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CHALLENGING THE STATUS QUO IN DME

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FACULTY

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This continuing medical education activity is jointly provided by Wills Eye Hospital and MedEdicus LLC.

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Distributed with RETINA THE JOURNAL OF RETINAL AND VITREOUS DISEASES

Purpose and Target Audience

By 2030, the prevalence of diabetes is expected to increase by more than 50% to affect 55 million Americans. With this increase comes a significant challenge for clinicians to help prevent blindness due to diabetic eye disease for a growing number of patients. Although the advent of anti–vascular endothelial growth factor intravitreal injection revolutionized treatment of diabetic eye disease, including diabetic retinopathy and diabetic macular edema, a considerable proportion of patients with vision-threatening diabetic macular edema do not respond satisfactorily to treatment. Accumulating research suggests a multifactorial disease pathogenesis in these patients, with a strong inflammatory component driving progression in concert with abnormal angiogenesis. Corticosteroid treatment with the dexamethasone implant, fluocinolone acetonide implant, or triamcinolone intravitreal injection (used off-label) can improve outcomes for patients with persistent diabetic macular edema, provided that considering a switch in treatment does not come too late in the disease process. Selecting a corticosteroid should consider available evidence and pharmacologic differences that can affect the relative efficacy and safety of each agent for individual patients.

This activity is intended to educate retina specialists and other ophthalmologists caring for patients with diabetic macular edema.

Designation Statement

Wills Eye Hospital designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Accreditation

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Wills Eye Hospital and MedEdicus LLC. Wills Eye Hospital is accredited by the ACCME to provide continuing medical education for physicians.

Instructions

This course takes approximately 1.5 hours. Please read the monograph, consulting any additional references if needed. Once the materials have been reviewed, go to **https://tinyurl.com/challengingDME** to take a post test and course evaluation, after which you will be able to generate your CME certificate.

Learning Objectives

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

- Interpret evidence for inflammation as a driver of diabetic macular edema
- Apply the latest evidence for treatment optimization for patients with persistent diabetic macular edema
- Identify pharmacologic differences among intravitreal corticosteroids that affect their efficacy for treating persistent diabetic macular edema
- Relate pharmacokinetic differences among intravitreal corticosteroids to safety considerations for individual patients

Hardware & Software Requirements—Digital Edition

High-speed Internet connection (Broadband, Cable, or DSL)
Windows 2000 or higher
256 MBs or more of RAM
Internet Explorer 6.0 or higher
Windows Media player 10.0 or higher
Adobe Acrobat 7.0 or higher
Course content compatible with Mac OS

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CHALLENGING THE STATUS QUO IN DME

Introduction

Diabetes mellitus affects 30 million Americans, and another 84 million have prediabetes.[1] Costs associated with diabetes exceed $300 billion annually in the United States alone; 1 in 4 health care dollars is spent on diabetes and its complications.[2] Diabetic retinopathy (DR) is the leading cause of vision loss worldwide among people aged 20 to 74 years.[3] Approximately 28.5% to 40% of Americans diagnosed with diabetes have some degree of DR.[4,5] Of these, approximately 4.4% have vision-threatening DR. In addition, approximately 6% of Americans with diabetes will develop diabetic macular edema (DME), which accounts for most cases of vision-threatening DR.[6]

DME is a multifactorial disease. Vascular endothelial growth factor (VEGF) is known to play a key role in promoting edema through increased vascular permeability: to that end, anti-VEGF therapy is highly effective in treating DME. Some eyes, however, respond incompletely or not at all to anti-VEGF therapy, indicating a more complex pathophysiology. Recent studies have demonstrated a significant role for various components of the inflammatory cascade in the development and perpetuation of DME. Consequently, corticosteroids can be an effective therapy as well. In more refractory cases, macular laser photocoagulation or even vitrectomy might be necessary to control the disease.

This educational activity, based on a live continuing medical education symposium held during the 2019 Annual Meeting of the American Society of Retina Specialists, will review the multiple processes and pathways that contribute to the pathophysiology of this common, yet complex, disease. Current and emerging treatment modalities will be discussed, including new studies elucidating the management of eyes with treatment-refractory DME. Finally, a panel of expert retina specialists will present and discuss a series of case studies selected to illustrate the application of evidence-based medicine in the evaluation and management of patients with both straightforward and refractory DME.

Persistent DME Pathophysiology: Challenging Anti-VEGF–Centric Thinking

Judy E. Kim, MD

Despite decades of research and innovative scientific advancements in the diagnosis and management of DR, the pathogenesis and pathophysiology of DR remain incompletely characterized.[7] It appears, however, that chronic hyperglycemia in diabetes contributes to both retinal microvascular disease and retinal neurodegeneration, and that chronic inflammation mediates these deleterious effects in the neuronal and vascular components of the retina.

Diabetes triggers chronic inflammation through several key pathways. Direct diabetes effects—including hyperglycemia, insulin resistance, dyslipidemia, and arterial hypertension—lead to altered biochemical pathways involving the renin-angiotensin system, hexosamine pathways, protein kinase C, and advanced

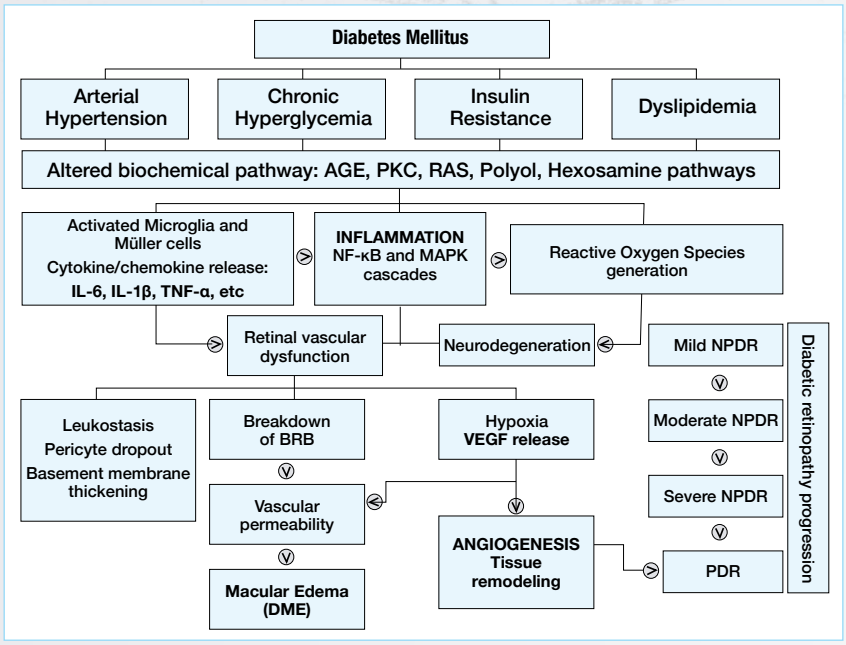

Figure 1. Inflammatory cascade in diabetic macular edema[7]

Abbreviations: AGE, advanced glycation end product; BRB, blood-retinal barrier; DME, diabetic macular edema; IL, interleukin; MAPK, mitogen-activated protein kinase; NF, nuclear factor; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PKC, protein kinase C; RAS, renin-angiotensin system; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

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glycation end products. These biochemical alterations, in turn, activate microglia and Müller cells, leading to cytokine and chemokine release; stimulate inflammation via the nuclear factor kB and mitogen-activated protein kinase cascades; and generate reactive oxygen species.

This multifaceted inflammatory cascade leads to retinal vascular leukostasis, pericyte dropout, basement membrane thickening, breakdown of the blood-retinal barrier with abnormal vascular permeability resulting in DME, and tissue hypoxia triggering the release of VEGF. This results in angiogenesis and tissue remodeling that manifest clinically as DR **(Figure 1)**.[7]

The role of VEGF in retinal vascular disease has been well documented in recent decades. VEGF exists as a family of 5 isomers (VEGF-A, -B, -C, -D, and -E), of which VEGF-A (hereafter referred to simply as VEGF) plays a key role in mediating angiogenesis and vascular permeability.[7] The breakdown of the blood-retinal barrier and the accumulation of retinal fluid are mediated by VEGF and other cytokines and growth factors produced by activated glial cells and the dysfunctional vascular endothelium. These biochemical signals upregulate expression of adhesion molecules, such as intercellular adhesion molecule 1, promoting the extravasation of inflammatory cells such as monocytes, which further exacerbates the inflammatory response. Ultimately, the environment within the diabetic macula develops a complex inflammatory milieu of prostaglandins,leukotrienes, chemokines, nitric oxide, platelet-activating factor, carbonic anhydrase, protein kinase C α, and various cytokines.[8-13]

As the ocular microenvironment becomes more inflammatory, clinical manifestations worsen. The incidence of DME increases as DR becomes more severe, suggesting that the development of DME might depend on prolonged untreated DR and key secondary disease drivers that are independent of VEGF. Vitreous concentrations of key inflammatory molecules—including VEGF and interleukin-6—are increased in eyes with diabetes compared with those without diabetes, and become profoundly elevated in eyes with DME.[14] Interestingly, among eyes with DR, aqueous levels of many of these proinflammatory molecules—but ***not*** VEGF—increase significantly with increasing diabetes severity.[15] Furthermore, corticosteroid therapy, but ***not*** anti-VEGF therapy, significantly reduces the aqueous concentrations of these inflammatory drivers in eyes with DME **(Table 1)**.[16]

The lesson here is that although anti-VEGF therapy is effective in suppressing VEGF activity, it does not have significant effects on inflammatory mediators that also drive DR and DME pathophysiology. Corticosteroids, on the other hand, have potent anti-inflammatory activity targeting soluble cytokines and leukocyte-mediated inflammation.[17]

In summary, DME is not driven solely by VEGF. Rather, inflammation plays a significant role in the pathophysiology of DME. Multiple inflammatory cytokines are significantly elevated in eyes with DME, and these levels increase with the severity of DR. Corticosteroid treatment, but not anti-VEGF therapy, reduces

Table 1. Corticosteroid Therapy, But Not Anti-VEGF Therapy, Significantly Reduces Aqueous Concentrations of Many Proinflammatory Molecules in Eyes With DME[16]

Aqueous Concentration, pg/mL	IVTA Group (n = 11)			IVBe Group (n = 11)		
	Preinjection	Postinjection	*P* Value	Preinjection	Postinjection	*P* Value
IL-6	29.9 (10.1-82.5)	13.8 (2.8-36.3)	< .01	26.7 (13.8-107.0)	24.0 (6.5-147.0)	.477
IL-8	28.2 (6.23-77.5)	25.3 (12.4-95.8)	.597	23.9 (11.1-39.7)	23.6 (11.0-74.2)	.374
IP-10	366.0 (171.0-1380)	249.0 (28.7-717.0)	.013	401.0 (126.0-1990)	433.0 (268.0-4570)	.110
MCP-1	3850 (2060-4380)	1090 (351-4150)	.010	3770 (2660-4490)	3840 (1790-4490)	.594
PDGF-AA	68.7 (31.4-141.0)	37.1 (10.9-89.7)	.016	81.0 (14.3-140.0)	72.7 (23.8-117.0)	.722
VEGF	55.0 (36.0-262.0)	10.5 (0.1-372.0)	.050	61.5 (31.8-200.1)	0.1 (0.1-28.3)	< .01

Abbreviations: DME, diabetic macular edema; IL, interleukin; IP, interferon-inducible protein; IVBe, intravitreal injection of bevacizumab; IVTA, intravitreal injection of triamcinolone acetonide; MCP, monocyte chemotactic protein; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

these elevated levels of proinflammatory molecules. Given the complementary actions of anti-VEGF and corticosteroid therapy, both therapies can be considered as treatment options for management of DME.

Although anti-VEGF therapy is effective in suppressing VEGF activity, it does not have significant effects on inflammatory mediators that also drive DR and DME pathophysiology.
– Judy E. Kim, MD

Identifying Treatment-Refractory DME: Challenging the Monotherapy Paradigm

Carl D. Regillo, MD

We have numerous therapeutic options for our patients with DME, including intravitreal VEGF blockade, intravitreal corticosteroids, focal macular laser photocoagulation, and pars plana vitrectomy. VEGF inhibition is our typical first-line therapy for several reasons. The efficacy of anti-VEGF therapy has been well established. The efficacy of ranibizumab[18] and that of aflibercept[19] were demonstrated in their respective phase 3 registration trials; additionally, the efficacy of ranibizumab was demonstrated in the Diabetic Retinopathy Clinical Research Network's (DRCRnet) Protocol I study.[20] The efficacy of bevacizumab (used off-label for DME) was established in DRCRnet's Protocol T study.[21,22] All 3 drugs were compared head-to-head in Protocol T. The ocular and systemic safety of anti-VEGF therapy has been thoroughly established in these clinical trials.[18-22]

RISE and RIDE were the first major clinical trials evaluating ranibizumab for DME.[18] These studies demonstrated a significant benefit of anti-VEGF therapy over sham injections. Of note, however, the improvement seen after the initiation of monthly injections begins immediately, but does not peak until approximately 12 to 18 months later **(Figure 2A)**,[18] suggesting that some eyes respond more slowly than others to therapy. This observation is mirrored in the studies' optical coherence tomography (OCT) data, which also demonstrated an ongoing reduction in central foveal thickness during the first 12 months of therapy **(Figure 2B)**.[18] Similar gradual improvement in visual acuity (VA) was seen in the VIVID and VISTA phase 3 trials of aflibercept for DME.[19]

DRCRnet's Protocol T evaluated 3 anti-VEGF agents—ranibizumab, aflibercept, and bevacizumab—in a head-to-head trial in eyes with DME.[21,22] After 2 years of treatment in an individualized fashion per protocol, the only significant difference in VA between groups was for aflibercept vs bevacizumab (12.8 vs 10.0 letters; $P = .02$).[21] However, when baseline VA was taken into account, aflibercept produced greater gains in mean VA than did ranibizumab or bevacizumab at 2 years in eyes with baseline VA of 20/50 or worse, whereas no differences were seen in eyes with better baseline VA. Commensurately, 75% of eyes in the aflibercept group (n = 97) achieved central foveal thickness < 250 μm at year 2 in the 20/50 or worse baseline VA group compared with 66% of eyes in the ranibizumab group (n = 89; $P = .08$) and 46% of eyes in the bevacizumab group (n = 91; $P < .001$).

Ocular adverse events were similar among groups and included inflammation (1%-3%), vitreous hemorrhage (5%-8%), and intraocular pressure (IOP) elevation (12%-17%).[21] Anti-Platelet Trialists' Collaboration adverse events were observed in 5%, 8%, and 12% of the 224 aflibercept-, 218 bevacizumab-, and 218 ranibizumab-treated patients, respectively ($P = .047$).

As effective as anti-VEGF therapy is against DME, a significant number of eyes manifest suboptimal responses to treatment, even when treated as part of a rigorous clinical trial **(Figure 3A)**.[23] In Protocol I, 40% of eyes had persistent DME after > 6 monthly ranibizumab injections, and 32% had associated reduced VA (20/32 or worse). In Protocol T, the percentages of eyes treated with aflibercept, ranibizumab, and bevacizumab that had persistent DME after > 6 monthly injections were 32%, 41%, and 66%, respectively; of these, 16%, 27%, and 39%, respectively, had associated reduced VA (20/32 or worse).[21,22] In fact, in Protocol I, the response to anti-VEGF therapy at 3 months was predictive of long-term (3-year) improvement in VA **(Figure 3B)**.[24] Eyes with large initial improvements in VA tended to maintain their gains; likewise, eyes with minimal initial improvement tended not to improve further during the remainder of the study.[24] In a separate analysis of Protocol I data, the likelihood of gaining ≥ 15 ETDRS letters was highest in the 143 eyes with early and consistent responses to therapy (42%), less in the 43 eyes with early but inconsistent responses (26%), even less in the 36 eyes with slow and variable responses (14%), and least in the 66 eyes with no response to therapy (8%).[25]

When managing patients whose DME responds suboptimally to primary anti-VEGF therapy, our options include switching to an alternate anti-VEGF agent, switching to or adding corticosteroid therapy, performing focal macular laser photocoagulation, or performing pars plana vitrectomy. Several studies have demonstrated improvement in DME after switching from other anti-VEGF agents to aflibercept, but these were mostly

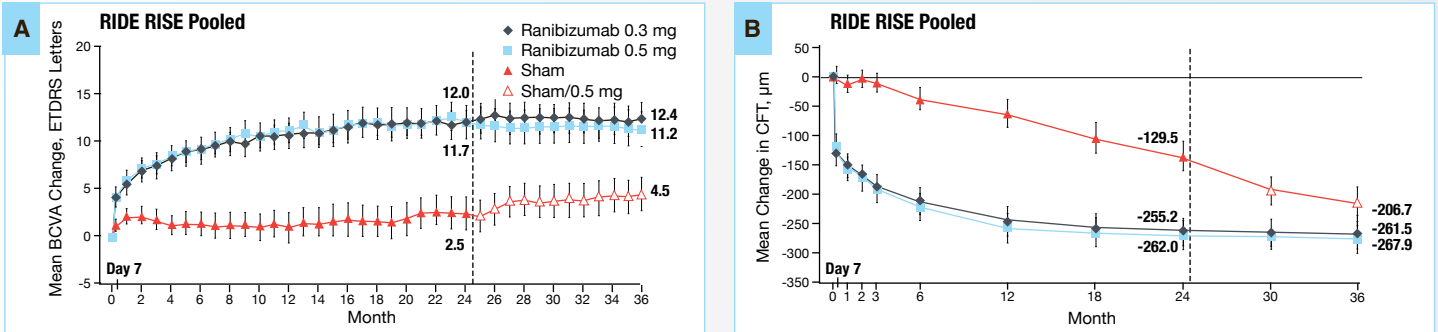

Figure 2. Visual acuity (A) and optical coherence tomography changes (B) over time in the RISE and RIDE phase 3 studies of ranibizumab for diabetic macular edema[18]

Abbreviations: BCVA, best-corrected visual acuity; CFT, central foveal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study.

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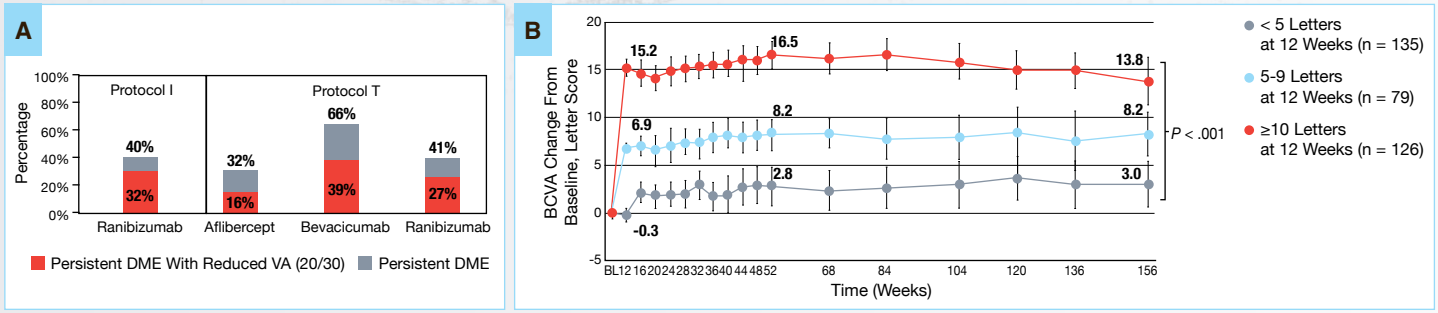

Figure 3. Heterogeneous response to anti–vascular endothelial growth factor therapy among patients with DME in the Protocol I and T studies (A and B) and VA improvement over time by response at 12 weeks in Protocol I (B)[23,24]

Abbreviations: BCVA, best-corrected visual acuity; BL, baseline; DME, diabetic macular edema; VA, visual acuity.

Figure 3A reprinted with permission from Diabetic Retinopathy Clinical Research Network. This figure is not presented on behalf of the Diabetic Retinopathy Clinical Research Network.

Figure 3B 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.

retrospective in nature and lacked control groups.[25-28] The DRCRnet has an ongoing prospective, randomized trial (Protocol AC) comparing aflibercept with bevacizumab with deferred aflibercept (reserved for suboptimal responders) that will better address the value of switching between anti-VEGF agents in suboptimally responding eyes.[29] The role of corticosteroids in DME is covered in the next section. Both laser and surgical procedures can be beneficial to eyes recalcitrant to pharmacotherapy, albeit with variable and inconsistent visual improvement and at higher risk for pars plana vitrectomy.

In summary, intravitreal VEGF blockade is the preferred first-line therapy for DME and is most effective when applied early in the disease process. The VEGF inhibitors with indications for treating DME (ranibizumab and aflibercept) are more effective than bevacizumab (used off-label). A substantial subset of eyes with DME will not achieve complete macular drying or optimal VA recovery with initial anti-VEGF therapy. An expert panel recently concluded that an eye can be considered a nonresponder if, after 3 to 6 injections, VA does not improve beyond 20/40 or if excess macular thickness has not been reduced by at least 50% after 3 to 4 monthly injections.[30] Options for these eyes include switching to an alternate anti-VEGF agent, switching to or adding corticosteroids, or using alternative approaches, such as focal laser or maybe even vitrectomy.

An eye can be considered a nonresponder if, after 3 to 6 injections, VA does not improve beyond 20/40 or if excess macular thickness has not been reduced by at least 50% after 3 to 4 monthly injections. Options for these eyes include switching to an alternate anti-VEGF agent, switching to or adding corticosteroids, or using alternative approaches, such as focal laser or maybe even vitrectomy.

– Carl D. Regillo, MD

Managing Persistent DME With Intravitreal Corticosteroids: Safety and Efficacy

Raj K. Maturi, MD

The role of corticosteroids in the treatment of DME was first raised in a small case series in 2002.[31] In that series, 16 eyes with DME unresponsive to 2 sessions of macular laser received intravitreal injections of triamcinolone acetonide 4 mg. Mean VA and central macular thickness improved over a 6-month follow-up period; but 1 eye experienced progression of cataract.

Building on this proof-of-concept study, DRCRnet conducted Protocol I, comparing ranibizumab plus prompt laser, ranibizumab plus deferred laser, triamcinolone plus prompt laser, and laser alone in eyes with DME.[20] In this study, both ranibizumab groups performed similarly (laser added no tangible benefits). Although the corticosteroid group manifested early visual gains, these were substantially reduced by the end of the first year, owing largely to cataract development and/or progression **(Figure 4A)**.[20] In eyes that were pseudophakic at study entry, the corticosteroid group's mean VA was similar to that of the ranibizumab groups through 2 years of follow-up **(Figure 4B)**.[20]

These findings support an important role for steroids as an alternative to anti-VEGF therapy in eyes with DME, but steroids do have issues that anti-VEGF therapy does not. In addition to the cataract progression noted previously, steroids can cause IOP elevations. With 2 mg of triamcinolone, the incidence of IOP elevations is approximately 10%, whereas with 4 mg, it rises to approximately 20% to 40%.[20,32,33] Cases of pseudoendophthalmitis have also been reported with the use of branded triamcinolone (Kenalog) used off-label, in which blurred vision, hypopyon, and pain mimic true infectious endophthalmitis.[34] A formulation of triamcinolone for intraocular use specifically has been developed, tested, and commercialized.[35]

Because the effectiveness of depot intravitreal corticosteroids is relatively short acting, several sustained-release corticosteroid products have been developed specifically for intraocular use. The dexamethasone implant incorporates a potent corticosteroid in a long-acting delivery system that provides sustained, localized drug release for 3 to 4 months.[36] In a pivotal study (MEAD) in eyes with DME recalcitrant to laser therapy, the primary end point—the proportion of eyes with a ≥ 15-letter improvement from baseline—was significantly higher in the 351 eyes receiving the 0.7-mg dexamethasone implant than in the 350 eyes receiving sham injections (22.2% vs 12.0%; $P < .001$) at the 3-year final study visit.[37] Among the IOP safety parameters assessed in the study, 32% of the 347 eyes receiving dexamethasone 0.7 mg manifested an IOP ≥ 25 mm Hg at any point during the study, 6.6% reached ≥ 35 mm Hg, 27.7% had an IOP rise ≥ 10 mm Hg from baseline, and 41.5% required IOP-lowering medical therapy. During the 3-year study, eyes received a series of dexamethasone implants because each gradually lost effect,

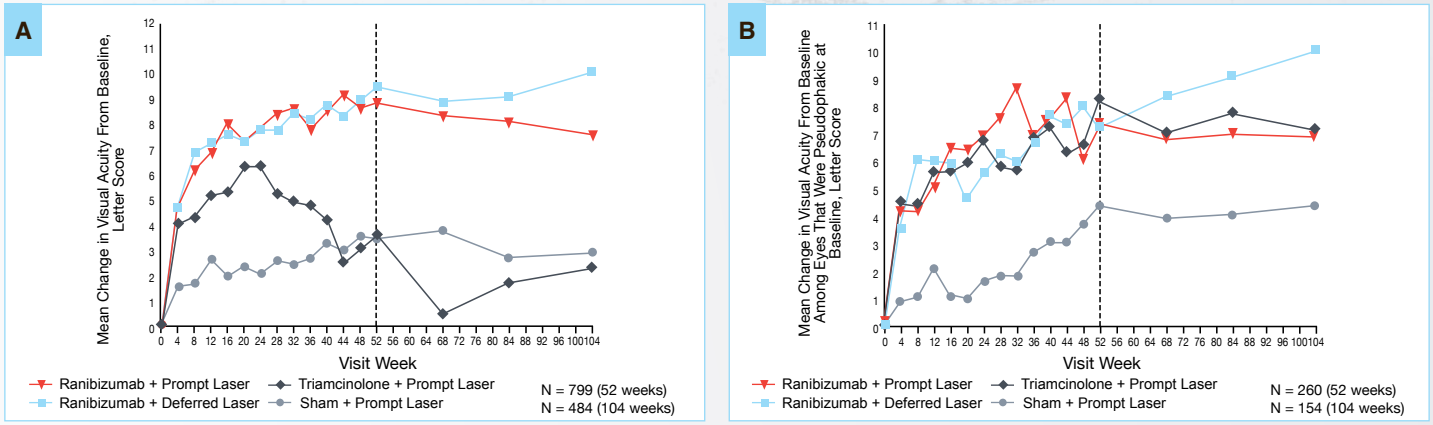

Figure 4. Visual acuity gains among all eyes (A) and the subgroup of pseudophakic eyes (B) in the Diabetic Retinopathy Clinical Research Network's Protocol I study[20]

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and the risk of a ≥ 10-mm Hg IOP rise in the study cohort increased for a short time after each new dexamethasone implant injection, although this effect was not cumulative **(Figure 5)**.[38]

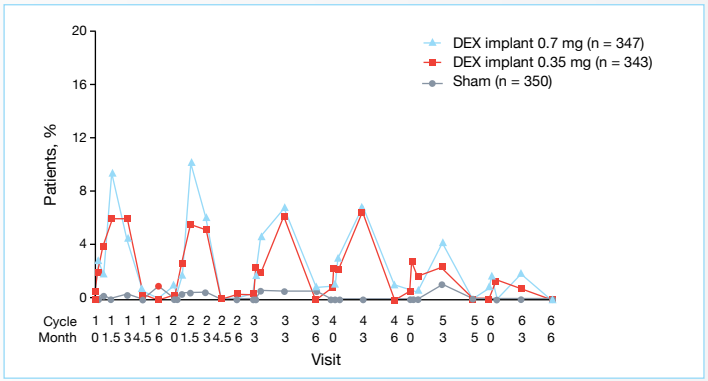

Figure 5. Proportion of eyes with a ≥ 10-mm Hg intraocular pressure increase from baseline by visit in the MEAD study[38]

Abbreviation: DEX, dexamethasone intravitreal implant.

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The fluocinolone acetonide (FAc) implant incorporates 0.19 mg of drug and elutes more slowly than the dexamethasone implant, providing therapeutic benefit for up to 36 months.[39] In the pivotal FAME study, also conducted in eyes with laser-unresponsive DME, 28.7% of the 376 eyes in the FAc implant group gained ≥ 15 letters at 3 years vs 18.9% of the 185 eyes in the sham group (P = .018). Up to 40% of eyes receiving the FAc implant will require medications for IOP elevations, and 5% will require surgical glaucoma management.

Both MEAD (dexamethasone) and FAME (FAc) evaluated the role of corticosteroid monotherapy on laser-unresponsive eyes. In the anti-VEGF era, it is perhaps more relevant to ask how effectively corticosteroid therapy adds to, or replaces, anti-VEGF therapy in suboptimally responsive eyes. The DRCRnet's Protocol U randomized eyes with DME with persistent edema after ≥ 3 injections of ranibizumab to continue ranibizumab coupled with either the dexamethasone 0.7-mg implant (n = 63) or sham implant injection (n = 64).[40] After 24 weeks, there was less than a 1-letter difference between the ranibizumab and ranibizumab/corticosteroid combination groups overall (P = .73), despite a significantly greater change in OCT central subfield thickness in the combination group (-110 μm vs -62 μm; P < .001). Significantly more anti–VEGF-refractory eyes with DME treated with combination therapy gained ≥ 15 letters than eyes treated with continued ranibizumab alone (11% vs 2%; P = .03). As in Protocol I, visual gains were better in pseudophakic eyes than in phakic eyes receiving corticosteroid combination therapy. Also, 29% of the 65 combination eyes vs 0% of the 64 ranibizumab-alone eyes (P < .001) required IOP-lowering medications. Elevations of IOP following administration of intravitreal corticosteroids can often be managed in the retina practice. An expert consensus panel outlined suggested thresholds for different treatments and when to refer to a glaucoma specialist, as detailed in **Table 2.**[30]

In Protocol U, significantly more anti–VEGF-refractory eyes with DME treated with combination therapy gained ≥ 15 letters than eyes treated with continued ranibizumab alone (11% vs 2%; P = .03).

– Raj K. Maturi, MD

Table 2. Expert Consensus Panel Recommendations for Treating Elevated Intraocular Pressure in the Retina Practice Following Intravitreal Corticosteroid Treatment[30]

Intraocular Pressure, mm Hg	Recommended Treatment*
< 22	Observation
22-25	Single topical medication
26-30	Fixed-combination topical medication
> 30	Fixed-combination topical medication OR Refer to a glaucoma specialist

* Assumes healthy optic nerves. If any optic nerve abnormality is observed, treatment should be more aggressive.

The therapeutic effectiveness of the various intravitreal steroids is determined by their potency and their solubility in vitreous. Lower solubility **(Table 3)** extends the duration of effectiveness but also limits the maximum dose.[41] The dexamethasone implant is more soluble than triamcinolone acetonide or FAc and releases a high level of drug immediately after implantation, which might translate to higher efficacy vs other corticosteroids immediately following implantation. The FAc implant releases drug more slowly, hence lasting longer. Studies in both rabbit and human eyes have

Table 3. Relative Solubility of Steroids Used to Treat Diabetic Macular Edema[41]

Corticosteroid	Water Solubility, µg/mL	Glucocorticoid Receptor Activation Potency, HeLa Cells		Mineralocorticoid Receptor Activation Potency, HeLa Cells	
		Absolute, nM	Relative to Cortisol, %	Absolute, nM	Relative to Cortisol, %
Cortisol	280	72	100	0.04	100
Prednisolone	223	8	900	0.015	267
Dexamethasone	100	3	2400	0.3	13
Fluocinolone acetonide	50	0.4	18,000	> 100	< 0.04
Triamcinolone acetonide	21	1	7200	> 100	< 0.04

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demonstrated that prior vitrectomy does not significantly alter the pharmacokinetic properties of these corticosteroid implants.[42,43]

In summary, corticosteroids are efficacious as a therapy for DME that does not respond to anti-VEGF therapy. Combination therapy with corticosteroid implants can improve central subfield thickness in eyes with chronic or anti-VEGF–refractory DME. Selecting a corticosteroid should take into account the duration of action/pharmacokinetics, dosing limitations, and safety profile of each drug.

Case 1: Assessing Response to Anti-VEGF Therapy in Newly Diagnosed Treatment-Naïve DME

From the Files of Carl D. Regillo, MD

A 58-year-old white male with diabetes presented for an annual diabetic eye examination. His right eye, which is phakic, was found to have severe nonproliferative DR and DME ***(Figure 6)****, with VA of 20/100. He received monthly injections of ranibizumab for 3 months, and his VA improved to 20/70. After an additional 3 monthly injections, his VA improved to 20/30.* ***Figure 7*** *shows his OCT images at each visit.*

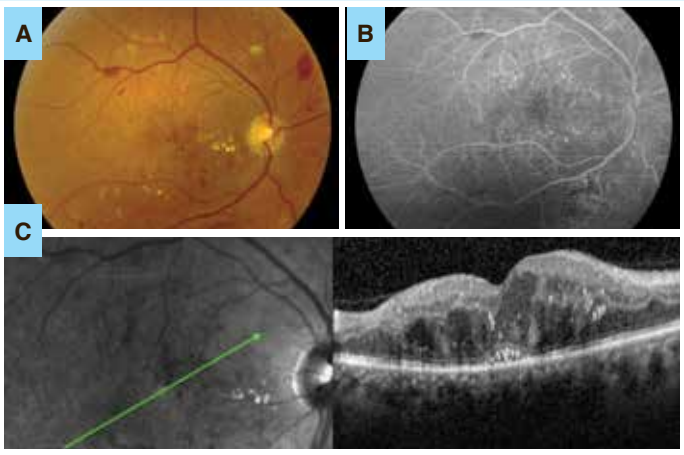

Figure 6. Color fundus photograph (A) and fluorescein angiography (B) and optical coherence tomography (C) images of the right eye of the patient presented in Case 1

Panel Discussion

Dr Regillo: After 7 monthly injections, his VA improved to 20/30, but some residual edema remains. What would you do now?

Dr Kim: This eye is responding to ranibizumab, although somewhat slowly, which is not unusual. There was no major

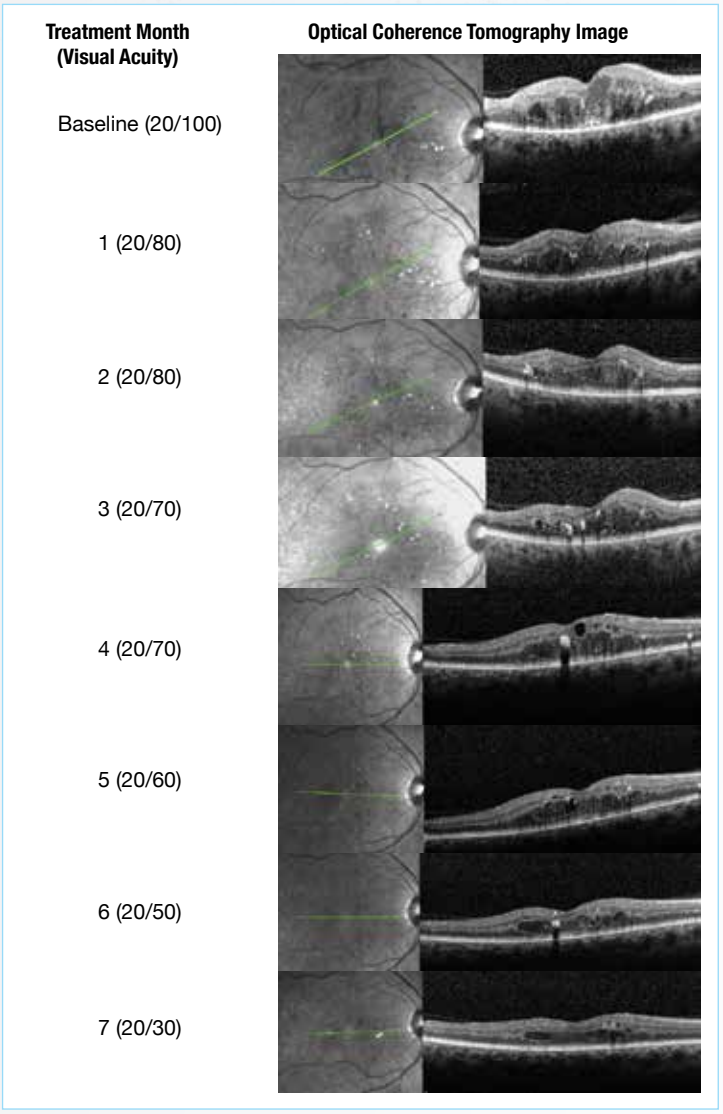

Figure 7. Optical coherence tomography images of the right eye of the patient presented in Case 1 over the course of treatment

improvement in vision at month 3, but edema was resolving. I agree with the decision to provide additional monthly anti-VEGF injections, which resulted in further VA and anatomic improvement at month 7. I would continue to treat monthly with ranibizumab until no further improvement in VA and anatomy for 2 consecutive visits, and then start to defer treatment and extend follow-up intervals to 2 months and then to 4 months. This so-called "Defer-and-Extend" treatment schedule was used in several DRCRnet studies.[44-46] If the VA declines or if the fluid recurs or worsens, resume anti-VEGF injections.

Dr Maturi: I would consider fluorescein angiography at this point. There might be a focal aneurysm outside the foveal avascular zone contributing to the ongoing leakage. There could be a role for focal laser photocoagulation in conjunction with ongoing anti-VEGF therapy.

Dr Regillo: I considered withholding further injections and observing, given that he had improved from 20/100 to 20/30. Because there was persistent edema, however, I continued monthly ranibizumab injections.

Take-Home Points

- Anti-VEGF therapy is the standard first-line therapy for DME in most eyes
- Some eyes respond more slowly than others
- So long as improvement continues, current therapy should be continued

Case 2. Chronic DME Responsive to Corticosteroid Therapy

From the Files of Raj K. Maturi, MD

*A 64-year-old male presented with an 18-year history of noninsulin-dependent diabetes. His blood glucose was well controlled, with HbA_{1c} levels in the 6.2% to 7.0% range, although earlier in his disease, his control was less optimal. He had a history of prior laser therapy for DME. He had hypertension and hypercholesterolemia as well. He had noticed intermittent blurred vision in the left eye for the past few weeks, which he described as a "cobweb", with no changes in the vision in the right eye. His VA at baseline was 20/60. On OCT, he was found to have recurrent DME in the left eye **(Figure 8)**. He received 4 monthly injections of bevacizumab, with some improvement in macular thickness **(Figure 8)**, followed by focal macular laser, which appeared to worsen his DME.*

*Given the patient's limited response to anti-VEGF therapy or focal macular laser, a dexamethasone implant was injected. Within 1 month, his macula was flat **(Figure 8)**. By 6 months postimplant, the edema recurred and a second implant was given, again resulting in macular flattening. Over the next 18 months, he received 2 additional dexamethasone implants—approximately 1 every 6 months—each of which successfully rescued his macula, resulting in flattening on OCT and stability of VA in the 20/50 to 20/60 range.*

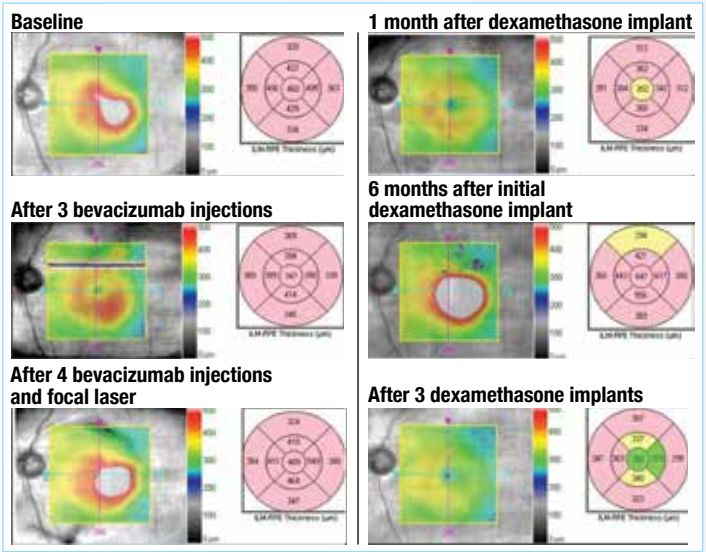

Figure 8. Optical coherence tomography images over the course of treatment for diabetic macular edema in the left eye of the patient presented in Case 2

Panel Discussion

Dr Regillo: This case illustrates a phenomenon I have observed in my own practice. I very rarely see a "slow responder" to dexamethasone or steroids in general. Steroids either work or not, and you typically know by month 1 whether the eye will respond. I think this speaks to the inflammatory component of DME's pathophysiology. There are more factors at play than simply VEGF. These proinflammatory processes respond well and quickly to corticosteroid therapy.

Dr Kim: That has been my experience as well. Interestingly, although the onset of effect from steroids is fairly uniform across patients, the duration of effect varies widely from patient to patient. When do you see patients again after starting corticosteroid treatment?

Dr Maturi: I see them again after 4 to 6 weeks, more for safety than for efficacy. As Dr Regillo pointed out, the therapeutic effect is typically present by then. The first posttreatment visit is more for monitoring IOP. If the IOP is acceptable at the first visit, I see them again approximately 3 months out. If they have had multiple prior dexamethasone implants without an IOP problem, I might skip the first visit and see them for the first time at 3 months.

Dr Regillo: Who are the patients in whom you would consider steroids to be contraindicated?

Dr Maturi: The biggest contraindication is the pseudophakic patient who had posterior capsule rupture during surgery or whose intraocular lens implant is not completely stable. In these settings, the corticosteroid implant can migrate from the posterior segment to the anterior chamber. Once this occurs, the eye will develop corneal edema and inflammation that might even produce a hypopyon mimicking endophthalmitis. In these cases, explantation can be easily achieved through a paracentesis. I make it a point not to touch the implant during explantation, if possible, because it can break up and leave small pieces behind.

Dr Regillo: The corneal edema in these cases tends to be inferior and worse over the implant and can be associated with Descemet folds. It might be less due to inflammation and more of a mechanical effect.

Dr Maturi: The second contraindication is a history of high IOP. If the eye has had a response to topical steroids, I typically do not use corticosteroid implants.

Take-Home Points

- Some eyes with DME do not respond to anti-VEGF therapy
- Corticosteroid therapy can be effective in eyes not responding to anti-VEGF therapy, but is associated with side effects, including cataract formation and IOP elevation
- Eyes receiving corticosteroid therapy should be monitored closely for IOP elevation
- Corticosteroids should be avoided in eyes with a history of elevated IOP associated with prior corticosteroid therapy

Case 3. DME Refractory to Treatment

From the Files of Judy E. Kim, MD

A 61-year-old white female presented with type 2 diabetes, which she has had for 23 years. Her HbA_{1c} level was 11%, despite her best efforts. She had a body mass index of 49 kg/m^2, and had systemic hypertension. She was referred for evaluation of moderate nonproliferative DR with DME in both eyes, and had a history of focal and grid macular laser photocoagulation in both eyes. On examination, her VA was 20/30 OD and 20/50 OS.

Her IOP was 15 mm Hg OD and 17 mm Hg OS. ***Figure 9*** *shows significant fluid in the baseline OCT image of her left eye.*

A course of monthly intravitreal injections of bevacizumab initially resolved the retinal fluid, but breakthrough edema was observed despite repeated injections. The patient was switched to ranibizumab, with no appreciable effects, and was then switched to aflibercept, which dried the macula, but only for 6 to 8 weeks per injection. Supplementary triamcinolone acetonide was given in hopes of extending the anti-VEGF treatment interval, but without success. At this point, the vision in the left eye ranged between visits from 20/60 to 20/200. Because of multiple systemic medical issues, the patient missed several visits. A dexamethasone implant was injected, which resulted in near-complete fluid resolution ***(Figure 9)****, but after 3 to 4 months, severe edema recurred. At the same time, the patient's IOP rose significantly in the left eye, which was unresponsive to medical therapy and required a tube-shunt procedure. A second dexamethasone implant cleared the DME for only 2 months before recurring. To increase the duration of response, an FAc implant was then injected, which dried the macula for 6 months, but by 9 months postinjection, a slight recurrence of fluid was observed.*

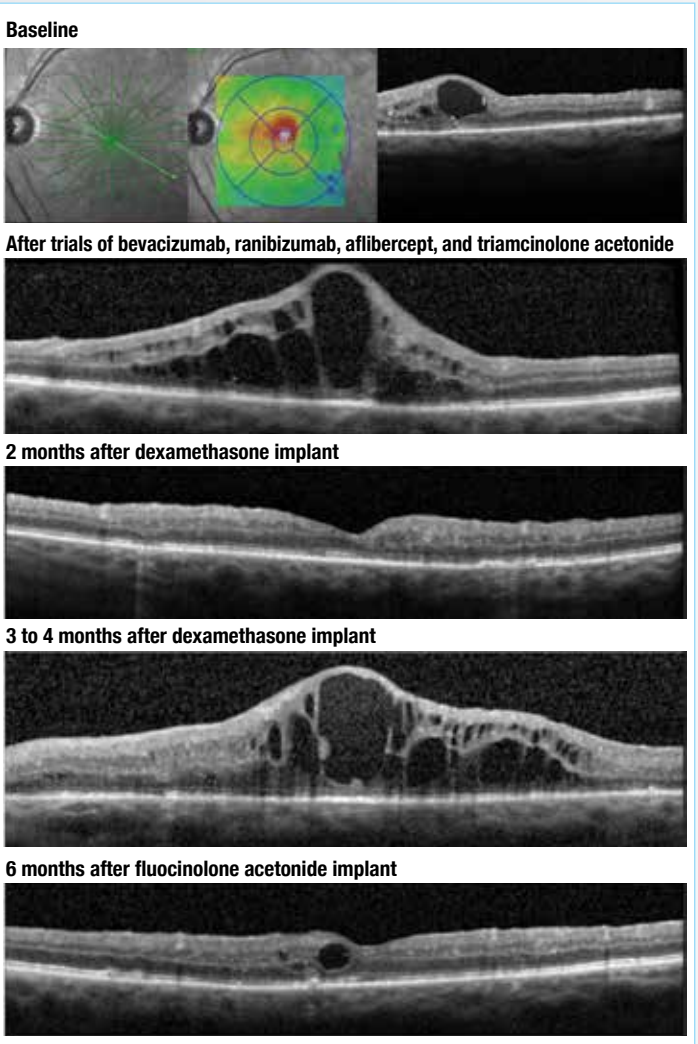

Figure 9. Optical coherence tomography images over the course of treatment of diabetic macular edema in the left eye of the patient presented in Case 3

Panel Discussion

Dr Kim: This patient has DME that breaks through even corticosteroid therapy. How would you manage her in the long term?

Dr Maturi: The eye has already had laser treatment. Vitrectomy remains an option. Her body mass index and other comorbidities, however, might confer a high risk to surgery.

Dr Regillo: We ideally would like to see more than 9 months of efficacy from an FAc implant, and we typically do. I suppose you could reinject the FAc implant annually if that is what it takes to control the disease.

Dr Maturi: With FAc on board, I wonder if supplemental dexamethasone implants might extend the overall duration of control between retreatments.

Dr Regillo: For that matter, it might be worth going back to monthly anti-VEGF therapy to see if that can extend the duration between corticosteroid retreatments. Although combination therapy was no better than ranibizumab alone on average in Protocol U,[40] it might benefit some patients and is worth trying in cases such as this one. This approach has the advantage of addressing both the inflammatory and noninflammatory components of the disease.

Dr Kim: I elected to supplement with monthly aflibercept and will consider repeat FAc implant, if needed, after at least 1 year from the previous implant.

Take-Home Points

- Some eyes with DME will be refractory to many, most, or all therapies available
- In eyes with DME refractory to treatment, combination therapy can be considered
- A more frequent dosing strategy might be required in some eyes

Summary

- Diabetes affects 30 million Americans; DR and DME are common ocular complications
- The pathophysiology of DME is multifactorial and complex
- The role of VEGF—and the benefit of anti-VEGF therapy in DME—has been established, but inflammation is a key component of the pathophysiology of DME that should not be overlooked
- A significant proportion of eyes with DME have suboptimal therapeutic response to anti-VEGF therapy
- Eyes with suboptimal response—manifested by lack of VA improvement, persistent edema, or both—after 3 to 6 monthly anti-VEGF injections should be considered for corticosteroid therapy
- Corticosteroids either *in place of* or *in addition to* anti-VEGF therapy can improve outcomes in some eyes with DME
- Various sustained-release corticosteroid-eluting implants have been developed to extend the therapeutic duration and to minimize treatment burden
- Pharmacologic differences, including solubility and peak drug release kinetics, should be considered when selecting a corticosteroid for individual patient scenarios
- Although steroids are effective in eyes with DME, complications do exist, including cataracts and elevated IOP

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For additional information, see **Instructions** on page 2.

1. Which of the following intravitreal corticosteroids likely has the highest efficacy immediately following injection/implantation owing to its relative solubility and pharmacokinetics?
   a. Dexamethasone
   b. FAc
   c. Triamcinolone acetonide

2. Which mediator of DME pathogenesis accumulates in the aqueous as the severity of DR increases AND is reduced upon corticosteroid treatment?
   a. VEGF
   b. Interleukin-6
   c. Angiopoietin-2
   d. Platelet-derived growth factor

3. Which of the following regarding VEGF is correct?
   a. VEGF level goes up statistically significantly with increasing DR severity
   b. VEGF level does not change statistically significantly with increasing DR severity
   c. VEGF level goes down statistically significantly with increasing DR severity
   d. Anti-VEGF therapy is more effective at statistically significantly lowering cytokine levels than are corticosteroids

4. How many anti-VEGF injections should be given to patients with DME before considering a treatment switch because of suboptimal response?
   a. 1 to 2
   b. 3 to 6
   c. 7 to 9
   d. 10 or more

5. Four weeks after receiving a dexamethasone implant, a patient's IOP rises from 15 mm Hg to 25 mm Hg. Which is a reasonable intervention for this patient?
   a. Observe IOP until next follow-up 2 months later without treatment
   b. Consider starting an IOP-lowering medication
   c. Refer the patient to a glaucoma specialist
   d. Switch to an FAc implant when retreatment is necessary

6. How does diabetes affect the ocular concentrations of inflammatory molecules?
   a. They are generally lower in eyes with diabetes than in those without diabetes
   b. They generally decrease with increasing severity of DR
   c. They are higher in eyes with DME than in those without DME
   d. They are unaffected by diabetes status

7. In Protocol I, ____ patients were classified as "nonresponders" to anti-VEGF treatment.
   a. 5%
   b. 10%
   c. 20%
   d. 40%

8. How do anti-VEGF and corticosteroid therapies affect ocular concentrations of inflammatory molecules?
   a. Anti-VEGF therapy lowers their concentrations
   b. Corticosteroids raise their concentrations
   c. Neither treatment affects their concentrations
   d. Corticosteroids, but not anti-VEGF therapy, lower their concentrations in most cases

9. A female patient presents with a 3-year history of DME. She was lost to follow-up and last received an anti-VEGF injection more than a year ago. Her vision has been decreased for at least 1 year. Her VA is now 20/100, and there is relatively severe central macular edema OCT. Which of the following best describes her clinical status?
   a. She has failed treatment with anti-VEGF therapy and should now receive steroids
   b. Combination treatment has a low likelihood of resolving her excess retinal thickness
   c. Her edema likely has a chronic component, and the affected eye might not achieve optimal VA gains
   d. She can expect full recovery of VA after restarting anti-VEGF therapy

10. Which corticosteroid is ***most*** limited in its maximum dose because of low water solubility?
    a. Cortisol
    b. Dexamethasone
    c. FAc
    d. Triamcinolone acetonide