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MANAGING DIABETIC MACULAR EDEMA: BEST PRACTICES IN REAL-WORLD SITUATIONS

Provided by evolve medical education

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a recorded webinar and two live case discussions.

ACTIVITY DESCRIPTION

This supplement focuses on relevant and timely discussions about treating patients with diabetic retinopathy (DR) and diabetic macular edema (DME). The COVID-19 pandemic has resulted in additional challenges for both patients and retina specialists. The esteemed faculty members examine clinical trial data and share their expertise on treatment options during these unprecedented times, methods for implementing treatment, and the role of inflammation, among other topics.

TARGET AUDIENCE

This certified CME activity is designed for retina specialists and ophthalmologists involved in the management of retinal diseases.

LEARNING OBJECTIVES

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

- **Identify** the role of inflammation in patients with DME and DR.
- **Implement** treatment regimens for patients with DME and DR.
- Through real-world and post-hoc analyses, **identify** the drawbacks to current use of anti-VEGFs in DME.
- **Differentiate** steroids in the management of DME while implementing strategies for treatment and patient outcomes.

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures Instructions for CME Credit.

1. Please rate your confidence in your ability to implement treatment regimens for patients with diabetic macular edema (DME) and diabetic retinopathy (DR) (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. In the DRCR Protocol I subanalysis, what percentage of eyes with DME received early and consistent therapeutic benefits from anti-VEGF treatment?

a. 25%
b. 50%
c. 75%
d. 100%

3. According to the literature, what impact does an intravitreal injection of bevacizumab have on concentrations of IL-6, IL-8, and other inflammatory chemokines implicated in DME?

a. The concentrations of the inflammatory chemokines increase.
b. The concentrations of the inflammatory chemokines decrease.
c. The concentrations of the inflammatory chemokines stay relatively stable.
d. The concentrations of some inflammatory chemokines decrease and the concentration of some inflammatory chemokines increase.

4. According to the "Shall we stay, or shall we switch" study, what outcome was noted in eyes with refractory DME?

a. Eyes that received a dexamethasone implant were more likely to gain at least 5 letters compared with eyes that were maintained on anti-VEGF.
b. Eyes that received anti-VEGF were more likely to gain at least 5 letters compared with eyes that received a dexamethasone implant.
c. Eyes that received a dexamethasone implant were more likely to lose at least 5 letters compared with eyes that were maintained on anti-VEGF.
d. Eyes that received dexamethasone implant and anti-VEGF performed equally with regard to letters gained.

5. The international retina group real-life 24-month multicenter study (IRGREL-DEX) demonstrated what percent of patients receiving a dexamethasone intravitreal implant needed subsequent intraocular pressure-lowering therapy?

a. ~5%
b. ~10%
c. ~15%
d. ~20%

6. Post-hoc analysis of randomized controlled trial data from DRCR.net Protocol I identified the fact that _____% of patients were nonresponders or suboptimal responders to anti-VEGF treatment.

a. 10%
b. 20%
c. 30%
d. 40%

7. Which of the following is true regarding the pathogenesis of DME upregulation of anti-VEGF?

a. DME involves the upregulation of numerus inflammatory mediators, including but not limited to anti-VEGF.
b. DME is a process that is independent of anti-VEGF.
c. DME does not involve anti-VEGF.

8. Which of the following drugs inhibits both VEGF-A and VEGF-B?

a. Bevacizumab
b. Ranibizumab
c. Pegaptanib
d. Aflibercept

9. Which of the following statements about the role of Ang-1/Ang-2 in diabetes is NOT true?

a. Elevated Ang-2 (but not Ang-1) is associated with worse metabolic indices and endothelial dysfunction.
b. Elevated Ang-2 (but not Ang-1) is associated with increased HbA1c levels.
c. Decreased levels of Ang-2 are found in the vitreous of patients with proliferative DR.
d. Elevated Ang-2/Ang-1 ratio is found in the vitreous of patients with nonproliferative DR and DME.

Managing Diabetic Macular Edema: Best Practices in Real-World Situations

Diabetic macular edema (DME) and diabetic retinopathy (DR) are the primary ocular complications of diabetes.[1] DR and DME not only cause vision impairment, but can cause irreversible blindness in a third of patients who develop them.[2] Intensive intravitreal anti-VEGF injections have become the gold standard treatment for DME and DR and have been proven to reduce the risk of progression and further vision impairment. However, these treatments come with a significant treatment burden and aren't uniformly effective, as some patients will not respond to anti-VEGF therapy regardless of treatment intensity. Further, anti-VEGF agents don't address the inflammatory component of DME/DR pathogenesis, which may hinder their effectiveness. The following activity brings together thought leaders in the DME space to discuss how inflammation factors into DME development, how treatments can be improved for maximum effectiveness, and novel agents in the pipeline.

—Sophie J. Bakri, MD, Moderator

THE ROLE OF INFLAMMATION AND STEROID USE IN DME TREATMENT

Q | SOPHIE J. BAKRI, MD: During our discussion, we will identify the role of inflammation in patients with DME and DR, identify treatment regimens for patients with DME and DR, and review the drawbacks of our current use of anti-VEGF agents in DME. We'll also touch on strategies to improve treatment and patient outcomes.
Dr. Kuppermann, what is the role of inflammation in patients DME and DR?

BARUCH D. KUPPERMANN, MD, PHD: Inflammation seems to be quite important in DME pathogenesis and may impact the effectiveness of our anti-VEGF agents. Anti-VEGF agents are the first-line therapy for patients with most retinal diseases, including wet age-related macular degeneration (AMD), retinal vein occlusion, and DME. However, the success rate of anti-VEGF agents in our patients with DME is quite a bit lower than it is for other diseases.

A 2012 subanalysis of the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I by Bressler et al looked at factors associated with changes in visual acuity (VA) and central subfield thickness (CST) at 1 year after intravitreal ranibizumab treatment for DME.[3] The goal was to determine if certain factors predict anti-VEGF treatment success or failure.

A total of 361 eyes were randomly assigned to either ranibizumab with prompt or deferred laser, laser alone, or triamcinolone acetonide plus laser. Study eyes were differentiated into one of four categories based on whether they had at least a 20% reduction from baseline CST at the 16-week, 32-week, and 1-year visit: early and consistent, early but inconsistent, slow and variable, and nonresponder.

When looking at the ranibizumab groups, only 50% had early and consistent responses. A surprisingly high number (23%) were considered nonresponders, with another 27% having intermediate responses. We know that this is suboptimal in many of our patients, and begs the question: Why is anti-VEGF treatment effective in some disease states but not others?

A key reason for this could be inflammation, which is an important component of DME. Historically, we've focused on the role of retino-capillary damage and anatomic changes in DME, but that occurs quite late in the disease process. Inflammation, however, occurs almost immediately.

Understanding How Inflammation Causes DME Pathogenesis

Q | DR. BAKRI: Specifically, what is known about inflammation and DME pathogenesis?

DR. KUPPERMANN: It's a complicated process. Hyperglycemia and oxidative stress cause local inflammation through the activation of microglial cells. The microglial cells migrate into the subretinal space where they accumulate, become trapped, and start to produce nitric oxide and a variety of cytokines and chemokines that lead to increased levels of inflammatory mediators.[4-6] These inflammatory mediators and oxidative stress lead to dysfunction of the Mueller cells, causing intracellular fluid accumulation, resulting in intracellular edema. This cascade of events causes chronic inflammation, neurodegeneration, and then the subsequent vascular leakage and DME.

Dong et al studied the relationship between 27 aqueous humor cytokines and DR severity.[7] Undiluted aqueous humor samples were obtained from 102 nondiabetic patients and 136 diabetics who were divided into nine groups according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) severity scale. The ETDRS score was very low, with about 20% of diabetics having a score of 10 (Table 1).

The researchers measured cytokine levels, finding that diabetics had significantly higher concentrations of interleukin (IL)-1ß, IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), interferon gamma-induced protein-10, and VEGF in the aqueous humor compared with non-diabetic controls. In the diabetic group, the VEGF level

was about 1,000; in the control group, VEGF levels were below 100 (Table 1). Based on these data, there seems to be a trigger related to the onset of diabetes.

Although patients develop more advanced retinopathy over time, Table 1 shows that VEGF levels don't incrementally increase; they shoot up immediately in a binary fashion, as if a switch is thrown. However, if you look at the other cytokines and interleukins in Table 1, you see that they start low and increase over time. This may help explain the variable responses we see from patients who have DME getting VEGF inhibition.

In summary, retinopathy progresses with time and is associated with changes in the amounts of multiple cytokines relative to VEGF, not just VEGF.

TABLE 1. RELATIONSHIP BETWEEN AQUEOUS HUMOR CYTOKINES AND SEVERITY OF DR[7]

ETDRS retinopathy severity	N	Cytokine concentration (pg/mL)					
		VEGF	IL-1β	IL-6	IL-8	MCP-1	IP-10
10	28	967	10	32.1	22.8	252.2	2.1
20	23	952.8	11	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	1215.1	31.3
75	8	1051.4	27.6	147	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: IL, interleukin; IP, interferon-inducible protein; MCP, monocyte chemotactic protein; VEGF, vascular endothelial growth factor; DR, diabetic retinopathy; ETDRS, Early Treatment of Diabetic Retinopathy Score.

The Role of Steroids in Reducing Inflammation for DME Treatment

Q | DR. BAKRI: How can steroids be used to address the inflammatory components of DME pathogenesis?

DR. KUPPERMANN: There are a lot of data from clinical trials showing that if DME becomes chronic, it becomes unresponsive to anti-VEGF therapy but is responsive to steroid therapy. For example, Sohn et al looked at the effects of a single injection of triamcinolone acetonide or bevacizumab on cytokine levels in 11 DME patients with bilateral disease.[8] Patients were treated in the simplest way possible: triamcinolone acetonide in one eye and bevacizumab in the other eye, followed by cytokine level measurement.

Bevacizumab only reduced VEGF levels, whereas triamcinolone acetonide reduced IL-6, MCP-1, platelet-derived growth factor-AA, and VEGF (Table 2). We know that steroids are very effective at lowering the cytokine and VEGF levels. Table 2 shows that steroids are great VEGF inhibitors, lowering VEGF by about 80%, but that bevacizumab is a fantastic VEGF inhibitor, lowering VEGF levels by 99%.

You would think that if you lowered something as important as VEGF, there would be some collateral effects; upregulation, downregulation, something from these other inflammatory cytokines. However, they don't appear to budge; they remain at the level they were prior to injection. It's a bit of a mystery. It's almost as though there are two parallel pathways: the VEGF-mediated pathway, and then the other inflammatory cytokine and chemokine pathway. The authors noted that a steroid that could minimize adverse events and simultaneously address these components of pathogenesis would be of great benefit.

Researchers have argued that there are two types of patients: (1) patients who have a low level of VEGF but high levels of non-VEGF mediators, and (2) patients who have a high level of VEGF but who have low levels of non-VEGF mediators.[9-11] Patients in group 2 are exquisitely sensitive to VEGF inhibition, while patients in group 1 tend to be unresponsive to anti-VEGF therapy. The unresponsiveness could be because the other cytokines swamp the VEGF signal, causing these patients to not be as responsive to VEGF inhibition alone. These patients may need additional therapy, and it does seem that steroids are effective in treating both types of patients.[11,12]

For example, let's take the FAME study, which looked at patients with DME treated either with fluocinolone acetonide or sham.[13] If patients didn't have a good response in terms of optical coherence tomography (OCT) thickness after 6 weeks, then they could be treated at will. Most of those patients received bevacizumab. Researchers looked at the median duration of DME prior to enrollment, which was roughly 2 years, and then analyzed the outcomes. Fluocinolone acetonide worked just as well on patients with chronic DME as

TABLE 2. STEROIDS ADDRESS THE MULTIFACTORIAL NATURE OF DME[8]

Cytokine Conc., 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	.477
IL-8	28.2	25.3	0.597	23.9	23.6	.374
IP-10	366	249	0.013	401	433	.11
MCP-1	3850	1090	0.01	3770	3840	.594
PDGF-AA	68.7	37.1	0.016	81	72.7	.722
VEGF	55	10.5	0.05	61.5	0.1	< .01

Bilateral injection of patients with DME (1 eye IVTA*, 1 eye bevacizumab*)
Abbreviations: IL, interleukin; IP, interferon-inducible protein; IVBe, intravitreal bevacizumab; IVTA, intravitreal triamcinolone acetonide; MCP, monocyte chemotactic protein; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.
*Not licensed for ophthalmic use; [a]Wilcoxon signed rank test.

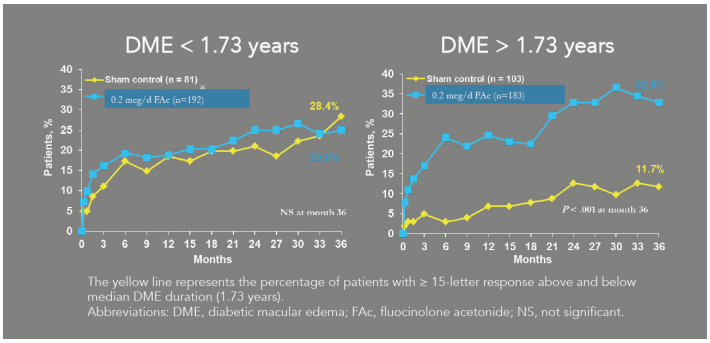


Figure 1. Fluocinolone acetonide implant study for macular edema: treatment effect seen in FAME by duration of DME at baseline (pooled data).[13]

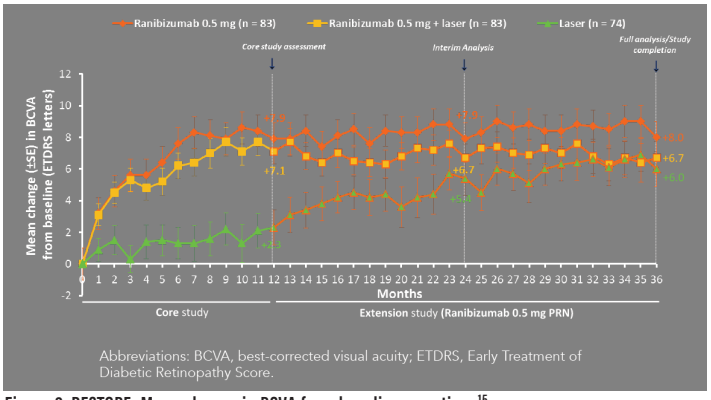


Figure 2. RESTORE: Mean change in BCVA from baseline over time.[15]

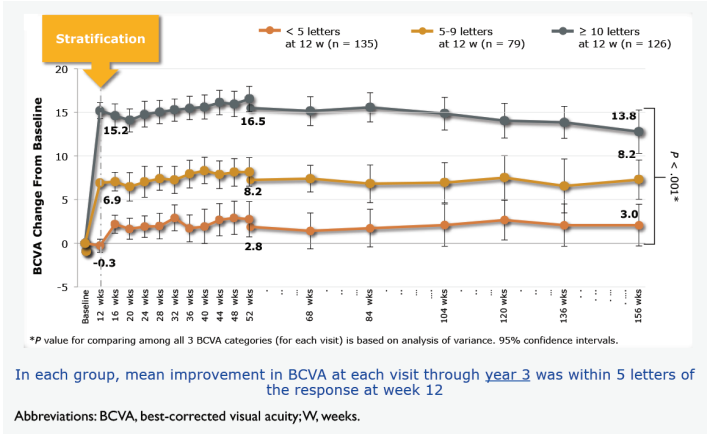


Figure 3. Subanalysis of DRCR.net Protocol I.[16]

patients with less chronic disease (Figure 1). However, the patients with chronic disease treated with something other than steroids, like anti-VEGF therapy, had a much weaker response.

Understanding How Disease Duration Impacts Anti-VEGF Response and Outcomes

Q | DR. BAKRI: As you mentioned, there is some evidence that as DME becomes chronic, the responsiveness to VEGF inhibition is reduced. What does the literature tell us about this?

DR. KUPPERMANN: In both the RISE and RIDE trials, the control populations received 24 months of sham therapy.[14] After that time, investigators were finally able to give patients what they wanted—ranibizumab 0.5 mg. By then it was too late; the control populations demonstrated minimal response to monthly ranibizumab. This is because after 24 months of sham, the disease became chronic, resulting in basically no response to VEGF inhibition. Ranibizumab was not effective at improving their vision. Early on, however, these eyes were very sensitive to VEGF inhibition.

There are other examples of this as well. The RESTORE extension trial looked at 208 patients from the core study who received either ranibizumab 0.5 mg (n = 83), ranibizumab 0.5 mg plus laser (n = 83), or laser alone (n = 74).[15] Patients were eligible to receive individualized ranibizumab treatment as of month 12 guided by best-corrected visual acuity (BCVA) and disease progression criteria at the investigators' discretion. Concomitant laser treatment was allowed according to the ETDRS guidelines. In patients treated with ranibizumab in the core phase, mean BCVA gain at month 12 was maintained to month 36. In patients treated with laser alone, mean BCVA progressively improved from month 12 to month 36 with ranibizumab (Figure 2).

If you look at the left side of Figure 2, you see that there's a green line that gradually builds over time, but there is clearly a blunted response compared to what you saw at baseline, represented by the yellow and orange lines. Again, even within 1 year, maybe even sooner, there's an attenuation to response to VEGF inhibition as eyes develop more chronic inflammation and more chronic macular edema.

Another example of this is an early sub-analysis of DRCR.net Protocol I, which assessed 340 eyes from the primary trial.[16] Patients received ranibizumab every 4 weeks and were evaluated at week 12 for response. At the 12-week evaluation, they were placed into three groups: (1) patients who gained 5 or fewer letters (40%); (2) patients who gained 5 to 9 letters (23%); and (3) patients who gained 10 or more letters (37%). Patients were then plotted over the next 3 years for their response, and what happened was the famous swim lanes depicted in Figure 3.

Eyes that gained fewer than 5 letters after three injections showed limited additional improvement for the study duration. These patients were unlikely to cross over to the 10-letter or more group; in fact, only 30% of eyes from the 5-letter or fewer group crossed over to the 10-letter or more group by the end of the study.

This shows that early response with as few as three injections of ranibizumab may be able to predict long-term outcomes. Upwards of 70% of patients will not have an improved response with time if their initial response is limited. This should help inform clinicians on the choice to continue the same therapy or switch therapies as soon as after three injections, depending on the degree of response. This was partially corroborated by DRCR.net Protocol T.[17,18] The outliers were bigger, and it wasn't quite as clean, but that same concept was true for ranibizumab, aflibercept, and bevacizumab.

In summary, we know that when anti-VEGF therapy is used in the first-line setting, three intravitreal injections are frequently predictive of long-term outcomes.

Dexamethasone Implant Versus Anti-VEGF Therapy

Q | DR. BAKRI: The dexamethasone implant is approved by the US Food and Drug Administration for the treatment of DME among other indications. We know that dexamethasone is six times stronger than triamcinolone acetonide.[19] How does the dexamethasone implant compare to anti-VEGF therapy?

DR. KUPPERMANN: If you look at real-life outcomes with the dexamethasone implant, response was quite robust with 6 to 9 letters gained with two to three injections in the first year. This is further corroborated by a host of studies showing similar responses in both treatment-naive and refractory patients.[11,20-24]

More recently, a study from Escobar-Barranco et al showed good response in patients with both treatment-naive or refractory diffuse DME. Patients with treatment-naive disease gained an average of 12 letters with a median reinjection time of 5 months; refractory patients gained 8 letters with a median reinjection time of 4 months.[11] The IRGREL-dexamethasone study from Iglicki et al told a similar story.[25] Refractory eyes gained about 7 letters, while treatment-naive eyes gained 11.

One of the more interesting studies is from Busch et al, the "Shall we stay, or shall we switch" study. Patients were treated with three monthly anti-VEGF injections and then evaluated.[26] If they were deemed to have refractory DME, they were randomly assigned to either switching to the dexamethasone implant or continuing anti-VEGF therapy. They were then evaluated for BCVA and OCT thickness change.

Eyes that were switched to the dexamethasone implant after three anti-VEGF injections and then deemed to be refractory showed a significant benefit with the switch compared with continuing anti-VEGF therapy, both in terms of vision and in OCT thickness. On average, eyes continuing with anti-VEGF therapy received 4.0 injections versus 1.4 injections in dexamethasone implant eyes. Eyes switched to the dexamethasone implant gained a mean of 6.1 letters after 12 months, compared with −0.4 letters for anti-VEGF-treated eyes. They were also more likely to gain at least 5 letters and at least 10 letters after 12 months than eyes maintained on anti-VEGF therapy. The authors concluded that in a real-world setting, switching patients with refractory DME to the dexamethasone implant results in better visual and anatomic outcomes at 1 year.

This was further corroborated in a metaanalysis from Khan et al, who looked at a number of studies with more than 3,800 total patients, all of whom had at least six prior anti-VEGF treatments and then were either switched to dexamethasone implant or continued on anti-VEGF therapy.[27] All studies favored switching to the dexamethasone implant compared to staying with anti-VEGF therapy.

Q | DR. BAKRI: These real-world studies have great outcomes. The DRCR.net Protocol U phase 2 study, however, had different results. Protocol U evaluated the efficacy of combination dexamethasone and ranibizumab versus ranibizumab monotherapy in 236 patients with persistent center-involved DME.[28] The primary outcome was mean change in BCVA from baseline to week 24. There was no significant difference in VA between the two treatment arms at 24 weeks. Why do you think the results of Protocol U differ from the real-world studies?

DR. KUPPERMANN: Protocol U was a flawed study. It was intended to be in pseudophakic eyes, but included phakic eyes because, in reality, including only pseudophakic eyes was more difficult to enroll than anticipated. If you look at the pseudophakic subset, there was a trend toward better outcomes in the dexamethasone implant plus ranibizumab arm compared to the ranibizumab alone arm. This was a nominal difference and not statistically significant because it was underpowered. There were better OCT outcomes as well in the combo group, which was statistically significant. There was good anatomic evidence but allowing phakic eyes blunted the response in vision.

DR. BAKRI: What adverse events should clinicians look for with the dexamethasone implant?

DR. KUPPERMANN: There's a lot of evidence that after poor responsiveness to three to six injections of anti-VEGF therapy, switching to the dexamethasone implant or to steroids seems to be an effective option. However, there are some concerns. Briefly, as with any steroid, there is the risk of elevated intraocular pressure (IOP). About 40% of dexamethasone patients in the MEAD study needed IOP-lowering medications.[12] In real-world studies, this occurs less frequently (15 to 20%).[25]

Additionally, steroids cause cataracts. The good news is that postcataract surgery, when there can be a lot of inflammation, the dexamethasone implant does a wonderful job managing inflammation. In fact, one of the relative recommendations for using the dexamethasone implant is in the perioperative period surrounding cataract surgery.

As mentioned earlier, we know that three anti-VEGF injections can be predictive of long-term outcomes. Therefore, when I think about patient selection for the dexamethasone implant, in addition to pseudophakic eyes, my biggest indication is the suboptimal response after three to six anti-VEGF injections regardless of phakic status. I also consider if the fellow eye had a poor response to anti-VEGF therapy. If one eye was unresponsive, should we try it again in the other eye? I usually do, but more and more I'm considering going straight to the dexamethasone implant when the fellow eye was poorly responsive to anti-VEGF therapy.

To conclude, there's a significant subset of patients who have poor responsiveness to anti-VEGF therapy. The dexamethasone implant appears effective in treating treatment-naive patients and eyes with chronic disease.

Determining When—and if—to Switch Therapy

Q | DR. BAKRI: The swimming lanes from the subanalysis of DRCR.net Protocol I clearly showed that patients start off in one lane and after 12 weeks you know what lane

they're going to end up in for visual outcomes. Have Protocol I data altered your decision on when to switch therapies?

DR. KUPPERMANN: There's not a one-size-fits-all approach for these patients. When to switch depends on many patient-specific variables such as their vision and response on OCT. I look at response patterns over time. For example, after one injection, was there a 20% reduction of excess macular thickness? After the second injection, was there another 20% reduction? If so, then I'm satisfied with the direction we're going and want it to continue. However, if there was a modest response of 20% on the first injection and no further response on injections two or three, then I'll consider switching the patient to the dexamethasone implant.

DR. BAKRI: Do you think it's important to monitor the OCT monthly after each injection within the loading dose?

DR. KUPPERMANN: I prefer to do an OCT each time because it helps me assess responsiveness early on. That said, I understand an OCT during each appointment isn't efficient. Some clinicians skip the OCT after they've committed to the loading doses. Although I wouldn't argue with someone taking that approach, I do think you lose important data that will help guide you in subsequent management . Therefore, I argue that it's worth doing.

SWITCHING AGENTS: REAL-WORLD CASE STUDIES

Case 1: Insulin-dependent Diabetic

DR. BAKRI: Our first case is a 63-year-old man with insulin-dependent diabetes, high cholesterol, hypertension, and a 10.2 HbA1c. He has an ocular history of focal laser and panretinal photocoagulation (PRP) in both eyes. VA was 20/40 in the right eye and hand motions in the left. He presented with DME in the right eye and vitreous and subhyaloid hemorrhages in the left. We will focus on the right eye for this case discussion; the left eye was managed with vitrectomy.

Before presenting to us, he had received multiple injections of bevacizumab in the right eye, the last of which was 9 weeks prior. Nine weeks after the bevacizumab injection, vision was 20/30 in the right eye, but macular edema was present. We proceeded with bevacizumab every 4 weeks for three more injections. After that series of injections, the patient still had macular edema on the OCT. We switched him to monthly aflibercept for three more injections. After those injections, his VA was 20/25; the macula looked pretty good with only a trace of edema.

We then decided to extend the interval to 6 weeks for two more aflibercept injections. The patient was lost-to-follow-up (LTFU) for 20 weeks due to transportation and weather issues. Figure 4 shows his images after 20 weeks. We gave an aflibercept injection that day, then shortened the interval to 4 weeks. Figure 5 shows the results after four additional aflibercept injections, 7 weeks after the last injection; there's no macular edema. We kept the patient at 7-week intervals for three more injections.

There was another LTFU of 12 weeks due to COVID-19. We went back to aflibercept every 4 weeks for a few more injections.

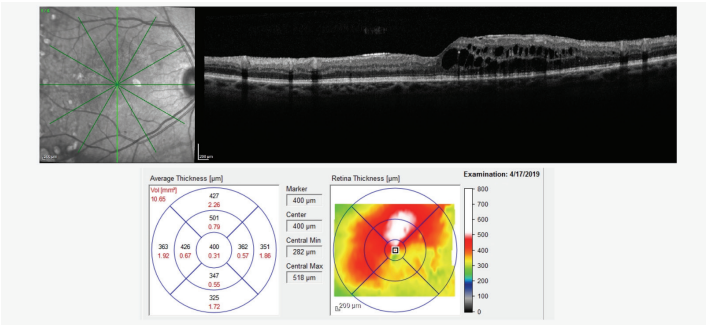


Figure 4. Case 1: 63-year-old male with insulin-dependent diabetes 20 weeks LTFU.

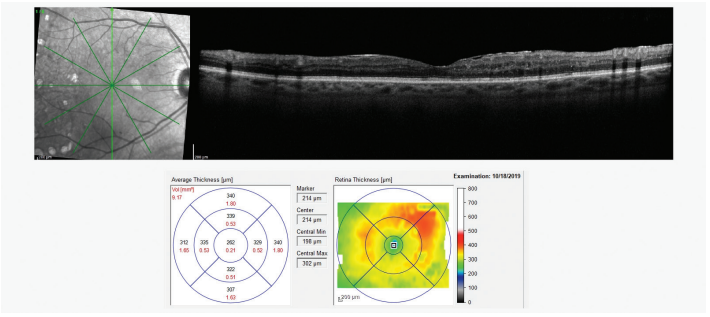


Figure 5. Case 1: 7 weeks after fourth aflibercept injection.

From what we know so far on this patient, aflibercept was effective up to 7 weeks, but we weren't able to assess any longer duration. Throughout the 20 months with this patient, there were two adverse circumstances that caused a delayed follow-up and fluid recurrence. In hindsight, should I have done anything differently?

PETER K. KAISER, MD: The issue with this patient isn't response to anti-VEGF injections, it's delayed follow-up. If the patient was followed up regularly and weren't responding to aflibercept, then we could consider switching them to a long-term steroid injection. I would not be comfortable switching to the dexamethasone implant in this patient because of these follow-up issues. It is very important than after using a dexamethasone implant, we check the patient's IOP at around 6 to 8 weeks after injection. Given this patient's history, I'm not confident they would return.

DR. KUPPERMANN: I'd also defer any consideration of the dexamethasone implant in this case, given that the patient is showing a response to anti-VEGF injections with 7-week durability. Yes, that's shorter than the dexamethasone implant, but I'm also concerned the patient won't return for the required follow-up visits to assess their IOP. If there are no pressure increases after the first couple of implant injections, then I'd be more comfortable with the LTFU potential. But there has to be a very clear commitment from the patient that they will show up to the initial follow-up appointments for me to feel comfortable about that switch. VEGF inhibition seems to be effective. I'm not sure this is a candidate for steroid therapy.

Case 2: Significant Edema

DR. KAISER: This is a 54-year-old man with type 2 insulin-depen-

dent diabetes with a VA of 20/80 who has significant DME, especially outer retinal cystic and intraretinal changes, and ischemia. This is his first visit to a physician in years and he denies previous treatment. There are also some hyper-reflective foci on the OCT, as shown in Figure 6. How would you treat this patient?

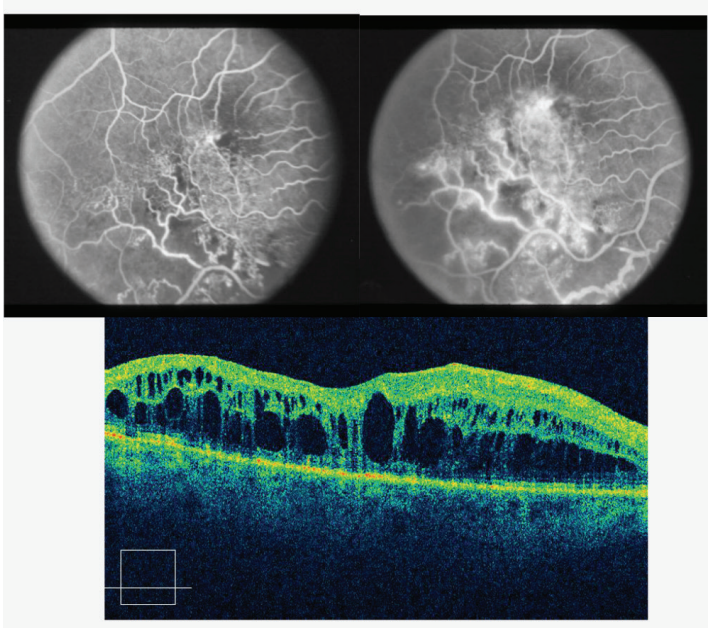


Figure 6. Case 2: Patient with 20/80 VA and significant edema.

DR. KUPPERMANN: There appears to be some vein occlusion as well. I start almost every case with anti-VEGF inhibition, typically aflibercept. The diffuse nature of the edema makes me think a steroid may be useful, but I would first start with VEGF inhibition.

DR. BAKRI: Although it is tempting to go straight to a steroid, we usually start with anti-VEGF agents because of pressure increases and the other issues that come with steroid use. I do wonder whether a steroid may be a more effective. We know that steroids are neuroprotective as well.

DR. KUPPERMANN: I would first want to get the edema under control and see if there's any disease state modification. I'd start with at least three anti-VEGF injections before considering moving to a steroid. I would certainly not delay switching to the dexamethasone implant if the patient was nonresponsive after three injections.

DR. KAISER: We treated this patient with bevacizumab. It didn't work well, so we switched him to aflibercept. That didn't work well either, so we switched to the dexamethasone implant. The edema improved, but the vision didn't improve as much as we'd like. That's one of the problems we have with these chronic cases. The patient's outer retina looks ratty, which is an indication that anti-VEGF isn't going to work as well as we hope. Anatomically, we can do well, but VA wise, the response isn't there.

Case 3: Poorly Controlled DR

DR. KUPPERMANN: This is a patient who ended up with bilateral dexamethasone implants after a limited amount of anti-VEGF exposure. I was referred this patient after a cataract surgery in the right eye with decreased vision. He has a history of bilateral DR and hypertensive retinopathy that is very poorly controlled. His systolic blood pressure is 180 to 190. He has chronic kidney failure and poorly controlled HbA1c of 9.8%.

His right eye is 20/100 VA with central thickening. I gave an aflibercept injection, and he came back 6 weeks later. His vision is marginally better at 20/80, but the macular edema is far worse than it was at the beginning.

In his treatment-naive, left eye, which was phakic, he had a lot of edema that came on suddenly, all in the 6-week time frame after the initial aflibercept injection in the fellow eye. He felt as though he was losing vision in both eyes and was imploring me for help. I decided to give a dexamethasone implant in the left eye. I already started aflibercept in his right eye, which had no response after the initial injection, but I decided to try another aflibercept injection.

Five weeks later, the right eye was not any better after two aflibercept injections. Meanwhile, the left eye demonstrated an excellent anatomic response to dexamethasone implant (Figure 7).

I decided to inject the right eye with the dexamethasone implant after two aflibercept injections, given the strong response to dexamethasone implant in the fellow eye. This was unusual for me, as I would typically give at least three anti-VEGF injections before considering switching, even in a pseudophakic eye. He had a beautiful response 9 weeks out with his vision continuing to improve (Figure 8).

DR. KAISER: Are you going to continue the steroids in this patient or are you going to go back to anti-VEGF now that you've flattened them?

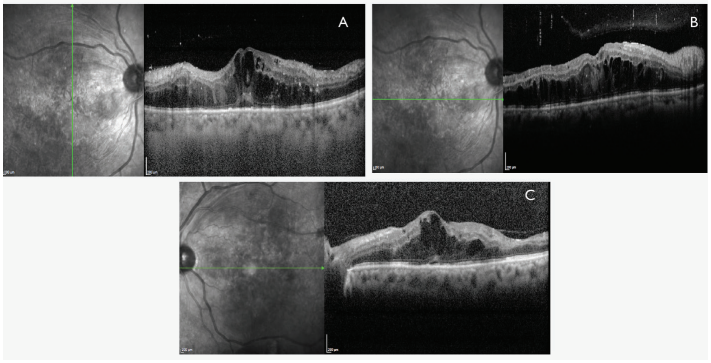


Figure 7. Case 3: Patient 5 weeks post second aflibercept injection OD (A, B) and dexamethasone implant OS (C).

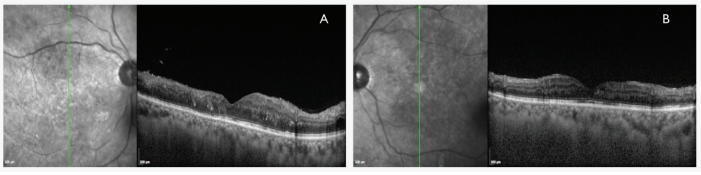


Figure 8. Case 3: Patient 4 weeks after dexamethasone implant OD (A); 9 weeks post dexamethasone implant OS (B).

DR. KUPPERMANN: I've been continuing the dexamethasone implants. He keeps needing them, and he continues to show a good response to dexamethasone implant with good IOP.

DRAWBACKS TO CURRENT ANTI-VEGFS IN DIABETIC MACULAR EDEMA

Q | DR. BAKRI: Dr. Weng, what are some of the drawbacks of our current anti-VEGF treatments in patients with DME?

CHRISTINA Y. WENG, MD, MBA: There's no doubt that anti-VEGFs have revolutionized the way we treat retinal disease, including DME. Although anti-VEGFs remain the gold standard, there are well-known downsides such as cost, potential systemic side effects, and patient discomfort during administration. More importantly, anti-VEGFs have limited durability, thereby conveying a heavy treatment burden on our patients. This limited durability also means that patients are subjected to injection-related risks like endophthalmitis and retinal detachment. Although these complications are rare, it's important to consider that these risks do compound over one's lifetime with repeated injections.

The second larger issue is that anti-VEGF agents are not universally effective because they only target VEGF; they don't target other inflammatory mediators that may be involved in DME pathogenesis. There will be some patients who have an incomplete response to anti-VEGF treatment or may be refractory to treatment altogether.

Real-World Patients Versus Clinical Trial Outcomes

DR. WENG: In focusing on the issues of durability and lack of universal efficacy, here are two real-life examples of my own patients who illustrate these concepts.

The first patient is a 69-year-old man with insulin-dependent diabetes and bilateral DME. He is 20/50 and 20/60 in his right and left eyes, respectively. He's done very well on anti-VEGF monotherapy for the last 2.5 years. However, he has required injections every 4 to 8 weeks. He has a heavy treatment burden, especially since he prefers not to have same-day bilateral injections.

The second patient is a 43-year-old man with noninsulin-dependent diabetes. He has severe bilateral DME with profound amounts of subretinal and intraretinal fluid. He's 20/50 in both eyes. After four monthly anti-VEGF injections, there's slight improvement, but significant fluid remains. I transitioned him to dexamethasone, and he had a remarkable response, both anatomically and visually. This patient is a great example that not everyone may respond completely to anti-VEGF monotherapy, likely because of a significant inflammatory component to his DME.

How do these examples compare with the results from our major DME trials? Let's start off with RISE and RIDE, the landmark phase 3 trials that evaluated ranibizumab versus sham in the treatment of DME.[29] Both studies met their primary endpoint, showing that more patients gained 15 or more letters from baseline to 24 months in the treatment groups versus sham. Patients treated with ranibizumab also had greater reduction in macular thickening, and patients treated with ranibizumab gained between 11 to almost 13 letters over the course of the study (Figure 9).

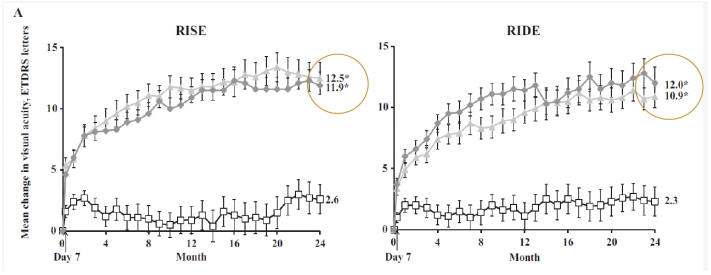


Figure 9. VA outcomes in the RISE and RIDE Trials.[29]

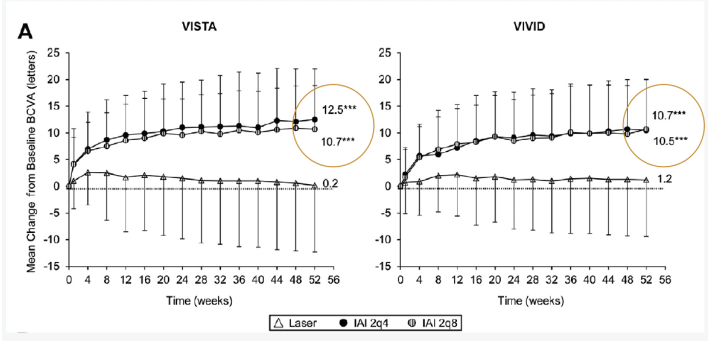


Figure 10. VA outcomes in VISTA and VIVID.[30]

VIVID and VISTA, the phase 3 registration trials that compared aflibercept given every 4 or 8 weeks versus laser for DME, also met their primary endpoint. Greater BVCA gains and anatomic improvements were seen at week 52 in patients treated with aflibercept versus those treated with laser.[30] Figure 10 shows that patients treated with aflibercept gained anywhere between 10 and 12 letters.

Finally, Protocol T from the Diabetic Retinopathy Clinical Research Research Network compared aflibercept, bevacizumab, and ranibizumab head-to-head in the treatment of DME. From baseline to 1 year, the mean VA letter score improved by 10 to 13 letters with all three agents.[17,18]

The commonality between these last three trials are double-digit VA gains. Where are the double-digit gains in the real world? Interestingly, the 5-year extension results of Protocol T showed that between years 2 and 5, when patients are managed at clinician discretion rather than trial protocol, patients will lose a few letters.[17] Although the overall VA still improved from baseline by about 7.4 letters, it did decrease by 4.7 letters from the 2-year timepoint despite stable OCT. Of note, there was a median of four injections given in the extension phase.

These are important points because they illustrate what can happen even in our "best" patients. We know that those who are enrolled in our clinical trials tend to have a higher level of compliance, they tend to have a greater level of motivation, and even in these "best" patients, they may not achieve those double-digit gains long-term. Although the reason for that is likely multifactorial, potential undertreatment is a factor to be considered.

Undertreatment, Noncompliance Drives Mediocre Outcomes

DR. WENG: If you look at real-world studies, this gap in the visual outcomes becomes even more evident. For example, a real-world study looking at approximately 15,000 eyes from the Vestrum database showed much more modest visual gains of only 4 to 5.5 letters at 12 months among eyes treated with anti-VEGF.[31] This is a whole line worse than the outcomes from Protocol T. Interestingly, undertreatment might not have been solely to blame here because the mean number of injections was seven versus nine in Protocol T.

Another large database study of nearly 30,000 eyes showed similar findings.[32] At 1 year, a mean of 6.4 anti-VEGF injections were given, leading to a VA gain of 4.2 letters. More injections led to greater VA improvements. That's a recurrent theme; the more injections you receive, the better your visual outcomes in general.

Figure 11 summarizes the results of a recently published study that included more than 13,000 treatment-naive patients with DME from the IRIS database.[33] The authors analyzed how patients with DME were managed at the 28- and 365-day timepoints after diagnosis, and found that 75% of patients received no treatment within 28 days of their DME diagnosis. This database included all-comers regardless of baseline VA. Even 1 year out, 60% were still observed. Among those who were treated with anti-VEGF, they tended to have a lower mean VA and also achieved greater levels of 1-year VA improvement, especially if they received six injections or more. This drives home the point that more frequent injections leads to better visual outcomes.

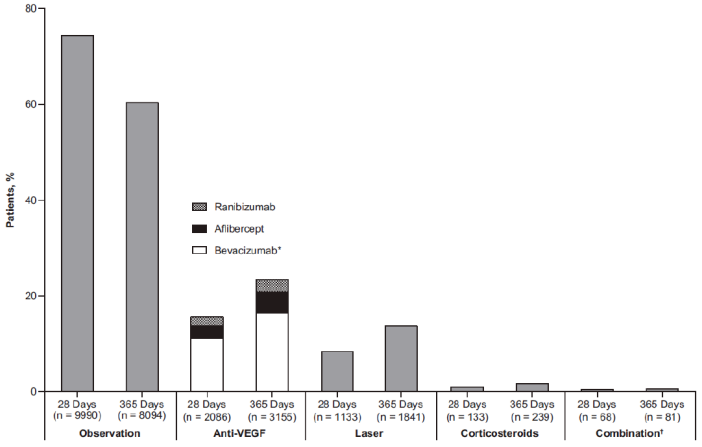
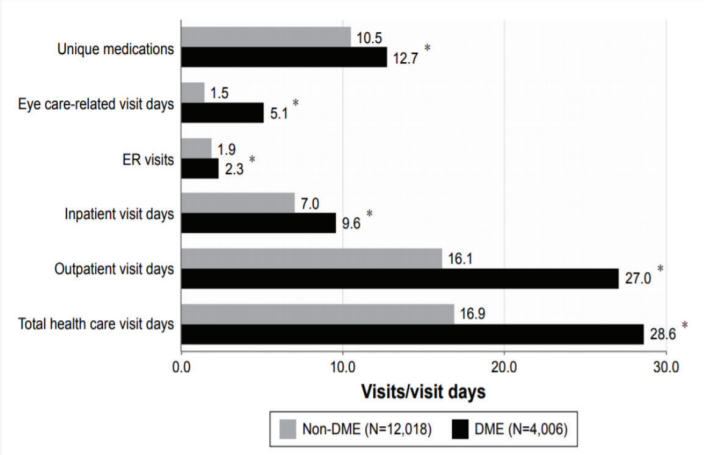


Figure 11. IRIS Registry data analysis.[33]



Abbreviations: DME, diabetic macular edema; ER, emergency room.

Figure 12. Utilization of medical services by DME status.[36]

We can't talk about undertreatment without talking about compliance. Two studies address this. Gao et al found that 25% of patients with nonproliferative diabetic retinopathy (NPDR) and DME were LTFU.[34] They defined that as no subsequent visits for 12 months following an injection. The factors that were associated with a greater risk of LTFU were lower income, lower baseline VA, severe NPDR, and Hispanic, American Indian, or Pacific Islander race.

Another study looked at the differences in compliance between AMD and DME patients, finding that DME patients were more than twice as likely to have at least one break-off, which was defined as tardiness in follow-up of greater than 100 days.[35] Not surprisingly, there was a significant correlation between the number of break-offs and change in VA.

Figure 12 looks at the use of medical services based on one's DME status, illustrating that diabetics with DME tend to be on more medications, have more emergency room visits, and spend more time in the hospital as inpatients compared to diabetics without DME.[36] Diabetics with DME have 29 health care visit days in a year, which is more than two visits a month. Given that many of these patients are working-age people with families, it's no wonder they struggle with the heavy treatment burden required in the management of DME with anti-VEGF.

Making Sense of Suboptimal Responders Despite Aggressive Therapy

DR. WENG: We know that despite aggressive anti-VEGF therapy, a significant portion of patients continue to have persistent DME. Some data suggest that persistent DME may limit visual gains. In a subanalysis of Protocol I,[16] which showed that despite receiving similar numbers of ranibizumab injections, patients' mean BCVA through year 3 was within 5 letters of their response at week 12 (Figure 13). We can interpret the Protocol I data in two ways. First, it could mean that some patients are destined to be poor or super-responders and not much can be done to alter that course. However, it could also suggest that someone's early response has predictive value, and thus if someone isn't responding as well as they should, there may be an opportunity early on to switch or combine therapy to generate a greater response.

We know that limited treatment durability and undertreatment limits the visual potential for some DME patients. However, even with monthly anti-VEGF injections, a significant proportion of patients may have incomplete drying or persistent fluid. For example, let's take a look at the 24-week post-hoc analysis of Protocol T.[37]

The treatment algorithm followed in Protocol T is perhaps different from the way some of us practice in the real world. All patients

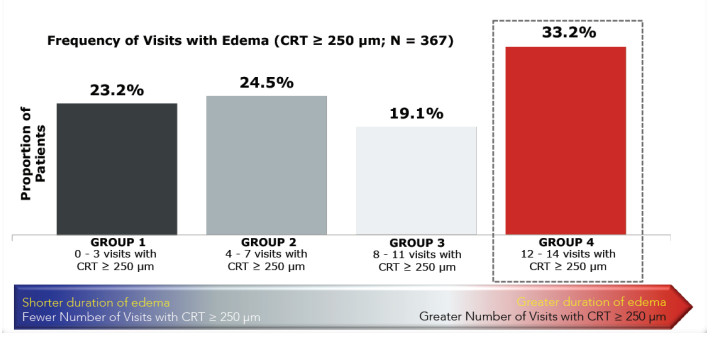


Figure 13. Post-hoc analysis of Protocol I.[38]

received six monthly injections unless they were 20/20 with normal OCT after three injections. After the six injections, anti-VEGF was only given if there was a significant improvement or worsening, and no injections were given if there was persistent, stable DME. The researchers divided the patients into three cohorts based on letter gains and CST decrease at week 12.

Persistent DME was noted in 31.6% (aflibercept), 65.6% (bevacizumab), and 41.5% (ranibizumab) of eyes.[37] Among these, rates of chronic persistent DME through 2 years were 44.2% to 68.2%, depending on treatment group. The data suggest that in the aflibercept and ranibizumab groups, visual outcomes were slightly worse for eyes with persistent DME compared to eyes without persistent DME. However, there wasn't much difference seen between the groups at 2 years. This points to an opportunity to get these patients drier, which potentially could lead to better VA gains. Could these patients have done better if managed with a different agent or perhaps a combination of agents, rather than continuing on with their monotherapy? The authors concluded that despite DME persistence through 2 years in a subgroup of patients, meaningful gains in VA continue to be achieved. Furthermore, there were very few patients with 10 or more letter losses. However, it's important to remember that this is only a 2-year follow-up, and there are data that suggest that persistent fluid in DME may have detrimental effects in terms of visual prognosis.

One such example is a post-hoc analysis of Protocol I by Sadda et al.[38] Patients in Protocol I were stratified based on the number of visits over the course of a year where there was edema present, defined as a central retinal thickness that exceeded 250 µm based on time-domain OCT. Despite intense anti-VEGF treatment, one-third of patients had persistent edema for 12 to 14 visits over year 1, and more than half had edema at eight or more visits over the course of that year.

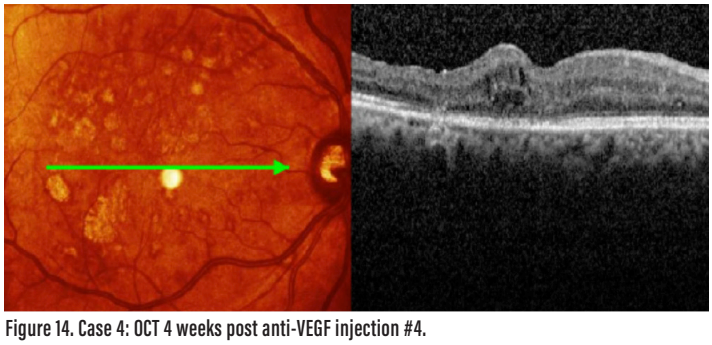


Figure 14. Case 4: OCT 4 weeks post anti-VEGF injection #4.

Next, the investigators looked at mean BCVA change from baseline at 12 months based on their categories. After 12 months, patients with edema at 12 to 14 visits gained significantly fewer letters than those with edema at three or fewer visits (Figure 14). This observation held true at years 2 and 3, although it lost statistical significance at year 3.

Strategies to Improve DME Treatment in the Real World

Q | DR. BAKRI: Dr. Weng, given the data and the issues you covered, how could the management of DME be improved in the real-world setting?

DR. WENG: We need therapies that work better and last longer. There are several promising candidates in the pipeline. More durable agents may also mitigate these frequent anatomic fluctuations, which some have suggested may be harmful. One way to treat suboptimal response to anti-VEGF may be to target other disease mediators in addition to VEGF. We also need agents that can offer improved safety and comfort. As Dr. Kuppermann said, it would be great to have reliable biomarkers that can help optimize treatment or drug regimens for our patients. I'd also like to be able to better identify patients at risk for noncompliance so that appropriate safeguards could be implemented. Lower cost therapeutics would also meaningfully impact the field from a societal standpoint.

DR. BAKRI: In reviewing Protocol T extension data, you mentioned that the CSTs were stable during that time period, yet the vision declined. Why is that?

DR. WENG: It's interesting because the decline that you see in the extension also differs from what we saw in the longer-term follow-up of studies like RISE/RIDE, VIVID/VISTA, and Protocol I.[16,29,30,38] It's hard to say why that is. Patients were not followed or treated on a standardized regimen. It's possible that patients were undertreated, as they received a median of four injections in that extension period, between years 2 and 5. There was persistent fluid in a not-insignificant proportion of patients as well, but we also see similar things with the Protocol I follow-up. Protocol I patients received a similar number of injections in their extension phase and they also had a significant proportion with persistent fluid. There has to be more going on.

Perhaps the patients in Protocol T extension phase weren't monitored frequently enough. In Protocol I, patients had about 20 visits between years 3 and 5, whereas they only were seen about 14 times on average in the extension phase from years 2 to 5 in Protocol T. It is also important to note that only two-thirds of patients in Protocol T completed the extension phase.

The bottom line is that regimented clinical trial outcomes don't seem to carry over to the real-world setting. We do see

improvement, but there are other things, such as ischemia and disease progression, that could be negatively impacting visual acuity gains. Patients with diabetes also tend to acquire more comorbidities over time. All of that could influence what we are seeing.

DR. BAKRI: One thing you mentioned is that there's often a delay in treatment of DME. We also know that many retina specialists watch DME for longer, even when patients are getting treated and just not responding. Why do you think these delays exist?

DR. WENG: The IRIS database study was really eye-opening for me in showing how many people with DME we're observing. Protocol V showed us that observation is a valid and safe option for patients with very good VA of 20/20 to 20/25.[39] However, this has not been shown for lower levels of vision. Providers seems to feel less urgency with DME than with AMD. It might be because DME is slower-acting; we don't see the acute tumbling of VA that you do with wet AMD. That said, it's very important that we don't become complacent. If you wait and observe the patient too long, you may be leaving potential for VA improvements on the table.

Case Study: The Dexamethasone Implant in a Patient LTFU

DR. WENG: This patient is a 54-year-old man with insulin-dependent diabetes and DME in his right eye. He has a moderately good level of control, with an HbA1c of 8.3. He is from the Middle East but is working long-term in the United States. In his home country, he received multiple anti-VEGF injections and had pretty aggressive focal laser. He's pseudophakic in both eyes. When he first came to me, he had blurry vision and metamorphopsia. His VA was down to 20/40 -2, and his IOP was normal. His silt-lamp examination was unremarkable, with the exception of a posterior chamber IOL and absent vitreous. His DFE revealed focal laser scars and some manifestations of NPDR.

His cup-to-disc ratio was about 0.5 with no evidence of proliferative disease. Because he said that the anti-VEGF had been working so well for him at home, he requested specifically that we continue the same treatment here.

His presenting OCT showed some thickening, especially nasal to the foveal center. Four weeks after his first anti-VEGF injection, his VA improved by about 1 line. Anatomically, he responded slightly, but there was still some thickening, especially nasal to the foveal center.

We brought him back 4 weeks after his second anti-VEGF, and while he has responded nasal to his fovea, it seems like he has worsened temporal to his fovea. His VA has decreased to 20/50 +2.

I gave him a third anti-VEGF injection and brought him back 4 weeks later. There was not much change in his VA or anatomy. I asked him if he felt that the injections were helping, and he responded enthusiastically that they were, and said that he enjoyed good vision one week after an injection which seemed to wane by week 3. I gave him his fourth anti-VEGF injection and brought him back 2 weeks later to confirm that he was responding. His VA was 20/25 +1 and his fluid was essentially gone.

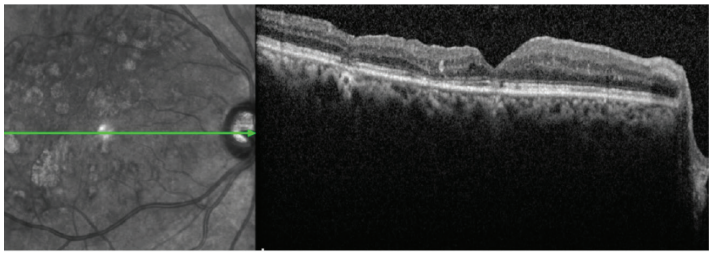


Figure 15. Case 4: OCT following dexamethasone implant after LTFU for 13 weeks.

Four weeks after his fourth anti-VEGF, his fluid had recurred in the temporal macula (Figure 14). We discussed introducing the dexamethasone implant into his therapy, and he was more than happy to try it. I told him he needed to come back in 6 weeks so I could check for an efficacy and IOP response. This was early March when travel restrictions due to COVID-19 were just beginning. The week after his dexamethasone injection, he went home to the Middle East to visit his family for one week, but got stuck there for 13 weeks, missing his follow-up appointment. I didn't see him again in the clinic until July.

Figure 15 shows his OCT when he returned to the clinic. He looked excellent. There were a couple of cysts in the perifoveal area, just temporal to the foveal center, but he was 20/20 -2 with normal IOP.

This case is very pertinent to the times we're in right now. Our diabetic patients have unique challenges with compliance, and COVID-19 has added even more. Part of me takes comfort in putting in these longer-durability steroid products because you know that the patient will be covered even if they can't or don't come in. On the flip side, I understand the concerns that some of my colleagues have regarding IOP and the consequences of LTFU if there is an issue.

Finally, it's important to note that this patient was vitrectomized. In my experience, anti-VEGFs don't seem to last as long in patients without vitreous. I am quicker to pull out steroids for these patients because I think they're very helpful.

Q | **DR. BAKRI:** Do you change your technique for steroid implant injection in vitrectomized patients?

DR. WENG: Studies have been done in model eyes to show that the pellet of dexamethasone can be ejected with rapid velocity without the dampening that vitreous usually provides. In rare circumstances, it can cause mechanical traumatic injury to the retina or lens. In patients who are vitrectomized, I still bevel my entry while stabilizing the globe with a pair of forceps on the eye, but I depress the injector button much more slowly than I would for a patient who is not vitrectomized. This slows down the speed with which the pellet is injected and allows it to be more safely deposited into the vitreous cavity.

DR. BAKRI: Do you have any concerns about wound closure?

DR. WENG: There's a thought that vitreous helps plug the injection entry site, and I do believe that's probably true. So, in patients who have a very thorough vitrectomy as this man did, I am careful to roll over the entry site with a cotton-tipped applicator as soon as I'm withdrawing the injector.

EMERGING TREATMENTS FOR DME

DR. BAKRI: Dr. Kaiser, we just discussed some of the different pathways DME affects, as well as the drawbacks of anti-VEGF treatment. Where do we go from here in developing more effective and durable treatments for DME?

DR. KAISER: Thank you, Dr. Bakri. Hyperglycemia causes many changes in the body, including hypoxia, inflammation, and oxidative stress. All of these abnormalities can be attacked with an anti-VEGF treatment, but there are other aspects of diabetes that are unique in allowing us to attack them from different modalities.

Steroids work on many of the inflammatory markers shown in Figure 16 including the formation of interleukins. The TIE2 pathway has been shown to be very involved in diabetic retinopathy, so angiopoietin-2 (Ang-2) blockers as well as TIE2 activators are being evaluated for DME. The kallikrein-kinin system is involved in the inflammatory portion of DME, so Plasma Kallikrein (PKal) inhibitors are on the horizon. Finally, integrins are very involved in the inflammation and oxidative stress we see in DME, so integrin inhibitors are being studied. At the end of the day, we're trying to prevent the breakdown of the blood-retinal barrier, and certainly any of these drugs have that possibility.

Figure 16 shows the different VEGF receptors, for which there are three. The main one involved in permeability and angiogenesis is VEGF receptor two, which is activated by VEGF-A and VEGF-C. VEGF-A is blocked by bevacizumab, ranibizumab, and aflibercept, which also blocks VEGF-B and placental growth factor (PGF). PGF is very involved in DME and only aflibercept blocks this.

If we look at some of the anti-VEGF drugs currently in clinical studies for DME, such as brolucizumab, abicipar pegol, KSI-301, and conbercept, they do differ. Brolucizumab, abicipar, and KSI-301 only block VEGF-A, and last longer than our currently approved anti-VEGF agents.[40,41] Abicipar has yet to be approved in any indication, but a phase III study in DME is starting soon. Brolucizumab is approved in AMD,[42,43] and the DME studies are fully enrolled (NCT04079231, NCT03917472, NCT03481660, and NCT03481634). Conbercept was developed in China (NCT02194634). It's currently in phase 3 clinical trial for AMD, and a diabetes study is about to start (NCT04254536).[44]

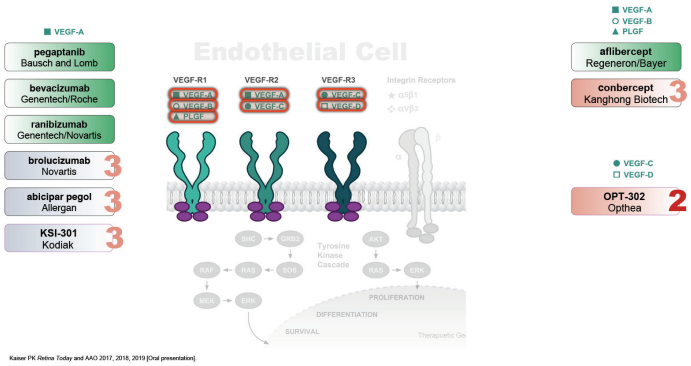


Figure 16. VEGF pathway inhibitors.

OPT-302

Another thing that's interesting in the VEGF pathway space is the idea of blocking VEGF-C in addition to A, B, and PGF. Opthea Limited has a drug called OPT-302 that may be able to produce pan-VEGF blockade when combined with current VEGF inhibitors as it is a VEGF-Trap molecule that blocks VEGF-C and VEGF-D.[45,46] It's too soon to say, but early studies using OPT-302 combined with other anti-VEGF agents show better results than with anti-VEGF alone. The company recently reported positive topline results of its phase 2a trial evaluating safety and efficacy of OPT-302 administered with aflibercept.[47] About 50% of patients gained 5 or more letters in BCVA at week 12, the primary efficacy endpoint.

KSI-301

KSI-301 is an interesting drug because it's a VEGF-A inhibitor, like our current medications, but can last much longer because it's based on a long acting, unique polymer. It's currently in phase 2/3 development. In the studies shown to date, KSI-301 lasted anywhere from 3 to 6 months (Figure 17). Efficacy and durability data were presented during the American Society of Retina Specialists 2020 Virtual Annual Meeting.[48] About 76% of DME eyes were extended to 4 months or longer, with 64% extended to 6 months or longer before first retreatment.

Importantly, we know that VEGF inhibitors can also improve DR in addition to the DME. Even though aflibercept and ranibizumab are approved for DR, most of us don't frequently use them in this setting because of the treatment burden. But if KSI-301 really lasts 6 months, we could use it in DR and actually improve DR severity scores. To me, that's a very exciting part about this drug.

Risuteganib

DR. KAISER: As I mentioned earlier, integrins are very involved in DME, including its angiogenesis, inflammation development, increased permeability, and even fibrosis. Risuteganib is a pan-integrin inhibitor that was used in two phase 2 DME studies.[49] A double masked, placebo-controlled, randomized, multicenter, 5-month phase 2b trial included five arms: Risuteganib 0.5 mg or 1.0 mg as a sequential therapy after a single treatment of 1.25 mg bevacizumab

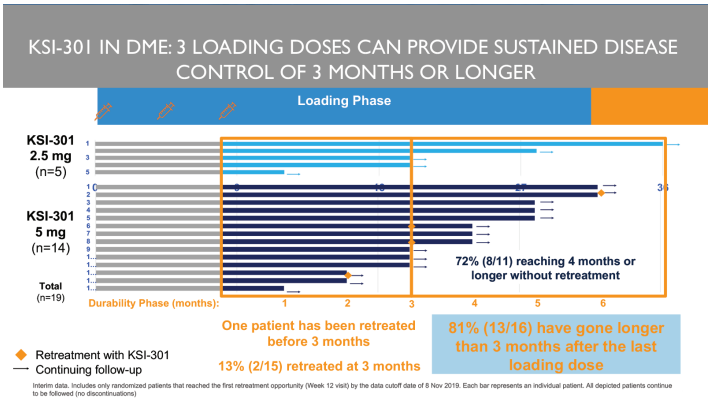


Figure 17. KSI-301 phase 1 data.[48]

(week 0) followed by three risuteganib injections (weeks 1, 4, and 8), and 12 weeks off treatment; risuteganib 0.5 mg or 1.0 mg given in combination with bevacizumab 1.25 mg at weeks 1, 4, and 8, and 12 weeks off treatment; and 1.25 mg bevacizumab control arm of 5 monthly injections.[50] Patients in the Risuteganib with bevacizumab pre-treatment (sequential) group gained 7.1 letters compared with 6.7 letters in the bevacizumab control group.

To me, the interesting thing about risuteganib is that a phase 2b dry AMD study was also performed using this drug, and it was shown to reduce oxidative stress and maybe even provide some neuroprotection. It could be that we are reaching a plateau with many of our anti-VEGF agents in terms of our ability to reduce the neurodegeneration that's occurring in diabetic patients. Integrin inhibitors may actually be working at the neurodegeneration stage as opposed to the leakage stage. We'll see how the phase 3 trials in DME, and dry AMD develop.

The Tie-2 Pathway

DR. KAISER: The big area of excitement for all of us is the Tie-2 pathway. Angiopoietin-2 (Ang-2), an inhibitor of Tie-2, is elevated in diabetics.[51] Ang-2, but not Ang-1, is associated with increased HbA1c levels.[52,53] Furthermore, elevated Ang-2 in vitreous of proliferative DR patients correlate with VEGF levels; samples taken from the eyes of patients with proliferative disease have higher Ang-2.[54] The other problem is that Ang-1, the activator of Tie-2, is actually reduced in patients with diabetes, so this pathway we know is very involved.[55,56] In fact, looking at vitreous samples, Ang-2 levels are elevated whereas Ang-1 levels are pretty stable.

What we want is the opposite: high Ang-1 and low Ang-2 levels.

Why is that? The Tie-2 pathway is very complicated. The agonist is Ang-1, which comes in trimer and higher forms, and only that can cause the Tie-2 receptor to aggregate. This aggregation of the Tie-2 receptors causes phosphorylation and downstream activation leading to enhanced endothelial cell survival, tightening of tight junctions, reduced leakage, and a potent anti-inflammatory effect.[57] We want the Tie-2 receptor to be activated, and Ang-1 is what does that.

Ang-2 on the other hand, exists only in a dimer form and as such is not able to cause aggregation of the Tie-2 receptor, which leads to the receptor being inactivated.[57] Deactivating Tie-2 causes increased vascular leakage, pericyte detachment, increased inflammation, and decreased deposition of tight junctions at the endothelial cell border. All these things lead to leakage, angiogenesis, and inflammation. In addition, Ang-2 actually activates the integrins, which further damages the pathology we see in diabetics.

It makes sense then that we would want to try and inactivate Ang-2. This has been looked at by many companies. Genentech/Roche has a drug called faricimab, which blocks both Ang-2 and VEGF-A. Faricimab performed significantly better than ranibizumab in the phase 2 BOULEVARD trial.[40,58,59] In treatment-naive patients, 6.0 mg faricimab, 1.5 mg faricimab, and 0.3 mg ranibizumab resulted in mean improvements of 13.9, 11.7, and 10.3 letters from baseline, respectively. But it also worked in previously treated patients as well, with dose-dependent reductions in CST, improvements in DRSS score, and longer time to retreatment during the observation period compared with ranibizumab. Faricimab is in phase 3 testing (NCT04432831).

Another drug targeting Tie-2 that has me excited is AXT107. It's an integrin inhibitor but it works on both the VEGF and Tie-2 receptors.[60] Why is that important? Because if you block certain integrins, you can't activate the VEGF receptor. Moreover, If you activate Tie-2 with AXT107, then both Ang-2 and Ang-1 become activators of Tie-2. The preclinical studies of AXT107 show that it works comparably to aflibercept.[61] At day 30, both AXT107 and aflibercept show leakage inhibition, but AXT107 reduces leakage by 55% compared to aflibercept. By day 60, aflibercept is inactive, but AXT107 is still active and inhibiting leakage. What is really interesting about this drug is that when injected intravitreally in animals, it actually lasts about a year. AXT107 is entering clinical studies very shortly, so we'll have to see, but the pre-clinical work is very compelling.

The Kinin-Kallikrein System

DR. KAISER: Back in medical school, we learned that the kinin-kallikrein system is involved in inflammation, coagulation, and pain. The key word here is inflammation because if we look at a diabetic eye, the plasma kallikrein system is actually very activated, leading to inflammation, vasodilation, and increased vascular permeability (Figure 18).

When you look at samples taken from patients' eyes, PKal levels, which is an indicator of the kallikrein system's activity, is different than their VEGF levels. In many cases, for instance with Ang-2 and VEGF, the worse the diabetes the higher the levels. However, that's not the case with PKAL; some patients have elevated PKAL but not elevated VEGF.

Many companies are looking at blocking PKal, including Oxurion (TG-149), Takeda (Lanadelumab), Rezolute (RZ402), Verseon (VE-4839), and Boehringer Ingelheim (BI-1026706 and BI-1467335). We look forward to seeing the results of some of these studies shortly.

Dexamethasone γ-Cyclodextrin Nanoparticle Eye Drops

DR. KAISER: As Dr. Kuppermann and Dr. Weng discussed, steroids work well. We have a new eye drop in development that uses the

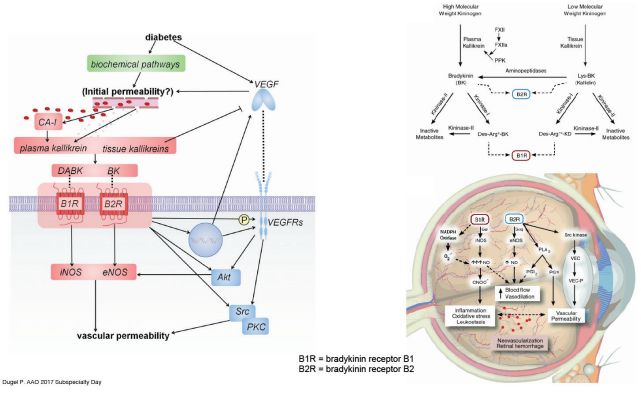


Figure 18. KKS and the diabetic eye.

Oculis SNP Technology.[62] This technology allows for the sustained delivery of drug molecules into the eye, providing more durability and better penetration. It contains dexamethasone, which we know is one of the more powerful steroids. In the phase 2 studies using this eye drop, they had some pretty impressive results, with significant improvement in VA and a decrease in macular thickness. The problem with this drug is that to get approved, it still needs to be noninferior to anti-VEGF medications. That's a very high bar. We'll see what happens in the clinical trials.

DR. BAKRI: If everything goes well and according to the timeline, what do you see receiving approval first, second, and third?

DR. KAISER: Brolucizumab is the furthest along, assuming there's no issues with inflammation in diabetic patients. Faricimab will follow with conbercept not too far behind. KSI-301, which is the long-term polymer anti-VEGF, is in phase 3 development. All these drugs are anti-VEGF inhibitors; they're really not something that is going to push the bar forward. They may increase our durability and reduce the number of injections, but the novel drugs pushing far forward will take considerably longer to come to market.

DR. BAKRI: Many thanks to the panel for your insights into the best practices in the treatment of DME. ■

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MANAGING DIABETIC MACULAR EDEMA: BEST PRACTICES IN REAL-WORLD SITUATIONS

Release Date: October 2020
Expiration Date: October 2021

INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please go to http://evolvemeded.com/online-courses/2017-supplement. If you are experiencing problems with the online test, please email us at info@evolvemeded.com. Certificates are issued electronically, therefore, please provide your email address below.

Please type or print clearly, or we will be unable to issue your certificate.

Name _____

Phone (required) _____ ❑ Email (required) _____

Address _____

City _____ State _____ Zip _____

License Number _____

OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ > 20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ 50+

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Identify the role of inflammation in patients with DME and DR.	_____	_____	_____
Implement treatment regimens for patients with DME and DR.	_____	_____	_____
Through real-world and post-hoc analyses, **identify** the drawbacks to current use of anti-VEGFs in DME.	_____	_____	_____
Differentiate steroids in the management of DME while implementing strategies for treatment and patient outcomes.	_____	_____	_____

POSTTEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation

1. Based on this activity, please rate your confidence in your ability to implement treatment regimens for patients with diabetic macular edema (DME) and diabetic retinopathy (DR) (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. In the DRCR.net Protocol I subanalysis, what percentage of eyes with DME received early and consistent therapeutic benefits from anti-VEGF treatment?

a. 25%
b. 50%
c. 75%
d. 100%

3. According to the literature, what impact does an intravitreal injection of bevacizumab have on concentrations of IL-6, IL-8, and other inflammatory chemokines implicated in DME?

a. The concentrations of the inflammatory chemokines increase.
b. The concentrations of the inflammatory chemokines decrease.
c. The concentrations of the inflammatory chemokines stay relatively stable.
d. The concentrations of some inflammatory chemokines decrease and the concentration of some inflammatory chemokines increase.

4. According to the "Shall we stay, or shall we switch" study, what outcome was noted in eyes with refractory DME?

a. Eyes that received a dexamethasone implant were more likely to gain at least 5 letters compared with eyes that were maintained on anti-VEGF.
b. Eyes that received anti-VEGF were more likely to gain at least 5 letters compared with eyes that received a dexamethasone implant.
c. Eyes that received a dexamethasone implant were more likely to lose at least 5 letters compared with eyes that were maintained on anti-VEGF.
d. Eyes that received dexamethasone implant and anti-VEGF performed equally with regard to letters gained.

5. The international retina group real-life 24-month multicenter study (IRGREL-DEX) demonstrated what percent of patients receiving a dexamethasone intravitreal implant needed subsequent intraocular pressure-lowering therapy?

a. ~5%
b. ~10%
c. ~15%
d. ~20%

6. Post-hoc analysis of randomized controlled trial data from DRCR.net Protocol I identified the fact that _____% of patients were nonresponders or suboptimal responders to anti-VEGF treatment.

a. 10%
b. 20%
c. 30%
d. 40%

7. Which of the following is true regarding the pathogenesis of DME upregulation of anti-VEGF?

a. DME involves the upregulation of numerus inflammatory mediators, including but not limited to anti-VEGF.
b. DME is a process that is independent of anti-VEGF.
c. DME does not involve anti-VEGF.

8. Which of the following drugs inhibits both VEGF-A and VEGF-B?

a. Bevacizumab
b. Ranibizumab
c. Pegaptanib
d. Aflibercept

9. Which of the following statements about the role of Ang-1/Ang-2 in diabetes is NOT true?

a. Elevated Ang-2 (but not Ang-1) is associated with worse metabolic indices and endothelial dysfunction.
b. Elevated Ang-2 (but not Ang-1) is associated with increased HbA1c levels.
c. Decreased levels of Ang-2 are found in the vitreous of patients with proliferative DR.
d. Elevated Ang-2/Ang-1 ratio is found in the vitreous of patients with nonproliferative DR and DME.

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

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

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

This activity improved my competence in managing patients with this disease/condition/symptom. ____ Yes ____ No

Probability of changing practice behavior based on this activity: _____ High _____ Low ____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy ____

Change in nonpharmaceutical therapy ____

Change in diagnostic testing _____

Choice of treatment/management approach ____

Change in current practice for referral _____

Change in differential diagnosis _____

My practice has been reinforced _____

I do not plan to implement any new changes in practice ___

Please identify any barriers to change (check all that apply):

____ Cost

____ Lack of consensus or professional guidelines

____ Lack of administrative support

____ Lack of experience

____ Lack of time to assess/counsel patients

____ Lack of opportunity (patients)

____ Reimbursement/insurance issues

____ Lack of resources (equipment)

____ Patient compliance issues

____ No barriers

Other. Please specify: _____

_____

_____

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

____ Patient Care

____ Practice-Based Learning and Improvement

____ Professionalism

____ Medical Knowledge

____ Interpersonal and Communication Skills

____ System-Based Practice

Additional comments:

_____

____ **I certify that I have participated in this entire activity.**

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address: _____

_____