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# CASES IN REFINING MANAGEMENT OF DIABETIC MACULAR EDEMA


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## CME REVIEWER FOR NEW YORK EYE AND EAR INFIRMARY OF MOUNT SINAI

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The prevalence of diabetic retinopathy (DR) and diabetic macular edema (DME) is on the rise. Although antivascular endothelial growth factor therapy effectively treats DME and DR, it does not target the inflammatory aspect of DME. As such, a significant proportion of patients might not experience an improvement in their visual acuity or might continue to have persistent DME that threatens long-term potential for visual acuity gains. Using steroids as a complementary or alternative therapy can be useful in these patients. However, intraocular pressure elevations have been observed with the use of intravitreal steroid implants. Intraocular pressure elevation following intravitreal steroid administration follows a predictable course, and, in most cases, can be safely managed in the retina practice. The desired results of this activity are to update retina specialists and other ophthalmologists on current and new approaches to treating DR and DME.

### TARGET AUDIENCE

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### LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Recognize the different mechanisms of disease that drive treatment selection for patients with DME
- Explain the implications of persistent edema for selecting treatment for patients with DME
- Discuss management of IOP elevations due to intravitreal steroid implants
- Develop long-term treatment plans for patients with DME

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## INTRODUCTION

The prevalence of diabetes mellitus (DM) and diabetic retinopathy (DR), including diabetic macular edema (DME), is on the rise. In the next 12 years alone, DM prevalence is projected to increase by more than 50%, with the southern United States seeing the greatest increases.[1] Because the risk of DR and its progression rises with increasing levels of hemoglobin A1c,[2,3] the burden of DR will increase among poorly controlled patients with DM. Therapeutic options for the management of DR and DME have expanded significantly in recent years, and clinical trials offer insights into optimal treatment approaches. In this review, an experienced panel of retina specialists will put the management of DME into a modern context through the discussion of a series of cases. Our objectives are to review the underlying mechanisms of DME, the significance of persistent edema, and their implications for the selection of therapy. We will discuss options for treating eyes with DME, including the management of complications of therapy, such as cataract and glaucoma associated with steroid implants. At the completion of this activity, retina specialists and other ophthalmologists who treat DME will be better able to develop long-term strategies for the management of eyes with DME.

*—Baruch D. Kuppermann, MD, PhD (Chair)*

## LONG-TERM FLUID MANAGEMENT IN DIABETIC MACULAR EDEMA

***Charles C. Wykoff, MD, PhD***

Pharmacologic inhibition of vascular endothelial growth factor (VEGF) works very well in DME, improving macular fluid in many treated eyes. There are, however, at least 2 key limitations of current anti-VEGF therapy. One limitation is durability: the therapeutic effect does not last indefinitely, and repeated retreatments are often necessary. A second limitation is efficacy: many eyes never achieve optimal visual function even if their DME resolves.

Limited durability of anti-VEGF therapy imposes a substantial treatment burden in many eyes. In the DRCRnet's (Diabetic Retinopathy Clinical Research Network's) Protocol T study evaluating aflibercept, bevacizumab, or ranibizumab for DME, a median of 23 visits was required through 2 years, and the mean number of injections given during that time was 15 to 16, depending on the agent.[4] Treatment burden appears to diminish over time in many eyes. In the open-label extension following the pivotal RISE and RIDE trials of ranibizumab for DME, the annualized rate of ranibizumab injections in years 4 to 5 was fewer than 4, with approximately 25% of eyes requiring no additional injections during this period (n = 121 at month 54).[5] In the Protocol I study of ranibizumab for DME, by the fifth year of treatment, the annual number of clinical visits was only 4 to 5 and the ranibizumab injection rate was very low.[6] In the ENDURANCE open-label extension following the VIVID and VISTA trials of aflibercept for DME, the mean number of aflibercept injections given in years 4 and 5 was 4.5 and 3.4, respectively.[7,8]

Among the lessons learned from these long-term studies is that the visual gains achieved with initial anti-VEGF treatment for DME can persist for years. Although the treatment burden does diminish with time, it does not disappear completely. Many eyes will require ongoing retreatment on an as-needed basis.

A clinically relevant question that we have not yet answered from these trials is when to re-treat. At what point is the next injection warranted? There are several issues to consider. Should we hold injections as long as the visual acuity is stable? Should we inject if we see fluid recurring on optical coherence tomography (OCT) imaging, even if visual acuity is preserved? If fluid does not completely resolve with anti-VEGF therapy, should the treatment regimen be expanded to include other modalities, such as steroids, which might target other mechanisms of persistent edema? There is also the issue of DR. Anti-VEGF therapy not only treats DME, it also slows the progression of DR and can improve DR in many cases.[9] If the DME clears and further injections are withheld, but then the DR progresses to proliferative DR with associated visual loss, we might have missed an opportunity for disease modification by not continuing treatment once the DME had resolved. A case could be made for some frequency of long-term maintenance therapy in eyes with both DME and DR—including in eyes with good visual acuity and a dry macula—to preserve the central visual gains while holding off the DR.

## PATHOPHYSIOLOGY OF DIABETIC MACULAR EDEMA: MANAGING THE INFLAMMATORY COMPONENT

***Baruch D. Kuppermann, MD, PhD***

The pathophysiology of DME is complex and multifactorial. Hyperglycemia is the initial trigger and leads to alterations in the retinal microvasculature that promote vascular permeability and macular thickening from the resulting extravascular edema. High intravascular concentrations of glucose damage the pericytes—the small support cells that line the microvasculature and help maintain its health and function. In the eye and other tissues, glucose-mediated damage to retinal microvascular pericytes can lead to vasoconstriction, thickening of the capillary wall basement membrane, and, ultimately, tissue hypoxia and ischemia.[10] Ischemia promotes the release of VEGF, which not only increases vascular permeability, but is also proinflammatory.[11] Hyperglycemia and advanced glycosylation end products also cause oxidative stress that induces local tissue inflammation.[12] Local inflammation in the retina activates microglial cells, which then migrate into the subretinal space, where they accumulate and produce a variety of cytokines and other inflammatory mediators. These mediators, and their resulting oxidative stress, lead to dysfunction of the Müller cells and ultimately to intracellular edema, retinal excitotoxicity, and chronic inflammation. Dysfunction and disruption of the endothelial cellular junctions ensue, eventually leading to a modification of retinal blood flow, leukostasis, breakdown of the blood-retina barrier, vascular leakage, and extracellular edema **(Figure 1)**.[12-14] The pathologic result of both intracellular and extracellular edema manifests clinically as macular edema.

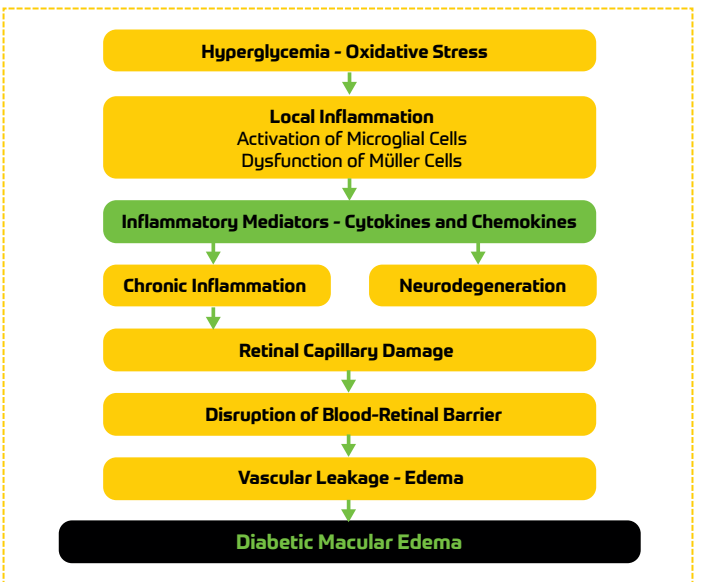


**Figure 1.** The multifactorial pathophysiology of diabetic macular edema[12-14]

**Table 1.** Relationship Between Aqueous Humor Cytokine Concentrations and Severity of Diabetic Retinopathy[15]

| ETDRS Retinopathy Severity Level | 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 | 252.5 | 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 |

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; IL, interleukin; IP-10, interferon-induced protein-10; MCP-1, monocyte chemoattractant protein-1; VEGF, vascular endothelial growth factor.

Clinical evidence for the role of inflammation in the pathophysiology of DME can be found in the aqueous humor, where concentrations of numerous inflammatory cytokines are significantly higher in diabetic eyes than in healthy control eyes.[15] The concentration of proinflammatory cytokines, such as interleukins, monocyte chemotactic protein-1, and interferon-induced protein-10, increased as DR severity worsened **(Table 1)**.[15]

The inflammatory aspect of DME provides a therapeutic target distinct from that of anti-VEGF therapy. Although VEGF inhibition does not significantly reduce the aqueous humor levels of the proinflammatory mediators listed previously, intravitreal injection of triamcinolone acetonide 4 mg does significantly reduce the aqueous humor levels **(Table 2)**.[16]

Using steroids as complementary therapy to VEGF inhibition can be useful in eyes that manifest incomplete therapeutic responses to anti-VEGF drugs alone. These eyes are common. In the Protocol I study, approximately 50% of 288 eyes with DME treated with ranibizumab demonstrated a rapid and persistent improvement in central subfield thickness (CST) on OCT **(Table 3)**.[17] Another 15% of these eyes had early but inconsistent responses, with early improvement that did not persist through the remainder of the study. Approximately 13% of the eyes were slow to improve and had variable long-term outcomes, whereas nearly 23% showed no clinically significant response to therapy.

**Table 3.** Subanalysis of DRCRnet Protocol I Data Demonstrating Predictive Value of Outcomes of Ranibizumab Treatment at Week 16[17]

| Categorization of OCT CSF Thickness Improvement of At Least 20% (1-Step Reduction of Log) From Baseline (N = 288) | | | |
|---|---|---|---|
| **Early and Consistent (n = 143)** | **Early but Inconsistent (n = 43)** | **Slow and Variable (n = 36)** | **Nonresponder (n = 66)** |
| Improved at the 16-week study visit and was sustained at the 32-week and 1-year study visits | Improved at the 16-week study visit but not at the 32-week or 1-year study visits | Did not improve at the 16-week study visit but did improve at the 32-week and/or 1-year study visits | Did not improve at the 16-week, 32-week, or 1-year study visit |
| 49.7% | 14.9% | 12.5% | 22.9% |

Abbreviations: CSF, central subfield thickness; DRCRnet, Diabetic Retinopathy Clinical Research Network; OCT, optical coherence tomography.

Steroids can be an appropriate therapy for eyes with chronic DME. In a long-term analysis of pooled data from the FAME (Fluocinolone Acetonide for Diabetic Macular Edema) studies comparing intravitreal fluocinolone acetonide implants to sham injections, 33% of 183 eyes with chronic DME (> 1.7 years) treated with fluocinolone acetonide gained ≥ 15 ETDRS (Early Treatment Diabetic Retinopathy Study) letters compared with only 12% of 103 eyes in the control group ($P < .001$).[18] In fact, in both the FAME A and FAME B studies, a significant difference between the fluocinolone acetonide group and the control group was seen only in eyes with chronic DME and not in eyes with shorter-duration DME.[18]

The effect of persistent edema in chronic DME was also seen in the RISE and RIDE ranibizumab trials.[19] The sham injection control group was allowed to receive ranibizumab after 2 years without treatment. In these eyes, there was minimal improvement in best-corrected visual acuity (BCVA) once they started receiving ranibizumab. Throughout a full year of dosing (year 3 of the study), the initially sham-treated group never achieved the visual acuity

**Table 2.** Effects of Anti-VEGF Therapy and a Steroid on Aqueous Humor Cytokine Levels[16]

| Cytokine | Cytokine Concentration, pg/mL | | | | | |
|---|---|---|---|---|---|---|
| | IVTA (n = 11) | | | Bevacizumab (n = 11) | | |
| | Preinjection | Postinjection | *P* Value* | Preinjection | Postinjection | *P* Value* |
| IL-6 | 29.9 | 13.8 | < .01 | 26.7 | 24.0 | .477 |
| IL-8 | 28.2 | 25.3 | .597 | 23.9 | 23.6 | .374 |
| IP-10 | 366.0 | 249.0 | .013 | 401.0 | 433.0 | .110 |
| MCP-1 | 3850 | 1090 | .010 | 3770 | 3840 | .594 |
| PDGF-AA | 68.7 | 37.1 | .016 | 81.0 | 72.7 | .722 |
| VEGF | 55.0 | 10.5 | .050 | 61.5 | 0.1 | < .01 |

Abbreviations: IL, interleukin; IP-10, interferon-induced protein-10; IVTA, intravitreal triamcinolone acetonide; MCP-1, monocyte chemoattractant protein-1; PDGF-AA, platelet-derived growth factor AA; VEGF, vascular endothelial growth factor.
* Wilcoxon signed rank text

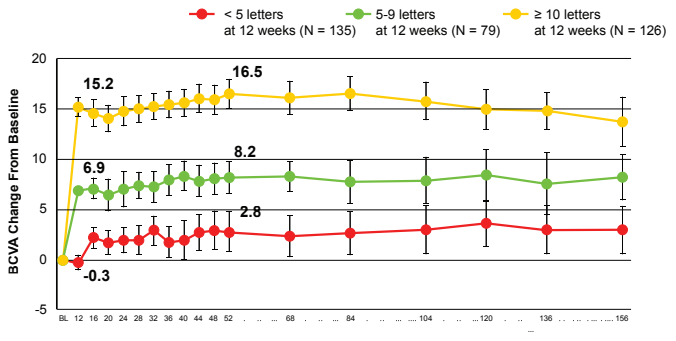


**Figure 2.** Visual gains at 12 weeks predicted visual gains at 3 years in the Protocol I study[21]

Abbreviations: BCVA, best-corrected visual acuity; BL, baseline.

Reprinted from *American Journal of Ophthalmology*, 172, Gonzalez VH, Campbell J, Holekamp NM, et al, Early and long-term responses to anti-vascular endothelial growth factor therapy in diabetic macular edema: analysis of Protocol I data, 72-79, Copyright 2016, with permission from Elsevier.

gains that were seen in the group treated with ranibizumab from the start. Similarly, in the RESTORE study comparing ranibizumab, macular laser, and a combination of the 2 for DME, eyes receiving only laser for the first 12 months and then crossed over to ranibizumab therapy required 2 years of treatment to achieve the visual gains achieved within less than 1 year in eyes receiving ranibizumab from the start.[20] These results suggest that perhaps there are inflammatory mediators that accrue during early untreated DME, so when anti-VEGF therapy is applied, it affects only 1 of the causes of DME in these eyes, leaving the inflammatory triggers untreated.

Data from a post hoc analysis of the DRCRnet's Protocol I data set demonstrate that we can identify the eyes that will not do well with anti-VEGF therapy alone quite quickly.[21] In this study, BCVA at 12 weeks—after 3 monthly injections—was highly predictive of BCVA at 3 years **(Figure 2)**.[21]

Eyes with DME that is refractory to anti-VEGF therapy often do well when steroid therapy is added to address the inflammatory component of the pathophysiology of DME. In 1 study, both refractory DME and treatment-naïve DME responded well to the dexamethasone implant, with mean improvements in BCVA of 8 and 12 ETDRS letters, respectively ($P < .001$), 6 months after implantation.[22] A meta-analysis of data from more than 3800 eyes with DME recalcitrant to ≥ 6 anti-VEGF injections demonstrated that the dexamethasone implant led to improved BCVA in all 15 included studies, by a statistically significant margin in most of the studies.[23]

## PANEL DISCUSSION: CONSIDERATIONS FOR SELECTING AND SWITCHING THERAPY

**DR KUPPERMANN:** On the basis of these data, I still start with anti-VEGF therapy for newly diagnosed and treatment-naïve DME. In eyes that do not manifest a clinically significant improvement in BCVA after a series of anti-VEGF injections, or in eyes with residual edema that is approaching chronic duration, I will often add or switch to steroid therapy in the form of the dexamethasone implant. But as Dr Wykoff pointed out previously, the threshold for making a change in therapy is not well defined. What should we consider to be the definition of a suboptimal response to anti-VEGF therapy?

**DR HOLEKAMP:** This is a difficult question. I consider both the visual acuity and the structural appearance of the macula on OCT. I do not have a specific answer. For me, it is more of an overall clinical impression rather than a hard-and-fast threshold of any type. One issue that I always consider is whether the patient has received rigorous anti-VEGF therapy. If therapy fails because it was suboptimally delivered, I will first increase the frequency of anti-VEGF therapy before declaring it a failure.

**DR WYKOFF:** There is no consensus on this issue. For me, it is an individualized decision for each patient. If the patient is improving and content with his/her visual acuity, I tend to stay the course with anti-VEGF therapy. If the improvement is slow or the patient is unhappy with the rate of improvement, I will consider adding a steroid earlier in the treatment course. I discuss this possibility broadly with my patients from the start. I tell them that several different medications can treat their condition; we can try several, and possibly combine them, to try to find the one that works best for them. I find that patients are more receptive to a change in therapy if I have told them ahead of time that it might be necessary.

## DRCRnet PROTOCOL U: DATA AND CLINICAL SIGNIFICANCE

***Nancy M. Holekamp, MD***

The previous sections have perfectly set up the topic of combined therapy for DME. Anti-VEGF therapy has transformed the treatment of DME. Nevertheless, a significant percentage of eyes will have persistent DME with or without reduced visual acuity after 6 or more anti-VEGF injections. In the DRCRnet's Protocol I and T studies, this percentage ranged from 32% to 66%, depending on the specific anti-VEGF agent.[4,24] In this section, we will review and discuss the recently released findings of the DRCRnet's Protocol U, Short-Term Evaluation of Combination Dexamethasone + Ranibizumab vs Ranibizumab Alone for Persistent Central-Involved DME Following Anti-VEGF Therapy.[25]

Protocol U was a prospective, multicenter clinical trial that included 129 eyes of 116 subjects with central-involving DME on clinical examination following a minimum of 3 injections with any anti-VEGF agent within the preceding 20 weeks.[25] Additionally, subjects were required to have a minimum elevation of CST on OCT that was both gender- and instrument-specific. Subjects with a history of glaucoma or a prior intraocular pressure (IOP) elevation in response to steroid therapy were ineligible. Treatment consisted of ranibizumab every 4 weeks with or without a dexamethasone implant at baseline and week 12. The primary outcome was mean change in visual acuity at 24 weeks, and the secondary outcome was mean change in OCT CST at 24 weeks.

Results at week 24 revealed a mean gain of 3.0 letters in the ranibizumab monotherapy group and a mean gain of 2.7 letters in the combination group ($P = .73$) **(Figure 3A)**.[25] In contrast, the mean change in CST was -62 µm in the ranibizumab monotherapy group and -110 µm in the combination group ($P < .001$) **(Figure 3B)**. Although combination therapy was more effective in drying out the macula, this did not translate into an overall improvement in visual acuity.

Looking at the data more closely, a ≥ 15-letter improvement was achieved in 11% of eyes receiving the combination vs in only 2% of eyes receiving monotherapy ($P = .03$).[25] This improvement, however, came at a cost. Intraocular pressure elevations were not observed in the ranibizumab monotherapy group, but did occur in 29% of eyes in the combination group ($P < .001$). Of these, 23% had IOP elevations ≥ 10 mm Hg and 15% had IOP elevations ≥ 30 mm Hg; 20% required IOP-lowering therapy to manage these IOP spikes.

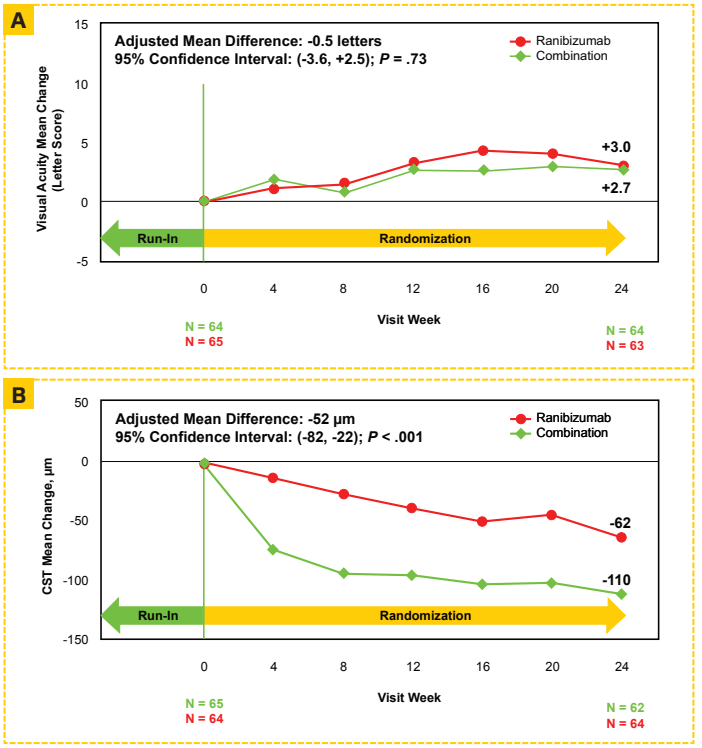


**Figure 3.** Mean visual acuity (A) and central subfield thickness (B) outcomes in the Protocol U study[25]

Abbreviation: CST, central subfield thickness.

Note: Outlying values were truncated to 3 standard deviations from the mean in Figure 3B. One image was nongradable because of low resolution.

Permissions request submitted.

One possible interpretation of the results is that perhaps the steroid was introduced too late in the DME disease process. If we wait too long to start a steroid, visual acuity will not improve even though the OCT appearance does improve. This has been demonstrated in other studies.[18-20]

## PANEL DISCUSSION: EFFECT OF PROTOCOL U FINDINGS ON CLINICAL PRACTICE

**DR HOLEKAMP:** Will the results of DRCRnet's Protocol U study change the way you treat DME? If so, how?

**DR KUPPERMANN:** Protocol U was originally designed to enroll only pseudophakic patients to avoid the cataractogenic effects of steroids on the crystalline lens.[25] Slow enrollment led to expansion of the eligibility criteria to allow phakic patients to participate. Although there were not enough pseudophakic patients to adequately power analysis of this subset, there was a trend toward better results in pseudophakic patients receiving combination therapy. Overall, however, there was no difference in visual outcomes. The study has not had much effect on my practice. I continue to start with anti-VEGF therapy and switch to the dexamethasone implant if I do not get the response I hoped for.

**DR WYKOFF:** In the era of anti-VEGF monotherapy, these data have affected my considerations in practice. Although visual acuity did not improve with the addition of a steroid, anatomy, as demonstrated through OCT changes, did improve.[25] I believe that chronic DME can be damaging. If I have already made the decision to treat a patient's DME, and I have not been completely successful with anti-VEGF monotherapy because of the presence of persistent fluid, these data indicate combination therapy can help me achieve my goal of fluid reduction.

**DR HOLEKAMP:** How common are IOP elevations after steroid therapy for DME?

**DR KUPPERMANN:** Across the various trials of steroids for DME, the probability of requiring topical IOP-lowering therapy ranges from 25% to 50%, depending on the steroid and the dose **(Table 4)**, whereas the probability of requiring glaucoma surgery is quite low.[25-28]

**Table 4.** Percentage of Patients With Intraocular Pressure Elevation or Who Required Surgical Intraocular Pressure Reduction Following Steroid Treatment for Diabetic Macular Edema in Clinical Trials

| Trial | Treatment | Patients With Elevated Intraocular Pressure, % | Patients Requiring Glaucoma Surgery, % |
|---|---|---|---|
| FAME[26] | Fluocinolone acetonide 0.2 µg/d (n = 375) | 37.1 | 4.8 |
| | Fluocinolone acetonide 0.5 µg/d (n = 393) | 45.5 | 8.1 |
| | Sham (n = 185) | 11.9 | 0.5 |
| MEAD[27] | Dexamethasone 0.7 mg (n = 347) | 27.7 | 1.2 |
| | Dexamethasone 0.35 mg (n = 343) | 24.8 | 1.2 |
| | Sham (n = 350) | 3.7 | 0.3 |
| Protocol I[28] | Triamcinolone 4 mg + prompt laser (n = 186) | 42 | 1 |
| | Ranibizumab 0.5 mg + prompt laser (n = 187) | 6 | 1 |
| | Ranibizumab 0.5 mg + deferred laser (n = 188) | 4 | 0 |
| | Sham + laser (n = 293) | 8 | < 1 |
| Protocol U[25] | Dexamethasone 700 µg/ ranibizumab 0.3 mg (n = 65) | 29.0 | 0 |
| | Sham/ranibizumab 0.3 mg (n = 64) | 0 | 0 |

Abbreviations: FAME, Fluocinolone Acetonide for Diabetic Macular Edema; MEAD, Macular Edema: Assessment of Implantable Dexamethasone in Diabetes.

**DR WYKOFF:** It is important to recognize that the rate of incisional glaucoma with the fluocinolone acetonide implant is likely much lower among patients who have received an appropriate prior course of steroid challenge without a clinically significant response.[26]

## CASE 1. DIABETIC MACULAR EDEMA NONRESPONSIVE TO ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY

***From the Files of Nancy M. Holekamp, MD***

A 59-year-old woman presented with a 2-year history of DME in both eyes, for which she received a number of anti-VEGF injections in both eyes from 4 different physicians. The most recent injection occurred approximately 6 weeks ago. She stated she has had DM for only 3 years, and it is managed with oral hypoglycemic agents. She was uninsured and did not obtain routine health maintenance, so it is likely she has had DM for far longer than 3 years.

Her chief complaint was blurry vision. On examination, her visual acuity was 20/50 OD and 20/30 OS. Intraocular pressures were normal at 14 mm Hg and 13 mm Hg, respectively. She had early nuclear sclerotic changes in both eyes. Her dilated fundus examination and OCT revealed moderately severe nonproliferative DR in both eyes and DME that was worse in the right eye than in the left eye **(Figure 4)**.

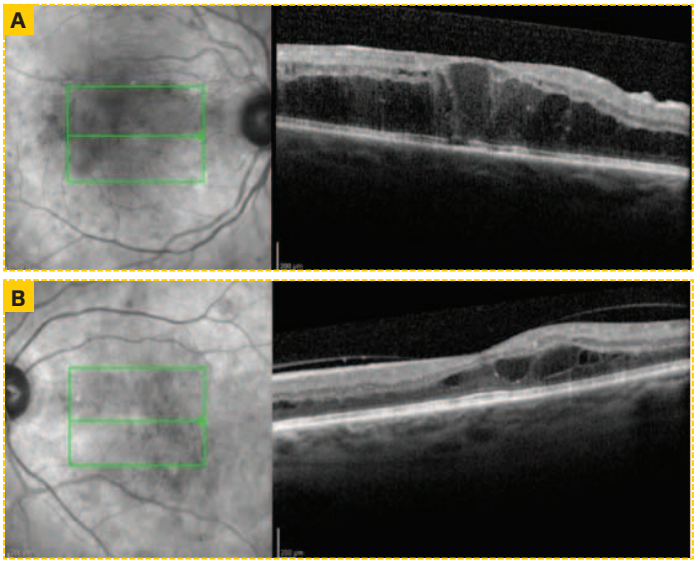


**Figure 4.** Baseline optical coherence tomography images of the right (A) and left (B) eyes of the patient presented in Case 1

A review of her medical record demonstrated that she never received regular monthly injections, but rather was consistently undertreated for the past few years. She received 4 monthly injections of bevacizumab in both eyes. At the completion of this series of treatments, her vision was essentially unchanged at 20/50 OD and 20/25 OS, her IOP remained normal (16 mm Hg OU), and the OCT appearance remained unchanged.

Since beginning her 4-injection treatment plan, she had acquired health insurance. Given that she essentially had no response to anti-VEGF therapy administered robustly and that she now had health insurance coverage, she was switched to the dexamethasone implant in the right eye. Within 1 month, the visual acuity in her right eye improved from 20/50 to 20/25, so she received a dexamethasone implant in the left eye. Another month later, her visual acuity was 20/32 OD and 20/16 OS. Her OCT appearance improved significantly as well **(Figure 5)**.

Over the ensuing 2 years, she received a total of 9 dexamethasone implants in each eye. Both eyes required cataract surgery after the fifth implant. She did not develop any IOP issues. Her visual acuity at last follow-up was 20/32 OD and 20/20 OS.

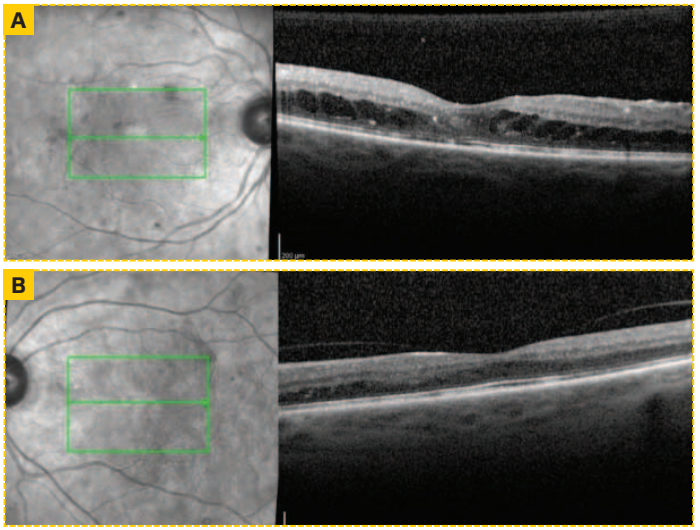


**Figure 5.** Optical coherence tomography images of the right (A) and left (B) eyes of the patient presented in Case 1 after receiving dexamethasone implants in both eyes

**DR HOLEKAMP:** There are several steroid options for treating DME. Once you decide to move from anti-VEGF therapy to steroids, which steroid do you use, and why?

**DR WYKOFF:** We have a choice between steroids that are approved specifically to treat DME—which include the dexamethasone and fluocinolone acetonide implants—and steroids that we might choose to use off-label to treat DME, specifically intravitreal triamcinolone acetonide. Several studies have demonstrated the efficacy and safety of steroids for DME **(Table 5)**.[29] Often, my preference would be to start with a shorter-acting steroid. I often like to see a meaningful therapeutic response and minimal deleterious effects on IOP before considering a longer-acting steroid.

**DR KUPPERMANN:** I also start with the dexamethasone implant for all the reasons that Dr Wykoff just described. In this case, the patient has demonstrated that she is responsive to steroids, that her IOP is unaffected by steroids, and that her lens status is no longer an issue. At this point, I would consider switching to a longer-acting steroid, such as the fluocinolone acetonide implant. There is, however, one important caveat. The dexamethasone implant's pharmacokinetics is such that the device delivers a large load of drug initially, and the level decreases over time.[30] The fluocinolone acetonide implant delivers the drug with more steady-state pharmacokinetics.[31] So we have to be attuned to the possibility that the patient can worsen during the transition from dexamethasone to fluocinolone acetonide because the overall drug dose might be reduced.

**DR WYKOFF:** One could consider transitioning this patient to the fluocinolone acetonide implant at some point. As Dr Kuppermann pointed out, doing so might not completely control the disease. The patient might still need an occasional additional dexamethasone implant or an anti-VEGF injection, but the overall treatment burden might be able to be reduced.

**DR HOLEKAMP:** There are several key takeaways from this case. If there is very little response to initial anti-VEGF therapy, it is reasonable to discontinue anti-VEGF therapy and switch to

**Table 5.** Clinical Trials Evaluating the Role of Steroids for the Treatment of DME[29]

| Study | Steroid | Number of Eyes | Study Design | Follow-Up | Major Conclusions |
|---|---|---|---|---|---|
| Gillies 2009 | Triamcinolone acetonide* | 69→44 | IVTA 4 mg vs sham; laser, if appropriate | 5 years | • Final VA comparable<br>• Delayed intervention did not compromise the possibility to respond (advanced DME) |
| DRCRnet 2009 | Triamcinolone acetonide* | 840→306 | IVTA 1 or 4 mg vs laser | 3 years | • Laser: +5 letters<br>• IVTA arms: 0 letters<br>• No real long-term advantage of IVTA despite laser |
| DRCRnet 2011 | Triamcinolone acetonide* | 854 | IVR 0.5 mg + prompt or deferred laser vs IVTA 4 mg + prompt laser vs laser | 2 years | • Compared with laser, IVR + laser groups improved VA; IVTA group did not<br>• In pseudophakic eyes, IVTA made a VA improvement equal to that with IVR |
| Pearson 2011 | Fluocinolone acetonide | 196 | Fluocinolone acetonide insert (0.59 mg) vs laser or observation | 3 years | • Better VA and CRT improvement in the IVFA group at 2 years, but not at 3 years<br>• High incidence of cataract and glaucoma |
| Campochiaro 2012 | Fluocinolone acetonide | 953→672 | Fluocinolone acetonide insert (0.2 or 0.5 µg/d) vs sham | 3 years | • Compared with sham, significant improvement in VA in IVFA groups<br>• More benefit in patients with DME duration ≥ 3 years<br>• Frequent cataracts, but good result after surgery |
| Haller 2010 | Dexamethasone | 171 | Dexamethasone implant (700 or 350 µg) vs sham | 6 months | • Visual acuity improvement ≥ 10 letters in more treated eyes, especially the 700-µg group<br>• IOP increase effectively treated with topical medication |

Abbreviations: CRT, central retinal thickness; DME, diabetic macular edema; DRCRnet, Diabetic Retinopathy Clinical Research Network; IOP, intraocular pressure; IVFA, intravitreal fluocinolone acetonide; IVR, intravitreal ranibizumab; IVTA, intravitreal triamcinolone acetonide; VA, visual acuity.
* Intravitreal triamcinolone acetonide is used off-label for DME

steroids. If DME does not respond well to anti-VEGF agents, switching to steroids can often lead to improvements in both visual acuity and central retinal thickness. I tend to start with a short-acting steroid, such as the dexamethasone implant, to assess both efficacy and safety before switching to a longer-acting steroid, such as fluocinolone acetonide. Cataract development is a known but manageable risk of steroid therapy; therefore, patients require monitoring of IOP.

## CASE 2. TRANSITIONING FROM SHORT-ACTING STEROIDS TO LONG-ACTING STEROIDS

### *From the Files of Nancy M. Holekamp, MD*

A 67-year-old woman with a 35-year-long history of DM presented with a 2-year history of DME in both eyes. Her medical history was significant for coronary artery disease, obesity (she had previously undergone gastric bypass surgery), and bladder repair. She was pseudophakic in both eyes. Her prior DR and DME treatments included vitrectomy in both eyes 4 years ago, focal macular laser in both eyes 2 years ago, 4 ranibizumab injections in both eyes 4 years ago, and dexamethasone implants in each eye every 3 months for the past 2 years.

On examination, her visual acuity was 20/25 OU. Her IOP was normal at 16 mm Hg OD and 19 mm Hg OS. She had DME on clinical examination in both eyes. **Figure 6** shows her OCT images. Her CST values were 300 µm OD and 331 µm OS.

The patient received a fluocinolone acetonide implant in each eye. Over the next 3 months, her right eye remained stable, whereas her left eye had a significant increase in CST to 422 µm. She received a dexamethasone implant in the left eye. Over the next 3 months, the right eye remained stable and the left eye's CST declined to 351 µm, with stable vision. Overall, the patient's visual acuity was stable at 20/32 OU. With the fluocinolone acetonide implant, her injection rate with the dexamethasone implants was greatly reduced.

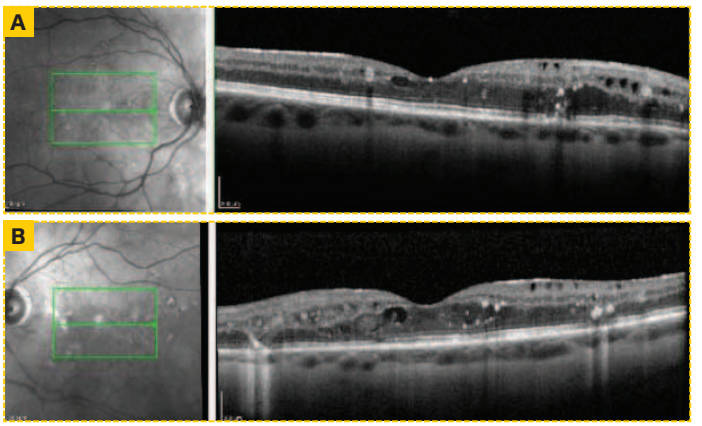


**Figure 6.** Baseline optical coherence tomography images of the right (A) and left (B) eyes of the patient presented in Case 2

**DR HOLEKAMP:** Would you have managed this patient any differently?

**DR WYKOFF:** Is there any role for anti-VEGF therapy in place of, or in addition to, dexamethasone after the fluocinolone acetonide implant?

**DR HOLEKAMP:** She received a series of 4 ranibizumab injections monthly at the beginning, with no appreciable improvement at all. This indicated to me that she was not an anti-VEGF therapy responder.

**DR KUPPERMANN:** Because she had undergone vitrectomy, the half-life of any drug—including anti-VEGF agents—will be considerably shortened. Even if you had tried more frequent injections and been successful, the treatment burden would still have supported the move to steroid therapy. Fortunately, the determinant of drug half-life with steroid implants is the device itself and not the presence or absence of vitreous humor.

**DR WYKOFF:** This case raises the issue of switching vs adding treatment. I might have added dexamethasone to the anti-VEGF therapy after those 4 injections to see if the combination provided adequate control with reasonable treatment burden.

**DR HOLEKAMP:** That is an excellent point. I prefer to use monotherapy whenever possible for both cost and safety reasons. I will monitor the DR and can always give an anti-VEGF injection later if needed. I will add that at the last follow-up, this patient's IOP in the left eye was 22 mm Hg after receiving the dexamethasone implant. Does this concern anyone?

**DR KUPPERMANN:** Elevations of IOP are common after steroid implants. In the pivotal MEAD (Macular Edema: Assessment of Implantable Dexamethasone in Diabetes) study of the dexamethasone implant for DME, approximately 30% of eyes had IOP elevations requiring the use of topical IOP-lowering therapy by year 3, and only 3 of the 690 implanted eyes required a trabeculectomy.[32] With the fluocinolone acetonide implant, the percentage of eyes needing IOP-lowering medications was similar, on the order of 35% to 40%, but approximately 5% of eyes required glaucoma surgery.[18] In general, because dexamethasone is a short-acting drug compared with fluocinolone acetonide or triamcinolone acetonide, the IOP elevations are easier to treat and will often resolve as the implant's drug level is depleted.

**DR WYKOFF:** You dosed the dexamethasone implant every 3 months before switching to the fluocinolone acetonide implant. When using the dexamethasone implant for chronic management, do you reinject every 90 days regardless of clinical status, do you inject based on clinical status, or do you wait until the current implant has completely dissolved?

**DR HOLEKAMP:** I typically dose every 3 months when using dexamethasone chronically. I do not wait until it dissolves because remnants can linger for months, and I do not wait until the vision or edema gets worse because it is better to keep it under control than to constantly play catch-up.

## CASE 3. RECALCITRANT DIABETIC MACULAR EDEMA

### *From the Files of Charles C. Wykoff, MD, PhD*

A 45-year-old man with type 1 DM had incurred a substantial treatment burden to manage DME in his left eye. Over approximately 2.5 years, he received 5 bevacizumab injections, focal and panretinal laser treatments, and 21 ranibizumab injections. When he received monthly injections, his visual acuity remained in the 20/25 range, his edema was well controlled, and he was happy. Every attempt to reduce the frequency of ranibizumab injections resulted in worsening vision and edema—even stretching to 5 to 6 weeks. Unlike the prior cases, this patient is not a suboptimal responder; rather, this is a patient in whom the beneficial effect of therapy has had a very short endurance period that is not getting longer over time.

Several options were considered. One was to switch to a different anti-VEGF agent, another was to switch to a steroid, and a third was to add a steroid and continue the anti-VEGF injections, hoping to extend the endurance and thereby reduce the frequency of injections. A switch to aflibercept was chosen. After 4 monthly aflibercept injections, the injections began to be spaced out. For a short while, the patient remained stable with an injection every 5 to 7 weeks until injection number 10, when worsening vision (now 20/40) and edema forced him back to a monthly injection schedule.

It was clear that anti-VEGF therapy alone, while effective when repeated monthly, posed an enormous treatment burden on this patient. He simply did not want to come in monthly because of employment commitments. To address this, a dexamethasone implant was injected. He responded well to the dexamethasone implant, but durability was still less than ideal, so combination dosing with aflibercept injections was attempted. During this time, he also developed a visible epiretinal membrane. When dry, however, his vision was still excellent at 20/25. With steroids, his IOP rose from the mid-teens to 23 mm Hg. Within 3 months, his edema was significantly worse, and his visual acuity dropped to 20/50. At this point, he was enrolled in a prospective clinical trial and received a suprachoroidal injection of triamcinolone acetonide, which is currently not approved for ophthalmic use and was used off-label. Triamcinolone acetonide treatment is in clinical development for a number of conditions, including noninfectious posterior uveitis and macular edema due to retinal vein occlusion, as well as for DME.[33,34] After completion of the clinical trial, he again had recurrence of DME, and dexamethasone implants (his third) were reinitiated, which held the visual gains and edema for 2 months. He then received another dexamethasone implant (his fourth), which restored visual acuity and reduced edema for another 2 months. The effect was again lost after just 2 months, so he received a fifth dexamethasone implant. His visual acuity at his last visit was 20/25 in his left eye.

**DR WYKOFF:** Any insight into how I might have managed this case differently?

**DR KUPPERMANN:** This case perfectly illustrates the fact that we must individualize treatment. This is an extreme case, but it is clear that this patient's treatment burden will remain significant. Given the presence and progression of the epiretinal membrane, did you consider vitrectomy for this patient?

**DR WYKOFF:** Vitrectomy is certainly an option in this case.

**DR KUPPERMANN:** I am not certain I would operate yet. Before going to surgery, I would try more aggressive combination therapy—perhaps a dexamethasone implant and an aflibercept injection at the same time. I would follow the implant with the injection a week later so that the aflibercept goes on board at the time the implant is releasing high levels of dexamethasone. Then, there will be high levels of both drugs active for approximately a month. Perhaps the patient would do well if both drugs were at peak activity simultaneously.

**DR WYKOFF:** At this point, he is being maintained on a dexamethasone implant approximately every 2 months.

**DR HOLEKAMP:** Are you having any difficulty getting reimbursed for this so often?

**DR WYKOFF:** I have not had that problem in my practice. Have you had issues with reimbursement for delivering these treatments more often than labeled?

**DR KUPPERMANN:** I have had no issues with reimbursement when using the dexamethasone implant more often than every 12 weeks or with anti-VEGF therapy more often than every 4 weeks. I have not, however, repeated a fluocinolone acetonide implant within 3 years of the first implant.

## CASE 4. MANAGING INTRAOCULAR PRESSURE ELEVATION

***From the Files of Baruch D. Kuppermann, MD, PhD***

***(Courtesy of Anat Loewenstein, MD, and Michaella Goldstein, MD)***

A 65-year-old woman presents with bilateral DME that is worse in the right eye. Her history was significant for regressed proliferative DR after panretinal photocoagulation in the right eye and severe nonproliferative DR in the left eye. She was pseudophakic bilaterally. Her prior treatments for DME were limited to the right eye and included focal laser and 3 bevacizumab injections.

On examination 5 weeks after the last of her 3 bevacizumab injections, visual acuity was 20/100 OD and 20/40 OS. Central macular thickness on OCT was 846 µm OD and 512 µm OS. She received a dexamethasone implant in the right eye, and within the first few weeks, her edema improved significantly (432 µm), as did her visual acuity (20/60). On the basis of this improvement in the right eye and worsening in the left eye (now 20/60 and 668 µm of edema), her left eye received an implant as well. By 8 to 12 weeks, the edema was essentially resolved (209 and 244 µm, respectively) and visual acuity was 20/50 OD and 20/40 OS.

The right eye held its gains for 20 weeks before recurrence of edema necessitated a second implant, and the left eye made it to 26 weeks before needing retreatment. Visual acuity and edema responded well to the second implant in each eye, but 6 weeks after the second implant, the left eye developed an IOP of 32 mm Hg.

**DR KUPPERMANN:** How does the panel manage IOP spikes of this magnitude following steroid therapy for DME?

**DR HOLEKAMP:** We have some guidance. An expert panel, using a modified Delphi approach, developed guidelines for the management of IOP spikes after steroid treatment for DME **(Table 6)**.[35] The panel's recommendations were to use a single topical agent for IOP spikes to 25 mm Hg or less, a fixed combination for IOP spikes between 26 mm Hg and 30 mm Hg, and either a fixed combination or a referral to a glaucoma specialist for IOP above 30 mm Hg.[35] In this case, I might also consider adding a prostaglandin analogue at bedtime because 32 mm Hg is quite high and early in the course at only 6 weeks postinjection. I do not typically refer to a glaucoma specialist unless I cannot get IOP controlled using medications.

**Table 6.** Retinal Expert Consensus Recommendations for Management of IOP Elevations After Steroid Therapy for Diabetic Macular Edema[35]

| IOP Level | Management |
|---|---|
| ≤ 25 mm Hg | Single, topical |
| 26-30 mm Hg | Fixed-combination drop |
| > 30 mm Hg | Fixed-combination drop and/or refer to glaucoma specialist |

Abbreviation: IOP, intraocular pressure.

**DR WYKOFF:** I will start with 1 drop, but if IOP remains elevated, I often have the patient return to his/her referring physician for IOP management while I manage the DME.

**DR KUPPERMANN:** Because this patient's IOP was observed at 32 mm Hg prior to the peak pharmacokinetic release of the drug, the potential existed for further IOP elevation **(Figure 7)**.[27] I opted for a fixed combination, and her IOP decreased to 18 mm Hg. Patients such as this one require careful monitoring and might need more aggressive treatment at a later time.

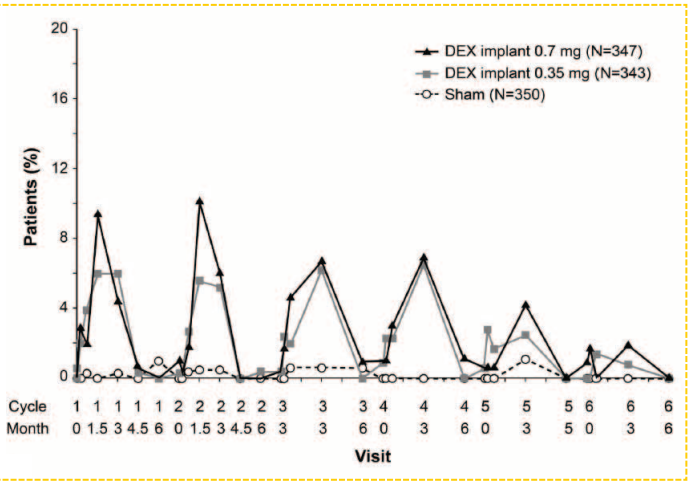


**Figure 7.** Percentage of patients in the MEAD trial with an intraocular pressure increase > 10 mm Hg after treatment with the dexamethasone implant at scheduled visits[27]

Abbreviations: DEX, dexamethasone; MEAD, Macular Edema: Assessment of Implantable Dexamethasone in Diabetes.

Reproduced with permission from Maturi RK, Pollack A, Uy HS, et al; Ozurdex MEAD Study Group, Intraocular pressure in patients with diabetic macular edema treated with dexamethasone intravitreal implant in the 3-year MEAD study, *Retina*, 36, 6, 1143-1152, https://journals.lww.com/retinajournal/pages/default.aspx.

### TAKE-HOME POINTS

- The prevalence of DM, DR, and DME continues to rise
- DME is a complex disease with a multifactorial pathophysiology that includes both VEGF and inflammation as drivers of edema
- Anti-VEGF therapy is the primary treatment for DME, but its effectiveness is limited by nonresponse in some eyes, limited durability in responsive eyes, and lack of clarity on retreatment strategies
- In eyes with suboptimal response or nonresponse to anti-VEGF therapy, steroid therapy can improve outcomes in DME
- Persistent DME can limit long-term visual outcomes, underscoring the importance of considering steroid therapy early in the course of the disease for suboptimal responders to anti-VEGF therapy
- Protocol U demonstrated improvement in structural but not functional outcomes when steroids were added to anti-VEGF therapy for DME
- Complications of steroid therapy include elevated IOP and cataract formation

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1. What are the key pathophysiologic triggers for DME?
   a. VEGF and IOP
   b. Hemoglobin A1c and VEGF
   c. Inflammation and VEGF
   d. Inflammation and hemoglobin A1c

2. Limitations of anti-VEGF therapy for DME include:
   a. Treatment burden due to the need for frequent injections
   b. The risk of IOP increase
   c. The risk of cataract formation
   d. Serious systemic side effects

3. A patient presents with a 3-year history of DME. She has seen several physicians and sporadically received only 1 to 2 anti-VEGF therapy injections from each. Her visual acuity and edema require further treatment. Which of the following best describes her clinical status?
   a. She has received and failed robust treatment with anti-VEGF therapy and should now receive steroids
   b. Inflammation is likely the only relevant trigger for her DME
   c. Her edema is chronic and might be more difficult to treat
   d. Steroids will be ineffective in managing her disease

4. A patient with newly diagnosed DME presents with a visual acuity of 20/50 and CST of 500 µm. Following 6 monthly injections of an anti-VEGF agent, her visual acuity and edema are unchanged. What is the next best step for her?
   a. Continue the injections as monotherapy
   b. Switch to a fluocinolone acetonide implant
   c. Add focal laser treatment
   d. Switch to a dexamethasone implant

5. A patient with DME has had 3 ranibizumab injections, with no appreciable effect on visual acuity or edema. Which of the following statements is supported by the findings of the DRCRnet's Protocol U study?
   a. Adding the dexamethasone implant will improve her visual acuity significantly more than simply continuing the monthly injections alone
   b. She has failed anti-VEGF therapy and her vision cannot be improved
   c. Her edema will likely improve if a dexamethasone implant is added to her treatment
   d. If she receives a dexamethasone implant, she has a 5% chance of developing elevated IOP

6. Eight weeks after receiving a dexamethasone implant, a patient's IOP rises from 14 mm Hg to 28 mm Hg. Which is a reasonable intervention for this patient?
   a. Observe IOP without treatment
   b. Start therapy with a fixed-combination IOP-lowering medication
   c. Refer the patient for glaucoma surgery
   d. Switch to a fluocinolone acetonide implant when retreatment is necessary

7. When counseling patients with DME about the long-term course of their disease and treatment, which point should be included?
   a. Everyone eventually requires steroids for DME treatment
   b. The treatment burden decreases over time for most patients
   c. Controlling blood glucose levels helps DR, but not DME
   d. There will always be some edema; therapy only reduces it, but cannot eliminate it