cataract surgery if they receive this implant. In addition, about 38% of patients treated with fluocinolone 0.19 mg needed at least one IOP-lowering medication, while 5% of these patients required IOP-lowering surgery.

STEROID DELIVERY SYSTEM: DEXAMETHASONE

The biodegradable dexamethasone 0.7 mg implant is injected into the eye via 22-gauge biplanar injection. In the MEAD study,[11] eyes were randomly assigned to receive dexamethasone 0.7 mg, 0.35 mg, or sham. Patients were assessed for retreatment eligibility every 3 months at a study-scheduled visit starting from month 6. Patients received up to seven treatments during the 3-year study period. The percentage of eyes that gained 15 or more letters from baseline was significantly

	Prior Steroid		Prior Anti-VEGF		Prior Laser	
Endpoint	DEX Implant 0.7 mg n = 58	Sham n = 61	DEX Implant 0.7 mg n = 25	Sham n = 26	DEX Implant 0.7 mg n = 231	Sham n = 243
Patients with BCVA ≥ 15-letter improvement from baseline at study end, %	27.6	8.2	28.0	7.7	21.2	11.9
Mean BCVA average change over 3 years (AUC approach), letters	4.9	-0.6	4.2	1.6	3.1	1.6
Mean CRT average change over 3 years (AUC approach), μm	-120.9	-29.7	-130.4	-42.1	-122.9	-39.3

Figure 7. In a subset of eyes previously treated with steroid or anti-VEGF therapy, about 28% gained 3 lines of visual acuity.

higher with dexamethasone 0.7 mg (22%) and dexamethasone 0.35 mg (18%) compared with sham (12%) at the year 3 final visit. Importantly, eyes were treated every 6 months, and we have learned that this is a 3-month therapy in most patients.

Eyes that were pseudophakic at baseline and treated with the dexamethasone 0.7 mg implant gained 6 to 7 letters. Phakic eyes also had an initial gain of about 6 to 7 letters, but visual acuity declined because of cataract formation. In a subset of eyes that had steroid or anti-VEGF therapy before enrollment in the trial, about 28% gained 3 lines of visual acuity, even in this under-dosed population (Figure 7).

About 61% of eyes in the MEAD trial[11] needed cataract surgery by the end of the study, and about 42% of eyes needed IOP-lowering therapy.[10] The dexamethasone implant delivers drug for about 3 months, and IOPs tended to spike and then decrease on a 6-month cycle, making it relatively easy to manage these patients. As the drug wears off, the IOP issue typically resolves, but during pressure spikes, patients needed to be treated with IOP-lowering therapy, typically for a limited period. The incidence of these adverse events with the dexamethasone implant is similar to what was found with the fluocinolone implant or intravitreal triamcinolone in the Protocol I study.[7] About 40% of eyes treated with steroids, whether triamcinolone or the dexamethasone or fluocinolone implants, need some form of IOP-lowering therapy; the degree of therapy required for maintenance may differ from steroid to steroid.

ANTI-VEGF THERAPY

The RISE and RIDE trials[1] gave the best results for the DME population at large, primarily because it entailed monthly injections.[1] Eyes were randomly assigned to sham injection versus ranibizumab 0.3 mg or 0.5 mg, with 24 monthly injections delivered. Roughly 40% of all treated eyes gained 3 lines of visual acuity.

Vision tends to plateau at about 18 months and is maintained through 36 months of monthly injections. Importantly, when eyes in the sham group were converted to active therapy (ranibizumab 0.5 mg) after 24 months, their visual acuity barely improved, indicating their now chronic DME had an inadequate or limited response to anti-VEGF therapy.

In the RESTORE study,[10] which employed an as-needed injection strategy, the sham control group was transitioned to active therapy after 1 year, and the response to anti-VEGF was slow and not as robust

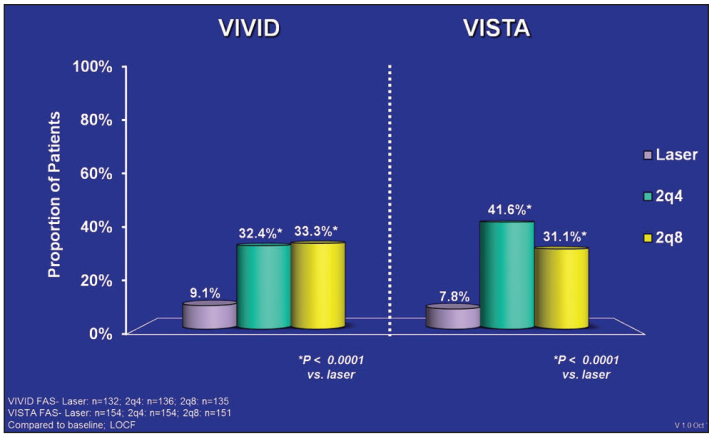

Figure 8. The overall proportion of eyes that gained 3 lines of visual acuity in the VIVID and VISTA trials of aflibercept was lower than in the RISE and RIDE trials of ranibizumab.

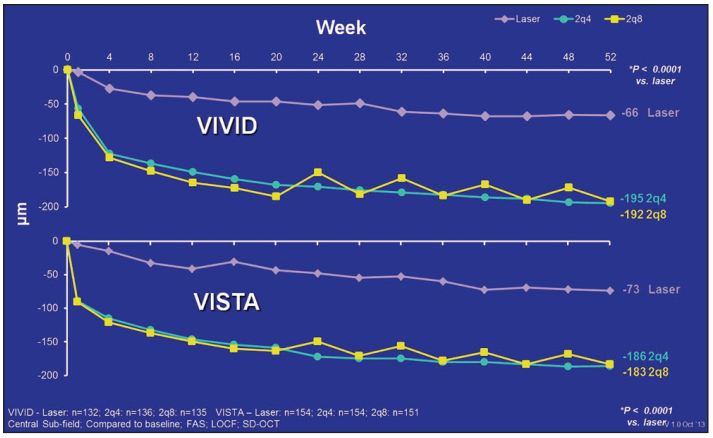

Figure 9. When the interval between injections was extended to every 8 weeks, the OCT pattern appears to be "saw-toothing," suggesting that 8 weeks may be beyond the drug's most desirable efficacy interval.

as the response initially seen in the treatment groups in the first 3 or 4 months. After about 2 years, they did catch up.

Again, we see this concept of a transition to chronic DME, when the effect of anti-VEGF therapy begins to diminish. This is where steroids appear to be robust therapeutic agents both early and late throughout the course of the disease.

With regard to safety, data from the RISE and RIDE trials[1] led to the decision by Genentech and the FDA to recommend the lower, 0.3-mg, dose of ranibizumab, given the increased risk of death and cerebrovascular accidents, even though they were not statistically significant.[12] This creates a dilemma for us in managing this population. To achieve the best results, we need to treat monthly, but monthly therapy carries the risk in this population for creating these fatal events.

In the VIVID and VISTA trials,[9] eyes received five loading doses of aflibercept, 2 mg, followed by injections every 4 weeks (2q4) or every 8 weeks (2q8); the control arm received focal laser photocoagulation. Mean visual acuity gains from baseline to week 52 in the aflibercept-treated eyes (2q4 and 2q8) versus those treated with laser were 12.5 and 10.7 versus 0.2 letters in VISTA, and 10.5 and 10.7 versus 1.2 letters in VIVID. The corresponding proportions of eyes gaining 15 letters or more were 41.6% and 31.1% versus 7.8% in VISTA, and 32.4% and 33.3% versus 9.1% in VIVID. The overall proportion of eyes that gained 3 lines of visual acuity was smaller in this trial than it was in the RISE and RIDE trials of ranibizumab (Figure 8).

Looking at mean change in central retinal thickness (Figure 9) we see that when the interval between injections was extended to every 8 weeks, the OCT pattern appears to be "saw-toothing," suggesting that 8 weeks may be beyond its most desirable efficacy interval, at least in some patients.

No untoward safety events were reported in the VIVID and VISTA trials.[9]

CONCLUSIONS

Anti-VEGF agents are effective therapy for DME. To achieve the best results, monthly injections must be administered for a prolonged period. The best outcomes thus far were seen in the RISE and RIDE trials,[1] with 22 injections administered over the first 2 years. In the sham control group, eyes were untreated for 2 years and, therefore, developed chronic DME. These eyes with chronic DME responded poorly to ranibizumab when it was finally utilized after 2 years of sham treatment. A theoretical concern exists regarding systemic side effects from anti-VEGF agents injected intravitreally. Real-world trials of anti-VEGF agents seem to achieve similar efficacy results: about 28% 3-line gainers and mean visual acuity gains of 7 to 8 letters.

Steroids also are effective for treating DME. In real-world trials, results are comparable to those achieved with anti-VEGF therapy but with fewer steroid injections. In a head-to-head trial, Protocol I,[8] steroids were equally effective as ranibizumab in pseudophakic patients.

We now have steroid delivery systems that are injected less frequently than anti-VEGF agents and have comparable efficacy. In fact, the fluocinolone implant had particularly good results with about 35% 3-line gainers in the subset of eyes with chronic DME. We also know that steroids work both early and late, whereas the anti-VEGF agents appear to work better early in the disease state.

Real-world trials seem to all result in 28% 3-line gainers with a BCVA gain of 7 to 8 letters after the first year, and this is seen with both steroids and anti-VEGF agents. ■

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Steroids and IOP: Balancing Visual Quality and Intraocular Pressure

Several factors are associated with the potential for pressure elevations from steroid exposure.

By Nathan Radcliffe, MD

Glaucoma is an optic neuropathy that causes optic nerve damage and visual field loss; elevated intraocular pressure (IOP) is also a component of this disease. Ocular hypertension is defined as elevated IOP without evidence of optic nerve damage or visual field loss.

Characteristic patterns of optic nerve damage may include cupping, thinning of the neuroretinal rim, and changes in the vasculature. Visual field progression may take many shapes and forms, but in glaucoma, we are most concerned with the change in visual function that has occurred as a result of optic nerve damage.

Steroid glaucoma is defined as elevation of IOP following the application of a steroid, with subsequent development of optic nerve damage, leading to visual function changes. Steroid ocular hypertension is defined as elevation of IOP following the application of a steroid but without evidence of optic nerve damage. For the most part, patients who have been exposed to ocular steroids do not have a long-standing history of nerve damage, therefore, more of these patients fall into the category of steroid ocular hypertension.

EFFECTS OF EXPOSURE TO OCULAR STEROIDS

In susceptible individuals, steroids can cause a condition similar to primary open-angle glaucoma (POAG).[1] About 5% of the population are high steroid responders, ie, people whose IOPs rise more than 15 mm Hg above their baseline upon exposure.[1] This pressure rise may occur as early as 1 day or as late as 12 weeks after intravitreal injection.[1] Many factors determine how quickly and how significantly the IOP rises.

RISK FACTORS FOR STEROID RESPONSE

Risk factors for steroid response include very young or old age, as well as a personal or family history of glaucoma or being a glaucoma suspect. Other risk factors have been suggested—diabetes, connective tissue disease, and high myopia, for example—but confirmatory data are lacking or conflicting. We do know that the risk of a steroid response is greater if the drug is administered at higher doses or intravitreally.[1]

MECHANISMS OF STEROID RESPONSE

A primary mechanism of steroid response is an increased resistance to aqueous outflow. Steroids induce physical and mechanical changes in the microstructure of the trabecular meshwork and potentially downstream. As well, leading to increased deposition of glycosaminoglycans in the trabecular meshwork. The steroids inhibit proteases and trabecular meshwork phagocytosis, which can cause a decrease in the breakdown of substances in the trabecular meshwork that are regularly being cleared. From a different perspective, we use laser trabeculoplasty to incite inflammation to clean out the trabecular meshwork. Perhaps steroids inhibit that same type of natural clearing of the meshwork. It is fascinating to see, at least anecdotally, that steroid responses can persist after the removal of the trabecular meshwork, such as after a trabeculotomy or any other trabecular bypass surgery, even after filtration surgery. The process is not fully understood, but it is linked to the outflow pathway.

PREDICTORS OF STEROID RESPONSE

Although we cannot predict with 100% accuracy who will have a pressure rise following steroid application, there are risk factors to consider. Investigators conducted a topical dexamethasone provocative test, administering four drops a day for 4 weeks, before performing an intravitreal triamcinolone injection.[2] In eyes that had a significant pressure rise from the dexamethasone, the pressure rise after intravitreal triamcinolone was 17 mm Hg compared with 5 mm Hg in eyes that did not have a pressure rise after the dexamethasone. This test had low sensitivity but high specificity, a high positive predictive value, and a moderate negative predictive value. If the topical test produced no response, there still could be a response from the intravitreal test, which makes sense because that is a more potent means of delivering a steroid. All responders demonstrated high pressure increases after the intravitreal injection.

We can gain some useful information by looking at how someone responded to a first trial of steroids delivered via intravitreal injections. We also gained a unique insight into how patients respond to steroids from the FAME trials.[3]

In the FAME trials, fluocinolone 0.2 mg was injected using a slow-release platform that delivered about 0.19 mcg per day to treat diabetic macular edema (DME). This study, which spanned 3 years, excluded patients who had a known history of uncontrolled IOP elevations related to steroid use that did not respond to topical therapy. Patients who had never received intravitreal triamcinolone were permitted in the trial.

Eighteen of 300 the patients who had undergone no prior steroid treatment and who were treated with the fluocinolone implant required IOP-lowering surgery in the study eye. None of the 72 patients who had undergone prior steroid treatment and did not develop uncontrolled pressures required glaucoma surgery. Given these outcomes, the FDA approved the fluocinolone implant for use in treating DME in patients who had undergone prior steroid treatment and did not experience a clinically significant IOP rise.

Several factors are associated with the potential for pressure elevations from steroid exposure, including the potency of the molecule, the location of administration, frequency and duration of use, penetration of the molecule, and dosage of the drug given. An almost

TABLE 1. ANTI-INFLAMMATORY AND IOP ELEVATIONS FOR DIFFERENT TOPICAL STERIOD PREPARATIONS		
Corticosteroid preparation	Rise in IOP (mm Hg)	Anti-inflammatory Potency
Dexamathasone 0.1%	22±2.9	24
Prednisolone 1.0%	10±1.7	2.3
Fluorometholone 0.1%	6.1±1.4	21
Hydrocortisone 0.5%	3.2±1.0	1
Tetrahydrotriamcinolone 0.25%	1.8±1.3	1.4
Medrysone 1.0%	1.0±1.3	1.7

Table. The relationship between anti-inflammatory potency of specific steroids and their associated pressure elevations is revealing.[2]

	Steroid related glaucoma	POAG
Age of Onset	Any age	60+ years
Inciting event	Steroid use	None
IOP range	Bimodal (old & young)	Twenties
Duration of IOP elevation	Weeks-months	Lifetime (decades)
Management	Topical medications	Topical medications, laser and surgery
Need for surgical intervention	Rare	Relatively common
Prognosis	Excellent	If detected early good. If detected late, poor

Figure. Significant differences exist between steroid-related glaucoma and POAG, necessitating different management approaches.

intrinsic relationship exists between the potency of a steroid molecule and the risk of pressure elevation, but the method of delivery is also a factor.

Looking at anti-inflammatory properties of specific steroids and their associated pressure elevations is also revealing (Table).[2] For example, fluorometholone has relatively high anti-inflammatory potency, but in this study, it was associated with a pressure rise of only 6 mm Hg. This is likely because fluorometholone does not penetrate as well as some of the other steroids, therefore, it is not reaching the outflow pathway where it can cause a pressure response. A key takeaway is that a pressure rise is not dependent on the molecule and its anti-inflammatory potency, but rather how it interacts with the ocular surface and ultimately how much of the drug reaches the target tissue.

NATURAL HISTORY OF STEROID-RELATED IOP RISE

In general, steroid-related IOP rises are transient and short-term. They can persist from a few weeks to several months, depending on the duration of the steroid therapy. Most steroid-related IOP elevations can be treated and controlled medically. In this situation, even though the pressure may be highly elevated, a single agent or several agents control the pressure for most people. A small percentage of eyes develop optic nerve damage and require surgical intervention.

Regarding the timing of a steroid-related pressure rise, one study found that patients who received intravitreal triamcinolone injection had elevated IOPs throughout the first year of treatment, indicating there is no specific time frame during which the pressure will rise.[4] Therefore, it is important to monitor these patients during therapy. In my opinion, patients receiving intravitreal steroid injections should have their pressures checked at least 4 times a year.

After starting intravitreal steroid therapy, patients' pressures should

Steroid-Related IOP elevations

By Nathan Radcliffe, MD

A 69-year-old man with panuveitis in the left eye was treated with the intravitreal dexamethasone implant and topical difluprednate for several years. He eventually required pressure-lowering medications. On examination, he exhibited subtle progression in the left eye, and his pressure was in the low 20s. Fundus photographs showed a slightly greater degree of cupping in the left eye, indicating some deterioration at the neuroretinal rim (Figure).

Given the evidence of progression and pressures in the 20s with medications, the topical difluprednate was stopped. At the time, there was some debate about whether stopping the topical agent made sense given that an intravitreal agent was on board. Two weeks later, however, the pressures returned to normal and the topical glaucoma medications were stopped.

Patients can have pressure elevations from topical or intravitreal steroids; however, in this case, stopping the topical steroid was easier than removing the implant or waiting for the drug being released from the implant to dissipate. Fortunately for this individual, stopping the topical agent was relatively easy, and he did well.

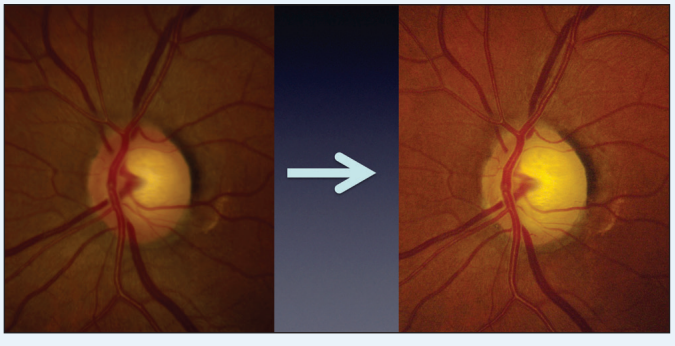

Figure. Fundus photographs showed a slightly greater degree of cupping in the left eye, indicating some deterioration at the neuroretinal rim.

If it makes sense to stop the steroid, I will do so. If the steroid is preserving central visual acuity and helping the patient have a higher vision-related quality of life, however, I usually will encourage the team to continue the steroid and allow me to manage the glaucoma with medications, laser treatment, or surgery.

be checked at 1 month to detect significant changes from baseline. We need to use our clinical judgment, as there is no percentage or absolute number. A pressure rise of 10 mm Hg to 20 mm Hg may not be significant as opposed to an increase from 20 mm Hg to 40 mm Hg. If a significant change occurs, the patient must be closely monitored to determine if it is just a single high reading or if the pressure is consistently elevated. If there is risk of optic nerve damage, medical therapy must be initiated and escalated, if necessary, until the target pressure is achieved. If maximum medical therapy does not reduce the pressure sufficiently, then other approaches, including laser trabeculectomy, must be considered.

This algorithm is different from our approach to managing POAG. The figure summarizes the main differences between these two presentations.

Initially, we manage both types of patients similarly, but patients with POAG will have this disease for the rest of their lives, and if the disease progresses, they will need more aggressive intervention, including surgery. The prognosis is more favorable for steroid-related pressure elevation. We know what is causing it, and we can withhold that therapy, or we can address the pressure aggressively, if needed, which is not the case with POAG.

Some glaucoma specialists do not consider laser trabeculoplasty for cases of steroid-related pressure elevation, but I believe this may change. We are starting to consider it as a first-line therapy for POAG, and we have some excellent data on its success for treating steroid-related pressure elevations.[5,6] Yuki and colleagues treated 148 eyes with selective laser trabeculoplasty after their IOPs rose post intravitreal triamcinolone. After 3 months, eyes treated with the laser had a 45% pressure reduction, which lasted for 9 months. One patient required surgery. Rubin and colleagues treated seven steroid responders who had high baseline IOPs of 38 mm Hg. After selective laser trabeculoplasty, the pressures were reduced to an average of 15 mm Hg at 6 months, with two eyes requiring surgery. These results are reassuring, and to me, they suggest that laser trabeculoplasty should be used earlier in the treatment of steroid-related pressure elevation.

SUMMARY

Steroid-related pressure elevations are caused by increased resistance to aqueous outflow. They are generally transient and related to the potency of the steroid and the duration of its use. Regular monitoring of IOPs after the application of steroids is important. A steroid-related IOP rise is usually managed medically, but laser is also effective. Surgical intervention is generally rare, and anecdotally, surgical intervention tends to work well in this group because the conjunctival inflammation is usually well controlled. The prognosis in general is good.

The cases included within this article illustrate some of the issues we face when treating steroid-related IOP elevations. ■

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Corticosteroids in DME: New Paradigms

These drugs are effective for our patients who are recalcitrant or not responding fully to anti-VEGF agents for their DME.

By Nancy M. Holekamp, MD

Any conversation about the treatment of diabetic macular edema (DME) must begin with anti-VEGF therapy. In the RISE and RIDE trials, ranibizumab demonstrated a 3-line gain in visual acuity in almost 40% of patients at 24 months, which was highly statistically significant compared with sham treatments.[1] Looking at this endpoint from another perspective, ranibizumab improved visual acuity to 20/40 or better in 57.2% of patients at the 2-year time point. Again, this was statistically significantly better than sham-treated eyes.

Although the development of anti-VEGF therapy for the treatment of DME was a game-changer, these agents are not solving the entire DME problem. In the RISE and RIDE trials,[1] 61% of patients did not achieve at least a 15-letter gain in visual acuity from baseline, and 43% of patients did not achieve 20/40 visual acuity. These were patients in a clinical trial who were receiving monthly anti-VEGF injections and were being monitored monthly, which is perhaps the best possible scenario. It has become apparent that we need to look elsewhere for therapy that will be effective for our patients who are recalcitrant or not responding fully to anti-VEGF agents for their DME. That is why corticosteroids have a place in the new paradigm for treatment of DME.

TRIAMCINOLONE: AN OFF-LABEL OPTION

Intravitreal triamcinolone has long been used off-label to treat DME. A preservative-free formulation is FDA-approved for certain ocular indications but not for the treatment of DME.

Intravitreal triamcinolone has been subjected to scientifically rigorous study by the Diabetic Retinopathy Clinical Research (DRCR) Network. One such study, Protocol I,[2] was a prospective, randomized clinical trial involving more than 850 eyes in which researchers compared sham plus prompt laser, ranibizumab plus prompt laser, ranibizumab plus deferred laser, and triamcinolone plus prompt laser. This was one of the first clinical trials to compare triamcinolone with an anti-VEGF agent.

The primary endpoint in Protocol I[2] was mean change in visual acuity at 52 weeks. At 1 year, the ranibizumab-treated eyes gained about 9 letters or almost 2 lines of visual acuity whether they received prompt or deferred laser. At about week 16 to week 20, eyes treated with triamcinolone plus prompt laser showed a significant improvement in visual acuity, almost matching the gains achieved by the ranibizumab-treated eyes. Shortly thereafter, however, a precipitous drop in visual acuity occurred in the triamcinolone-treated eyes, and at 52 weeks, outcomes for triamcinolone-treated eyes were no different than they were for eyes receiving a sham anti-VEGF injection or prompt laser. What explains this sharp decline after week 20?

One of the prominent side effects of corticosteroids is cataract formation. At 1 year, visual acuities of eyes that were phakic at baseline were no better than for eyes that received the sham anti-VEGF injections with prompt laser (Figure 1). For eyes that were pseudophakic at baseline, however, visual acuities for the triamcinolone-treated eyes equaled or surpassed those for the ranibizumab-treated eyes. During the 2 years of follow-up, 55% of eyes that were phakic at baseline had cataract surgery, which undoubtedly affected visual acuity results.

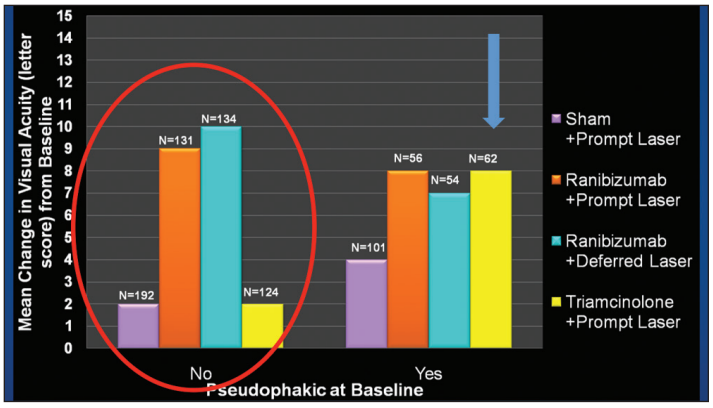

Figure 1. At 1 year, visual acuities of eyes that were phakic at baseline were no better than for eyes that received the sham anti-VEGF injections with prompt laser.[2]

Elevated Intraocular Pressure/Glaucoma	Sham +Prompt Laser N = 293	Ranibizumab +Prompt Laser N = 187	Ranibizumab +Deferred Laser N = 188	Triamcinolone +Prompt Laser N = 186
Increase ≥10 mmHg from baseline	8%	9%	6%	42%
IOP ≥30 mmHg	3%	2%	3%	27%
Initiation of IOP-lowering meds at any visit*	5%	5%	3%	28%
Number of eyes meeting ≥1 of the above	11%	11%	7%	50%
Glaucoma surgery**	<1%	1%	0	1%

*Excludes eyes with IOP lowering medications at baseline
**Includes 2 filter and 2 cilliary body destruction

Figure 2. Triamcinolone was associated with a significant risk of elevated IOP, requiring medical and possibly surgical therapy.[2]

In summarizing findings from the Protocol I study, the researchers noted that intravitreal triamcinolone combined with focal grid laser

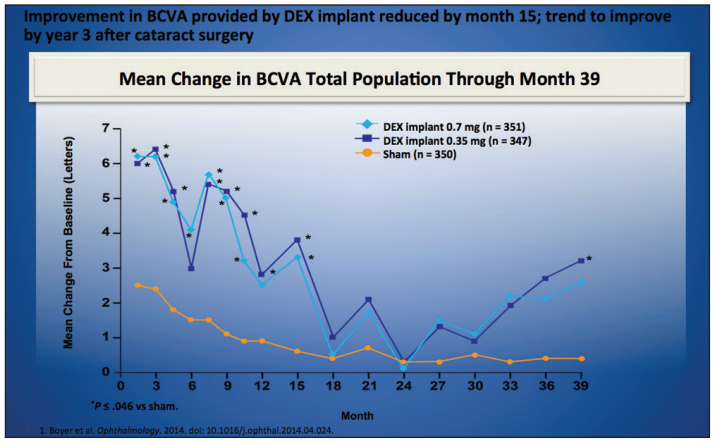

Figure 3. The mean change in visual acuity from baseline during months 18 to 24 is likely because of cataract formation in the eyes that were phakic at baseline, followed by cataract surgery after month 18.

did not result in superior visual outcomes compared with laser alone, despite a greater reduction in retinal thickening at 1 year but not at 2 years. In an analysis limited to pseudophakic eyes, however, the triamcinolone group's visual acuity outcomes appeared to be of similar magnitude to those of the two ranibizumab groups, but they were associated with an increased risk of IOP elevation.

DEXAMETHASONE INTRAVITREAL IMPLANT

The dexamethasone 0.7 mg intravitreal implant is FDA-approved for the treatment of DME. The dexamethasone implant is a sustained-release, biodegradable implant containing a solid polymer matrix containing 0.7 mg of dexamethasone. It degrades over time to lactic acid and glycolic acid in the vitreous cavity. It is administered by injection as an in-office procedure using a patented intravitreal applicator. In the 3-year, randomized, sham-controlled MEAD trial,[3] eyes were randomly assigned to treatment with dexamethasone 0.7 mg or 0.35 mg or sham. They were evaluated for retreatment with either a sham injection or the dexamethasone implant every 3 months after the 6-month visit, but retreatment was allowed no more than every 6 months. We have since learned that the dexamethasone implant probably lasts only 3 to 4 months, therefore, many eyes in this trial may have been undertreated. Nevertheless, a maximum of seven treatments were allowed over 3 years.

At the end of 3 years, 22.2% of eyes in the dexamethasone 0.7-mg group had gained 15 or more letters of visual acuity, compared with 18.4% in the dexamethasone 0.35 mg group, and 12% in the sham group. The difference between visual acuity gains with the dexamethasone 0.7 mg implant and the sham group was statistically significant ($P < .001$).

The mean change in visual acuity from baseline over 3 years reflects a complication of corticosteroids, because the vision drops, particularly during months 18 to 24, and then it starts to improve again (Figure 3). This is likely because of cataract formation in the eyes that were phakic at baseline, followed by cataract surgery after month 18.

In eyes that were phakic at baseline, 67.9% that were treated with the dexamethasone 0.7 mg implant had a cataract-related adverse

TABLE 1. IOP SAFETY PARAMETERS IN THE MEAD STUDY[3]

Parameter	DEX Implant 0.7 mg (n = 347)	DEX Implant 0.35 mg (n = 343)	Sham (n = 350)
IOP at any visit during the study, % (n)			
IOP ≥ 25 mm Hg	32.0 (111)	27.4 (94)	4.3 (15)
IOP ≥ 35 mm Hg	6.6 (23)	5.2 (18)	0.9 (3)
Increase of IOP ≥ 10 mm Hg from baseline	27.7 (96)	24.8 (85)	3.7 (13)
Use of IOP-lowering medication, % (n)	41.5 (144)	37.6 (129)	9.1 (32)

event, and 59.2% of those patients had cataract surgery during the 3-year trial. This is in contrast to the sham-treated eyes, where the rate of cataract removal was 7.2% at 3 years.

Once again, development of cataract in corticosteroid-treated eyes is not the whole story, as these eyes are also at risk for elevated IOPs. Overall, in the MEAD trial,[3] 36% of eyes that received the dexamethasone 0.7 mg implant had adverse events related to elevated IOPs or glaucoma, in contrast to 5.1% of sham-treated eyes (Table 1).

These statistics are not surprising, because these are well-known class effects for corticosteroid use in the eye.

FLUOCINOLONE INTRAVITREAL IMPLANT

The fluocinolone 0.19-mg intravitreal implant is FDA-approved for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP. This implant is a cylindrical tube, a fraction of the size of a grain of rice, that is inserted into the eye through a self-sealing wound via a 25-gauge applicator. This is a non-bioerodable drug delivery system, which stays in the eye, as opposed to the dexamethasone implant, which is injected into the eye and then slowly undergoes absorption or bioerosion over time. The fluocinolone implant releases a sub-microgram daily dose of the steroid over at least a 3-year period.

The FAME-A and FAME-B phase 3 clinical trials[4] compared fluocinolone acetonide 0.19 mg and 0.5 mg with sham injection. All patients had a diagnosis of DME and had received at least one previous laser treatment. These were eyes with chronic, long-standing DME and had undergone multiple prior treatments. Compared with eyes enrolled in the RISE/RIDE[1] and VIVID/VISTA[5] trials of aflibercept, eyes in the FAME trials[4] had worse visual acuities, ranging from 20/50 to 20/400. Also of note, optical coherence

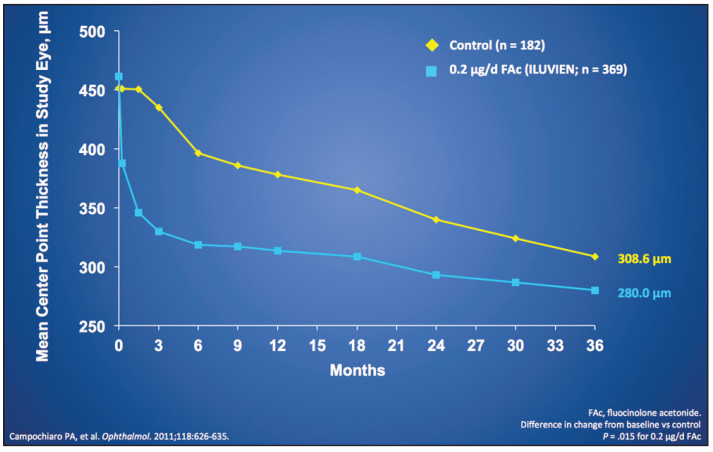

Figure 4. OCT showed an immediate reduction in the center thickness of fluocinolone-treated eyes; center thickness in the control eyes decreased slowly over time.

TABLE 2. IOP-RELATED EVENTS OVER 36 MONTHS[4]

Subjects, % (Study Eye)	Control (n = 185)	0.2 µg/d FAc (ILUVIEN) (n = 375)
IOP ≥ 30 mm Hg	4	20
Any IOP-lowering meds[a]	14	38
Incisional IOP-lowering surgery	1	5

tomography (OCT) was performed with the older time-domain technology in the FAME trials. One of the reasons for this is that the FAME trials[4] were initiated in 2005, before the anti-VEGF era began. Patients were monitored for 3 years. Additional laser therapy—in either treatment arm or the sham arm—was allowed after week 6 at the investigator's discretion. Re-treatment with fluocinolone could be considered at any point between month 12 and month 33, if eligible. The primary endpoint was at month 24 and the study ended at month 36.[6]

At the 2-year mark, 28.7% of eyes treated with fluocinolone met the primary endpoint, gaining 15 or more letters of visual acuity from baseline, while 16.2% of control eyes met the primary endpoint.

It is interesting to see that the control arm improved over time. These were eyes that received other corticosteroid injections or other laser treatments, and when the anti-VEGF era began, they received anti-VEGF injections. So the control arm could be considered a standard-of-care arm for that time frame.

FDA Labels for Corticosteroids

By Nancy M. Holekamp, MD

Intravitreal triamcinolone, 4 mg, has been used for more than a decade for treating DME. Although it has been rigorously studied by the DRCR Network, it is not approved for treating DME. In fact, the Kenalog label states, "not for intraocular use."

The dexamethasone 0.7-mg intravitreal implant received FDA approval in June 2014 for eyes with DME that are pseudophakic or scheduled for cataract surgery, because of its propensity to cause accelerated cataract growth. Three months later, the FDA approved a revised label, and the dexamethasone implant is now indicated to treat adults with DME, with no caveat about whether the patient is phakic or pseudophakic.

The fluocinolone 0.19-mg intravitreal implant received FDA approval in September 2014. According to the label, this implant, "… is indicated for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure." The FDA's goal is not to eliminate risks but to mitigate or reduce the risks associated with a certain drug, which in this case is an intraocular corticosteroid.

What does this mean? Some examples of previous treatment with a course of corticosteroid include:

- topical prednisolone acetate
- topical difluprednate 0.05%
- sub-Tenon triamcinolone
- intravitreal triamcinolone
- intravitreal dexamethasone
- oral prednisone

Clinicians must decide what constitutes a substantial prior course of corticosteroids for a specific patient. Most retina specialists likely would agree that a fair challenge would be intravitreal triamcinolone or intravitreal dexamethasone injection.

This begs the question: Did patients in the FAME trials who were previously treated with a course of corticosteroids (and hence meet the current FDA label) need IOP-lowering surgery. The answer is no (Figure). Of the patients enrolled in FAME-A and FAME-B,[1] 72 met the criteria of the current FDA label. Of those 72 patients, none required IOP-lowering surgery in the study eye. Of the 294 patients who had no prior exposure to corticosteroids, 18 required IOP-lowering surgery. Again, the purpose of the FDA label is to mitigate the risks, and we can minimize that risk by requiring all patients who receive the fluocinolone implant to have prior exposure to corticosteroids and not demonstrate elevated IOPs.

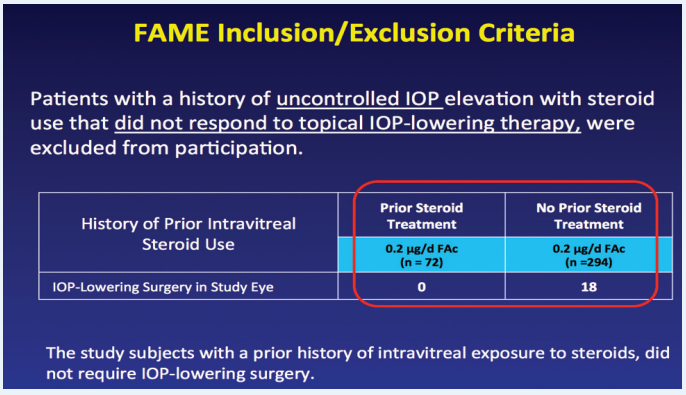

Figure. None of the patients who were previously treated with a corticosteroid and did not have a clinically significant rise in IOP required IOP-lowering surgery.[1]

The FDA label also includes the terminology, "… a clinically significant rise in intraocular pressure." Does this mean any increase in IOP? An increase requiring more than two IOP-lowering medications? An IOP uncontrolled by topical drops? An IOP increase requiring surgery? The exact meaning is unclear, but the FDA has stipulated that the only contraindication is for patients with glaucoma who have a cup-to-disc ratio of greater than 0.8. Therefore, none of the scenarios mentioned above related to IOP are contraindications for using the fluocinolone 0.19-mg implant.

The take-home message is this: The FDA regulates drugs and devices. It does not regulate the practice of medicine. Therefore, clinicians considering using the fluocinolone implant for patients with DME will decide what an appropriate course of prior corticosteroids would be and what a clinically significant elevation of IOP would be.

1. Campochiaro PA, Brown DM, Pearson A, et al.; FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118:626-635.

Fluocinolone-treated eyes showed an immediate reduction in the center thickness on OCT, while center thickness in the control eyes decreased slowly over time, but never caught up with the fluocinolone-treated eyes (Figure 4).

Cataract-related events occurred in 82% of fluocinolone-treated eyes compared with 50% of eyes in the control arm, where injections of other corticosteroids, such as triamcinolone acetonide, may have been given. Cataract extraction was performed in 80% of the fluocinolone-treated eyes and 27% of the control eyes.

Looking at IOP-related events, we see that the numbers are relatively small in the control arm: 4%, 14%, and 1% (Table 2). In contrast, in the fluocinolone-treated eyes, 20% had an IOP greater than 30; 38% required some form of IOP-lowering medication, and incisional IOP-lowering surgery was required in 5% of eyes.

The FAME study[4] met its primary endpoint of BCVA greater than or equal to 15-letter improvement from baseline at month 24, and these improvements were sustained to month 36. Retinal thickness decreased over the 36 months. Cataract development and IOP elevations were among the most common adverse events and consistent with well-characterized effects of this drug class.

SUMMARY

Corticosteroids are part of the new paradigm in the management and treatment of diabetic macular edema. Retina specialists can be reassured by clinical trial data for all three types of intravitreal corticosteroids that the expected steroid class adverse events of cataract and elevated IOP can be satisfactorily managed in patients with DME for whom this therapy is beneficial. ■

1. Nguyen QD, Brown DM, Marcus DM, et al.; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119:789-801.
2. Elman MJ, Aiello LP, Beck RW, et al.; Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117:1064–1077.
3. Boyer DS, Yoon YH, Belfort R Jr, et al.; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121:1904–1914.
4. Campochiaro PA, Brown DM, Pearson A, et al.; FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Ophthalmology. 2011;118:626-635.
5. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology*. 2014;121:2247-2254.
6. Campochiaro PA, Brown DM, Pearson A, et al.; FAME Study Group. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119:2125-2132.

Corticosteroid Implant for Severe, Persistent DME After Anti-VEGF Therapy

By Alexander Eaton, MD

This 68-year-old man has had type 2 diabetes for 20 years. He has minimal ATE risk factors and is pseudophakic. He developed diabetic macular edema (DME) in his right eye in 2010 and subsequently received bevacizumab, ranibizumab, and laser photocoagulation. He has had prior exposure to corticosteroids without a significant increase in intraocular pressure (IOP). Fluorescein angiography after these various treatments showed leakage and significant capillary dropout (Figure 1). OCT revealed significant macular edema. The patient's visual acuity was 20/50.

The patient received a combination of laser and two ranibizumab injections, which resulted in minimal improvement in the edema and worsening of visual acuity (20/80 OD) (Figure 2).

At this point, the question was: What should we do next? Should we continue with more anti-VEGF therapy? Is laser an option? Should we try intravitreal corticosteroids? Because of the patient's poor response to ranibizumab, I elected to treat with the fluocinolone acetonide 0.19-mg intravitreal implant.

Two weeks later, the patient's visual acuity had improved to 20/40, and the edema had largely cleared (Figure 3). Two months later, visual acuity was 20/50, and some trace edema was seen. No additional treatments were given. Fluorescein angiography showed reduced leakage following treatment with the fluocinolone implant (Figure 4).

The patient's IOP had risen to 25 mm Hg during this time, but was reduced and controlled with a combination of brimonidine and timolol.

This patient was a good candidate for corticosteroid treatment. He had severe, persistent DME after anti-VEGF therapy. He was pseudophakic and had previous triamcinolone in his fellow eye without a clinically significant increase in IOP. His visual acuity improved to 20/50 and the edema resolved. He had a mild IOP elevation, which was controlled with topical anti-glaucoma drops. This case also demonstrates that fluocinolone can be effective when there is extensive capillary drop out. The patient was satisfied with his treatment and outcome.

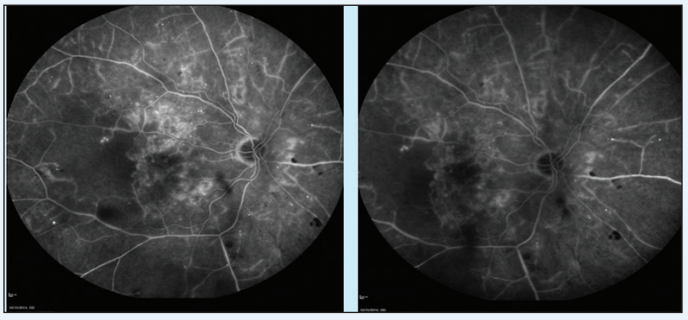

Figure 1. Leakage and significant capillary dropout persists after prior treatment with bevacizumab, ranibizumab, and laser.

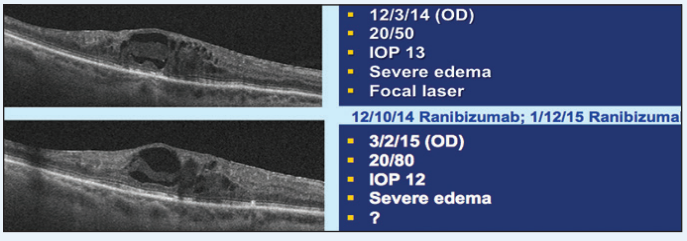

Figure 2. Laser photocoagulation and two ranibizumab treatments produced minimal improvement in the edema and worsening of visual acuity.

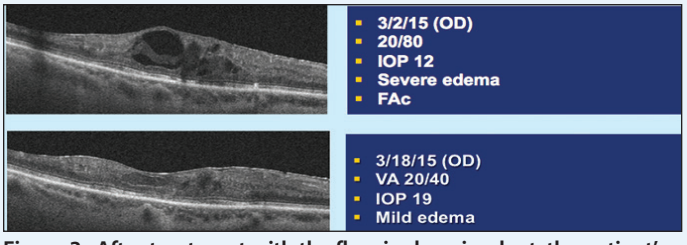

Figure 3. After treatment with the fluocinolone implant, the patient's visual acuity improved and a trace amount of edema remained.

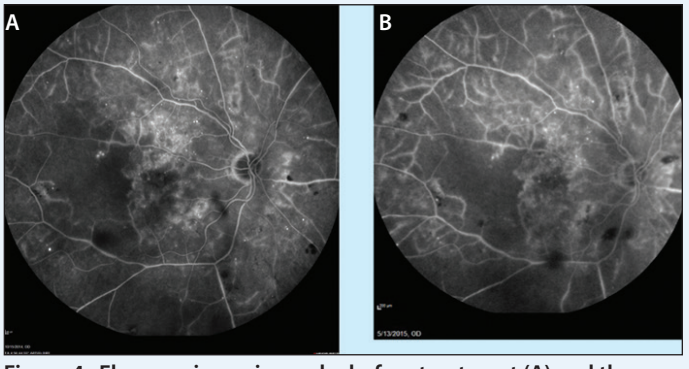

Figure 4. Fluorescein angiography before treatment (A) and then after treatment, which shows reduced leakage following fluocinolone treatment (B).

Recalcitrant DME After Anti-VEGF and Dexamethasone

By Szilárd Kiss, MD

This patient, a 66-year-old man, has type 2 diabetes of 20 years' duration. He has hypertension and hypercholesterolemia, and he is obese. His HbA1c is 7.6. Prior to his initial visit with me, the patient, who is phakic, had three focal laser treatments for diabetic macular edema (DME), which was affecting his vision.

On initial presentation, the patient's visual acuity was 20/70 in the right eye and 20/40 in the left eye. Both eyes had significant macular edema, worse in the left eye (Figure 1). Fluorescein angiography revealed diffuse microvascular abnormalities, leakage, and trimming of the vascular trees. In the macular regions of both eyes, some leakage corresponded to the swelling on optical coherence tomography (OCT).

After discussing treatment options, the patient and I elected to treat with ranibizumab. Following eight injections in each eye, the patient's visual acuity was 20/80 in the right eye and 20/70 in the left eye. OCT

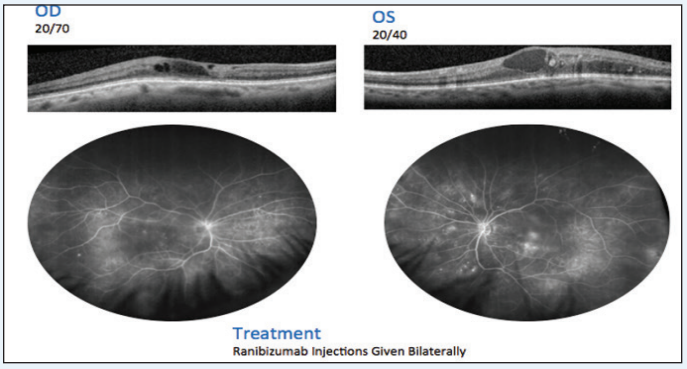

Figure 1. OCT showed significant macular edema, and fluorescein showed diffuse microvascular abnormalities, leakage, and trimming of the vascular trees.

Figure 2. Following eight bilateral ranibizumab injections, visual acuity worsened, and OCT showed continued, and even worsening, DME.

Figure 3. After three monthly bilateral aflibercept injections, visual acuity was unchanged, edema had improved but was still considerable, particularly in the left eye.

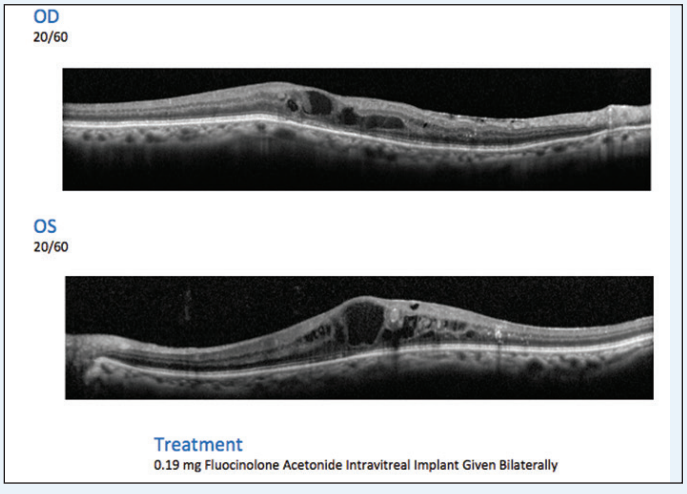

Figure 4. After dexamethasone, visual acuity improved slightly, but edema remained unchanged OD and was somewhat worse OS.

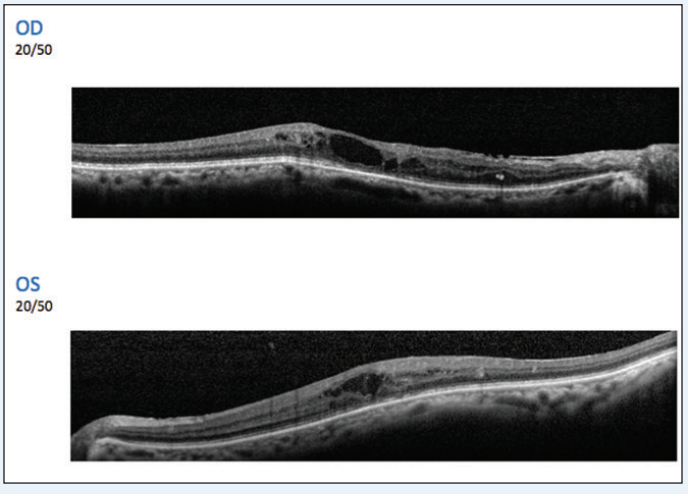

Figure 5. After fluocinolone, visual acuity improved to 20/50 OD and 20/50 OS. The edema improved but did not completely resolve.

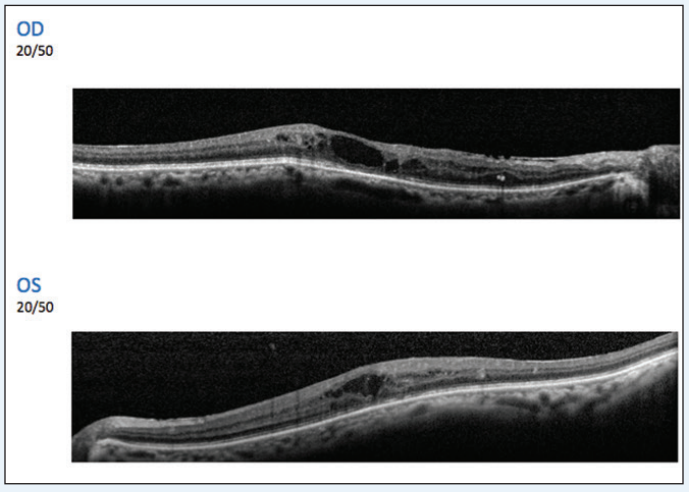

Figure 5. After fluocinolone, visual acuity improved to 20/50 OD and 20/50 OS. The edema improved but did not completely resolve.

showed continued, and even worsening, DME (Figure 2). The patient's blood pressure and HbA1c were unchanged from baseline.

At this point, we decided to switch to aflibercept. After three monthly injections in each eye, the patient's visual acuity was essentially unchanged. The edema had improved but was still considerable, particularly in the left eye (Figure 3).

Once again, we decided to change course and treat with the dexamethasone 0.7 mg intravitreal implant in each eye. Three months later, the patient's visual acuity improved slightly, but the edema was unchanged in the right eye and somewhat worse in the left eye (Figure 4).

At this point, the fluocinolone acetonide 0.19 mg implant became available, and the patient and I elected to switch to it rather than add an anti-VEGF agent. Because the patient's IOP did not change with the dexamethasone injections, I felt comfortable using the fluocinolone implant in both his eyes.

Two months after treatment with one fluocinolone implant in each eye, the patient's visual acuity improved to 20/50 in the right eye and 20/50 in the left eye. The edema improved but did not resolve completely (Figure 5).

Since I started caring for this patient, his edema was most improved with the fluocinolone implant. Interestingly, like many of my patients being treated with the fluocinolone implant, this patient reported improvement in his visual abilities, not necessarily the visual acuity that we measured in the examination room. I recently saw the patient about 8 months after fluocinolone treatment, and we elected not to treat at that time. He is doing well and is happy with his results.

Favorable Visual Acuity and Anatomic Outcomes With Fluocinolone Treatment

By Szilárd Kiss, MD

This 53-year-old man, who is phakic, was diagnosed with pre-diabetes 4 years prior to his visit to my clinic. He reported decreased vision in both eyes. He was controlling his condition with diet but had not seen any doctor since his pre-diabetes diagnosis. The patient's HbA1c was 7.9. He was taking only aspirin and had not received any therapy. After seeing me, the patient was diagnosed with type 2 diabetes and is now being treated for his diabetes.

On initial presentation, the patient's visual acuity was 20/200 in the right eye and 20/60 in the left eye. Optical coherence tomography (OCT) showed considerable macular thickening with exudate in both eyes (Figure 1). Ultra widefield color photographs showed nonproliferative diabetic retinopathy confined mostly to the posterior pole with exudation and intraretinal hemorrhages.

The patient was treated with four aflibercept injections in each eye, and his visual acuity improved to 20/150 in the right eye and remained 20/60 in the left eye. The macular edema improved somewhat but not to the extent we had hoped (Figure 2).

We decided to change course and use the dexamethasone implant in both eyes. Two months later, visual acuity improved to 20/100 in the right eye and 20/50 in the left eye. The macular edema in the right eye improved, but considerable retinal thickening with some intraretinal

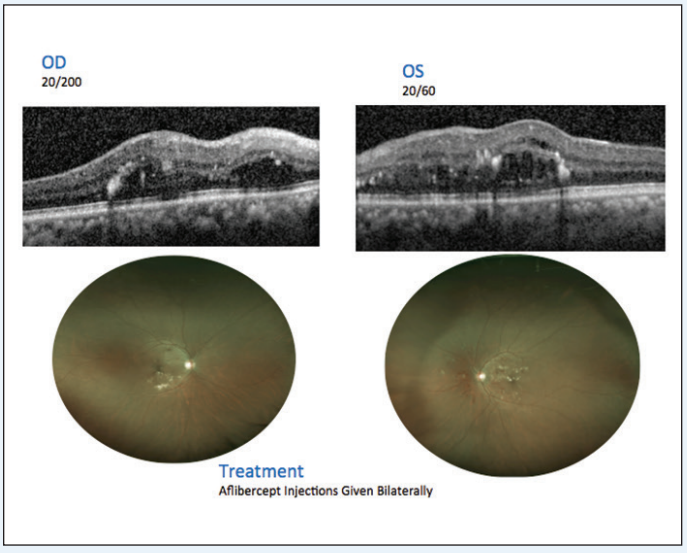

Figure 1. Patient had considerable macular thickening with exudate in both his eyes and nonproliferative diabetic retinopathy confined mostly to the posterior pole with exudation and intraretinal hemorrhages.

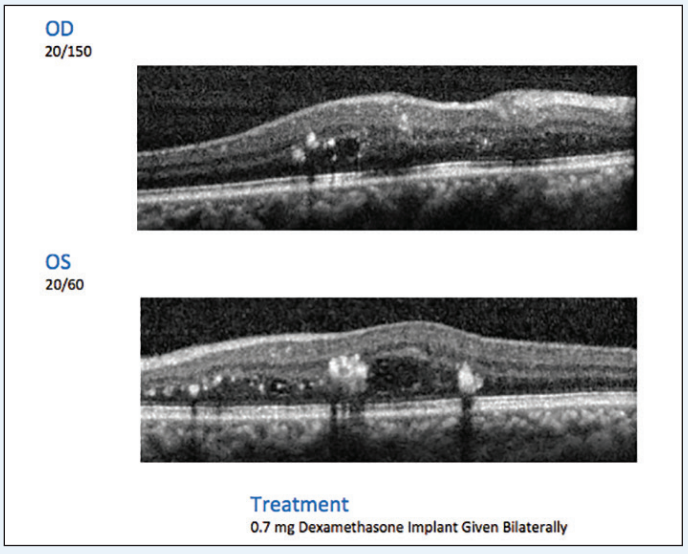

Figure 2. After four aflibercept injections in each eye, visual acuity and macular edema improved somewhat.

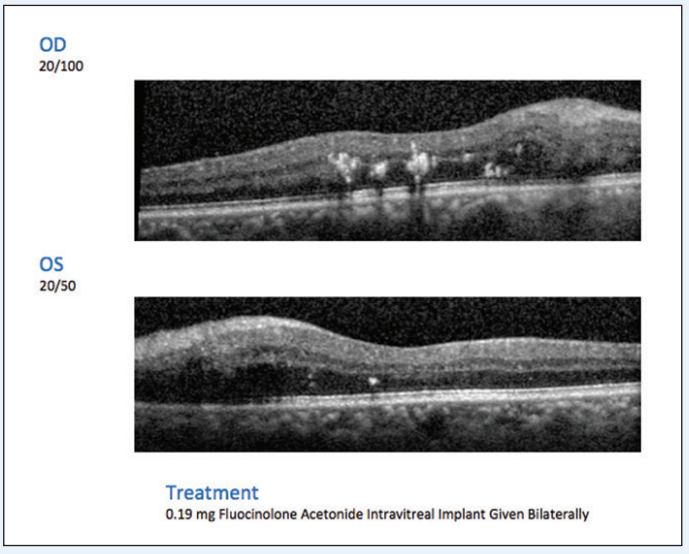

Figure 3. After treatment with the dexamethasone implant, visual acuity improved but considerable edema remained.

cystic changes and exudation remained (Figure 3). In the left eye, the visual acuity improved, but considerable edema persisted.

The patient and I elected to treat with the fluocinolone implant in each eye. Note that his intraocular pressure did not change significantly during his entire prior treatment course. One month following implantation of a fluocinolone device in each eye, the patient's visual acuity was 20/25 in the right eye and 20/30 in the left eye. Although OCT shows evidence of exudation, particularly in the left eye, there's considerable improvement and near resolution of the DME (Figure 4).

I will continue to monitor the patient and encourage him to control his blood pressure and blood sugar so that he will not require further treatment. We were both impressed with the visual and anatomic outcome following treatment with the fluocinolone intravitreal implant.

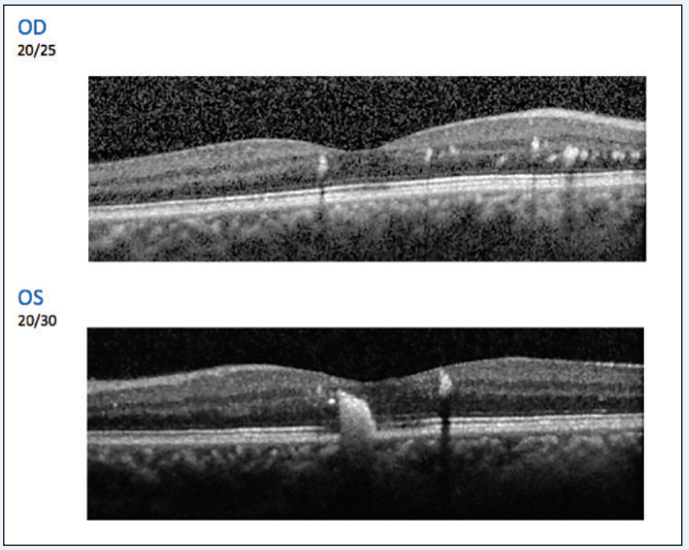

Figure 4. One month after fluocinolone treatment, visual acuity was 20/25 OD and 20/30 OS. DME has nearly resolved.

Anti-VEGF Therapy for Treatment-Naïve DME

By Alexander Eaton, MD

This 33-year-old woman has a 19-year history of type 1 diabetes, which is poorly controlled. Her ATE risk factors include hypertension and HbA1c levels ranging from 7.8 to 13.3. She is phakic and has diabetic macular edema (DME) in her left eye. She had no prior treatments for DME or diabetic retinopathy.

At the patient's initial visit, I noted a scaphoid hemorrhage inferiorly. Fluorescein angiography revealed extensive capillary drop-out and proliferative changes (Figure 1). Optical coherence tomography (OCT) showed significant macular edema. Her visual acuity was 20/50 OS.

About 1 month after initial treatment with laser photocoagulation and ranibizumab, the macular edema resolved, and the patient's visual acuity improved to 20/25. Six weeks later, I noted moderate recurrence of the edema. Treatment with ranibizumab again resolved the edema (Figure 2).

With treatment, the scaphoid hemorrhage improved markedly, and the hemorrhaging and leakage cleared significantly (Figure 3).

This patient was an ideal candidate for anti-VEGF therapy. She was young, phakic, and treatment-naïve, with severe DME and proliferative diabetic retinopathy. She responded well to treatment. Her visual acuity improved from 20/50 to 20/25, and the edema resolved. The patient was satisfied with her treatment and outcome.

The only downside in this case is a tendency for the edema to recur, probably about every 6 to 8 weeks. I will continue to treat with anti-VEGF therapy for the next several months. If the recurrences continue for a year or more, I will consider a longer-acting treatment option. However, as the patient has a clear lens, I am reluctant to move to a steroid, unless it is clear that ongoing treatment is needed or if the edema did not resolve completely with anti-VEGF therapy.

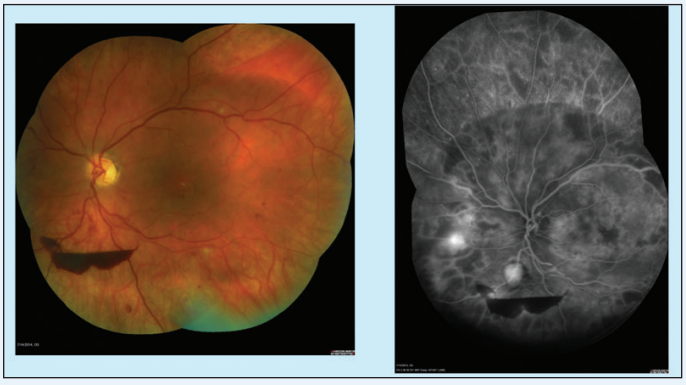

Figure 1. The patient had a scaphoid hemorrhage inferiorly, extensive capillary drop-out, proliferative changes, and macular edema.

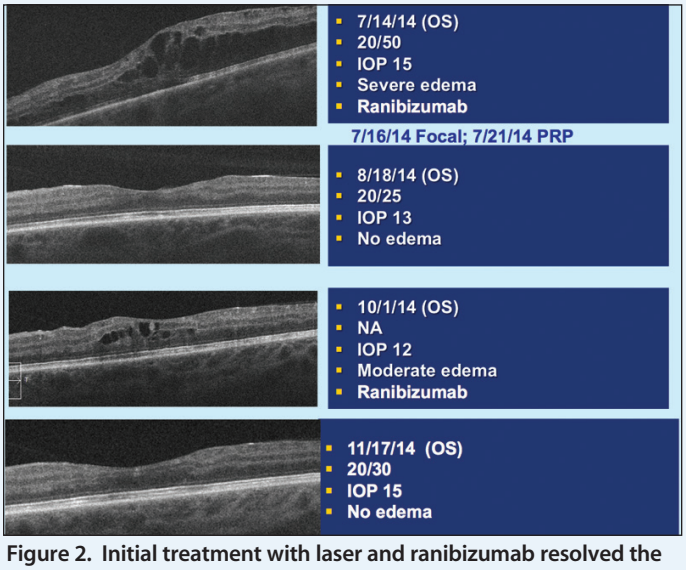

Figure 2. Initial treatment with laser and ranibizumab resolved the edema and improved vision. A recurrence at 6 weeks was re-treated with ranibizumab, which resolved the edema.

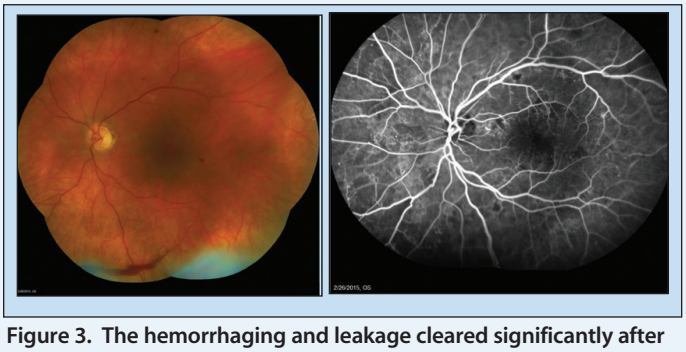

Figure 3. The hemorrhaging and leakage cleared significantly after treatment with ranibizumab.

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NEW PARADIGMS IN THE MANAGEMENT AND TREATMENT OF DIABETIC MACULAR EDEMA

1 *AMA PRA Category 1 Credit™* Expires March 1, 2017

1. In a study of Medicare fee-for-service beneficiaries receiving treatment for DME during a 3-year period, approximately what percentage of eyes appeared to have been "cured" with anti-VEGF monotherapy?

a. 0%
b. 25%
c. 50%
d. 75%

2. In the FAME phase 3 trials, what was the time point researchers employed to differentiate chronic from non-chronic DME?

a. 1 year
b. 18 months
c. 2 years
d. 3 years

3. Which of the following cytokines seems insensitive to the level of diabetic retinopathy present?

a. VEGF
b. IL-1b
c. IL-6
d. MCP-1

4. In a small study comparing triamcinolone and bevacizumab in eyes with DME, researchers found that the steroid reduced the levels of most of the cytokines and also lowered VEGF levels by what percentage?

a. 0%
b. 20%
c. 60%
d. 80%

5. Approximately what percentage of the population are high steroid responders, ie, people whose IOPs rise more than 15 mm Hg above their baseline upon exposure?

a. 5%
b. 15%
c. 18%
d. 25%

6. An almost intrinsic relationship exists between the risk of IOP elevation from steroid exposure and which of the following factors?

a. Location of administration
b. Potency of steroid molecule
c. Dosage of the steroid given
d. Duration of steroid use

7. Which of the following entry criteria for the FAME phase 3 clinical trials were significantly different from those for the RISE and RIDE and VIVID and VISTA trials?

a. Age
b. Ethnicity
c. Visual acuity
d. Diabetes duration

8. Which of the following is an example of previous treatment with a course of corticosteroid?

a. Topical prednisolone acetate
b. Intravitreal triamcinolone
c. Oral prednisone
d. All of the above

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Describe the current epidemiology of diabetic macular edema and diabetic retinopathy	———	———	———
Educate patients on the ophthalmic implications of systemic diabetes management	———	———	———
Assess clinical studies involving new approaches to treat DME	———	———	———
Use expert case examples to differentiate between clinical study dosing protocols and alternative dosing schedules	———	———	———
Evaluate treatment options and develop a treatment regimen that can reduce patient burden and practice capacity	———	———	———
Explain the early warning signs of elevated IOP	———	———	———
Identify effective management strategies for patients requiring intervention	———	———	———

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME). .

Name and e-mail _____

Do you feel the program was educationally sound and commercially balanced? ❒ Yes ❒ No

Comments regarding commercial bias:

_____

_____

Rate your knowledge/skill level prior to participating in this course: **5 = High, 1 = Low** _____

Rate your knowledge/skill level after participating in this course: **5 = High, 1 = Low** _____

Would you recommend this program to a colleague? ❒ Yes ❒ No

Do you feel the information presented will change your patient care? ❒ Yes ❒ No

Please identify how you will improve/change:

____ Change the management and/or treatment of patients. Please specify

_____

_____

____ Create/revise protocols, policies, and/or procedures. Please specify

_____

_____

If no, please identify the barriers to change.

_____

_____

Please list any additional topics you would like to have covered in future Evolve Medical Education LLC CME activities or other suggestions or comments.

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