Supplement to RETINA TODAY April 2015

CME ACTIVITY

New Paradigms in the Management and Treatment of Diabetic Macular Edema

David M. Brown, MD
Karl G. Csaky, MD, PhD
Nancy M. Holekamp, MD
Raj K. Maturi, MD

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A CME activity jointly sponsored by
The Dulaney Foundation and *Retina Today*
Supported by an unrestricted educational grant from Allergan.

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Supported by an unrestricted educational grant from Allergan
Release Date: April 2015
Expiration Date: April 2016

CONTENT SOURCE

This continuing medical education (CME) activity captures content from a live CME symposium held in October 2014 in Chicago, Illinois.

STATEMENT OF NEED

The impact of vision loss due to the ocular manifestations of diabetes is a major public health burden facing our society, given the large aging population at risk due to obesity and metabolic disease complications. Significant challenges lie ahead in addressing the needs of patients at risk for vision loss, as well as the impact on society that comes with an increasing population with impaired vision. Macular degeneration, retinal vein occlusion (RVO), and diabetic macular edema (DME) cause related physiologic problems for retinal specialists and ophthalmologists in the management of these conditions. Given the coincident systemic disease associated with diabetic retinopathy (DR), the present and predicted financial health care impact is substantial.

According to the 2012 Vision Problems in the US Report from the Prevent Blindness America foundation, DR affects more than 7.6 million individuals aged 40 years and older.[1] This contributes significantly to the more than $50 billion in direct economic costs to due vision disorders in this age group.

As new therapies enter the market, treatment options and dosing strategies can have an impact on the cost of treatment, which continues to be a major factor in treatment planning.[2] Clinicians need to consider multiple options in order to properly gauge the right treatment plan for any given patient's needs.

More broadly, the American Diabetes Association confirms that over 150 million people across the world are affected by diabetes. By 2025, that number is projected to reach 324 million, including 35% who are expected to develop diabetic retinopathy.[3] Monitoring, diagnosing and treating the vision care needs of this potential population of over 100 million persons is daunting. For nearly 20 years, DR has been documented as the leading cause of blindness and decreased vision-related quality of life in working-age Americans.[4-6] In recent years, new understanding of the pathophysiology of DME has focused researchers on the involvement of intracellular hyperglycemia, which induces free radicals (oxidative stress), protein kinase C (PKC) activation, and formation of advanced glycation end-products (AGE).[7] This process results in hypoxia, ischemia, inflammation, and alteration of vitreomacular interface. Inflammation produces an increase in VEGF production, endothelial dysfunction, leukocyte adhesion, and PKC production. In fact, DR is now considered to be a state of low-grade inflammation.[8]

DR is the most common microvascular complication of diabetes and remains one of the leading causes of blindness worldwide among adults aged 20 to 74 years. The two most important visual complications of DR are DME and proliferative DR (PDR). The prevalence of DR increases with the duration of diabetes, and nearly all individuals with type 1 diabetes and more than 60% of those with type 2, have some form of retinopathy after 20 years. According to a Wisconsin epidemiologic study of DR (WESDR),[9] 3.6% of younger-onset patients (type 1diabetes) and 1.6% of older-onset patients (type 2 diabetes) were legally blind.

A study conducted by the DRCR.net[10] has shown that patients treated with 0.5 mg ranibizumab plus prompt (n=187) or deferred (≥24 weeks) laser (n = 188) had better visual acuity outcomes at 1 year than patients who received sham injections plus prompt laser treatments (n = 293). Outcome measures in the study included change in visual acuity and mean central subfield thickness measurements. Visual acuity improvement (± standard deviation) was significantly better in the ranibizumab plus prompt laser group (+9 ± 12, $P < .001$) and in the ranibizumab plus deferred laser group (+9, ± 12, $P < .001$), compared to those undergoing sham injections plus prompt laser (+3 ±13) treatments. Visual acuity was not significantly better compared with patients treated with triamcinolone plus prompt laser (+4 ± 13, $P = .3$). Reduction in mean central subfield thickness was similar in all studied groups. Cataract progression and intraocular pressure increases were more frequent in the triamcinolone plus laser group.

More recently, researchers revealed the 2-year primary outcomes of RISE and RIDE,[11] which also focused on the treatment of DME. These phase 2 and 3 studies evaluated 0.3-mg and 0.5-mg doses of ranibizumab compared to sham injections, evaluating subjects who were randomized to sham treatments and focal/grid laser photocoagulation. The RISE and RIDE studies clearly demonstrated that monthly injections of ranibizumab were associated with significant improvement in visual acuity: 40% to 45% of patients gained 3 or more ETDRS lines of vision. Besides the gain in visual acuity, patients who were treated with ranibizumab overall had fewer complications from their underlying DR and less progression of the DR than those who were treated with sham injections. In addition, no statistically significant differences in side effects or serious systemic or ocular adverse events were associated with subjects treated with ranibizumab injections or sham injections.

In the READ-3 trial,[12] patients with DME were treated with multiple injections of either 0.5 mg or 2 mg of ranibizumab. The mean increase in visual acuity was 8.7 letters for the 0.5-mg group and 7.5 letters for the 2-mg group. Visual acuity and central retinal thickness changes were maintained up to the 1-year evaluation.

In 2011, the RESTORE study[13] demonstrated superior gains in best-corrected visual acuity at 1 year with ranibizumab with or without laser versus laser monotherapy. In

contrast to READ-2, the authors found greater reduction in foveal thickness in the anti-VEGF groups, as well as better vision-related quality of life. The number of total injections over the year for the injection-only group was 7.1 versus 4.8 in the combination therapy group.

The FAME Study[14] found that two doses of the fluocinolone implant significantly improved visual acuity in DME over 2 years. The insert can be administered in an outpatient procedure through a 25-gauge needle. However, the FDA indicated that it would require two additional clinical trials to resolve safety concerns raised by investigators.[15]

The DA VINCI study,[16] a phase 2 randomized clinical trial, showed that all doses and dosing regimens of aflibercept that were tested were superior to laser for centrally involved DME. A significant increase in BCVA from baseline was achieved at week 24 and was maintained or improved at week 52 for all aflibercept dosing groups. When aflibercept was administered every 2 months or on an as-needed basis, these regimens were just as effective as monthly treatments.

A new 2013 report from the PLACID[17] study demonstrated higher gains in BCVA up to 9 months posttreatment for diffuse DME in patients receiving dexamethasone intravitreal implant 0.7 mg combined with laser photocoagulation compared with laser alone, but no significant between-group differences at 12 months.

Also of recent note in 2013, two phase 3 comparison studies (VIVID-DME and VISTA-DME[18]) demonstrated positive 1-year results for treatment of DME comparing aflibercept to laser photocoagulation. Subjects were randomized into three arms: 2 mg of intravitreal aflibercept injected monthly, 2 mg of intravitreal aflibercept injected every other month (after five initial monthly injections), or laser photocoagulation. In both studies, the 2-mg aflibercept treatments demonstrated mean increases from baseline in visual acuity of 10.5 to 12.7 letters, while photocoagulation treatment demonstrated mean increases of 0.2 letters in VISTA-DME ($P < .0001$) and 1.2 letters in VIVID-DME ($P < .0001$). Ocular complications were reported as conjunctival hemorrhage, eye pain, and vitreous floaters. Three-year follow-up is planned.

Photocoagulation remains the gold standard for the treatment of DME. However, continuing increases in studies evaluating different therapies may lead to a better understanding of pathophysiology and lead to more efficacious treatments. Because of the continuation of research designed to investigate pathophysiology and the rapid evolution of multiple clinical trials with emerging treatments, updated information on new diagnostic and treatment trends have become increasingly important to retina specialists, as well as other ophthalmologists who treat patients with DME.

1. Prevent Blindness America, 2012 Vision Problems in the US. Available at: www.preventblindness.org/sites/default/files/national/documents/state-fact-sheets/VPUS%2BCOV_FS_US.pdf. Accessed March 25, 2015.
2. Managed Care Implications of Age-Related Ocular Conditions. Available at: www.ajmc.com/publications/supplement/2013/ACE011_13may_AgingEye/ACE011_13May_AgingEye_Cardarelli/#sthash.9vzoQ1SX.dpuf. Accessed March 25, 2015.
3. Hogan P, Dall T, Nikolov P; American Diabetes Association. Economic costs of diabetes in the US in 2002. *Diabetes Care*. 2003;26(3):917-932.
4. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Diabetes in America, 2nd ed. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 1995.
5. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVIII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology*. 1998;105:1801-1815.
6. Hariprasad SM, Mieler WF, Grassi M, et al. Vision-related quality of life in patients with diabetic macular oedema. *Br J Ophthalmol.* 2008;92:89-92.
7. Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol.* 2009;54(1):1-32.
8. Singh A, Stewart JM. Pathophysiology of diabetic macular edema. *Int Ophthalmol Clin.* 2009;49(2):1-11.
9. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, et al. American Diabetes Association. Diabetic retinopathy. *Diabetes Care.* 2003;26:226–9.
10. Elman MJ, Aiello, LP, Beck RW, et al; The Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117(6):1064-1077.e35
11. Brown DM, Nguyen QD, Marcus DM, et al; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120(10):2013-2022
12. Nguyen QD. READ 3: 0.5-mg vs 2.0-mg ranibizumab for diabetic macular edema. Presented at 2011 Retina Subspecialty Day/American Academy of Ophthalmology Annual Meeting; October 22, 2011; Orlando, FL.
13. The RESTORE Study Group. The RESTORE study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011;118:615-625.
14. Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118(4):626-635.e2.
15. Alimera Sciences receives complete response letter from FDA for ILUVIEN®. November 11, 2011. Available at: http://investor.alimerasciences.com/releases.cfm?Year=&ReleasesType=&PageNum=5. Accessed March 25, 2015.
16. Do DV, Nguyen QD, Boyer D, et al.; DA VINCI Study Group. One-year outcomes of the DA VINCI Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology*. 2012;119(8):1658-1665.
17. Callanan DG, Gupta S, Boyer DS, et al.; Ozurdex PLACID Study Group. Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema. *Ophthalmology*. 2013;120(9):1843-1851.
18. Regeneron and Bayer Report positive one-year results from two phase 3 trials of EYLEA® (aflibercept) injection for the treatment of diabetic macular edema. Available at: http://investor.regeneron.com/releasedetail.cfm?ReleaseID=782911. Accessed March 25, 2015.

TARGET AUDIENCE

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

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Discuss the pathophysiology and epidemiology of DME
- Differentiate existing DME therapy options from recent primary and secondary treatments
- Apply evidence-based medicine when treating macular edema and inflammation
- Evaluate the response or nonresponse to treatment: Decision tree modeling in treatment decisions
- Discuss important conditions to consider in using therapies in patients with significant comorbidities

METHOD OF INSTRUCTION

Participants should read the CME activity in its entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice

questions. To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses." Upon completing the activity and achieving a passing score of higher than 70% on the self-assessment test, you may print out a CME credit letter awarding 1 AMA PRA Category 1 Credit.™ The estimated time to complete this activity is 1 hour.

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FACULTY CREDENTIALS

David M. Brown, MD
Clinical Professor of Ophthalmology
Baylor College of Medicine
Retina Consultants of Houston
Houston, TX

Karl G. Csaky, MD, PhD
Director of the Harrington Molecular Laboratory
Retina Foundation of the Southwest
Texas Retina Associates
Dallas, TX

Nancy M. Holekamp, MD
Director of Retina Diseases and the Center for Macular Degeneration
Pepose Vision Institute
St. Louis, MO

Raj K. Maturi, MD
Clinical Associate Professor, Volunteer
Department of Ophthalmology
Indiana University School of Medicine
Midwest Eye Institute
Indianapolis, IN

FACULTY/STAFF DISCLOSURES

David M. Brown, MD, has had a financial agreement or affiliation during the past year with Genentech and Regeneron Pharmaceuticals.

Karl G. Csaky, MD, PhD, has had a financial agreement or affiliation during the past year with Acucela; Allergan; Genentech; Heidelberg Engineering; Novartis; Ophthotech; and Santen Pharmaceutical.

Nancy M. Holekamp, MD, has had a financial agreement or affiliation during the past year with Alimera Sciences; Allergan; Genentech; Katalyst Surgical; Ophthotech; and Regeneron Pharmaceuticals.

Raj K. Maturi, MD, has had a financial agreement or affiliation during the past year with Allergan; GlaxoSmithKline; KalVista; and Santen Pharmaceutical.

All of those involved in the planning, editing, and peer review of this educational activity report no relevant financial relationships.

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Anti-VEGF Therapy for Diabetic Macular Edema: Epidemiology and Pathophysiology

Rigorous studies confirm that anti-VEGF is a transformative breakthrough.

By David M. Brown, MD

Diabetic retinopathy (DR) affects a large percentage of the US population and is the leading cause of vision loss and new-onset blindness in working-age adults.[1] In Houston, where I practice, if you are black or Hispanic (which is half of our population), and you are aged older than 45 years, you have a greater than 20% chance of having diabetes.[2] In a city the size of Houston, which is now the third largest city in the United States, this means there are literally hundreds of thousands of people with diabetes in the metropolitan area. Clearly, this is an increasing health concern everywhere.

In this article, I discuss the pathophysiology of diabetic eye disease and the role of vascular endothelial growth factor (VEGF) in diabetic macular edema.

PATHOPHYSIOLOGY AND INCIDENCE

Diabetic retinopathy is characterized by capillary pericyte loss, endothelial cell loss, nonfunctional acellular capillaries, capillary basement membrane thickening, microaneurysm formation, and neovascularization.[3] Vascular endothelial growth factor is thought to be a key component in the pathogenesis of DR.[4] A vasoactive cytokine induces neovascularization and increases retinal capillary permeability, which leads to extracellular fluid accumulation and retinal edema.[5,6] Aqueous VEGF concentrations in the eyes of patients with diabetic macular edema (DME) were found to be elevated nearly five-fold compared with controls.[7]

Once retinal microvascular damage occurs, it induces hypoxia and a build-up of cytokines. This, in turn, leads to increased neovascularization, increased vascular permeability, and leakage. The central retina swells, resulting in DME.[8]

DME is the most common cause of vision loss in people with diabetes,[9] and until 15 months ago, we had no drug approved to treat it. Researchers have shown the longer the duration of diabetes, the more likely a person will develop proliferative diabetic retinopathy. Klein and colleagues reported an incidence rate of 15% to 20% in people who have been using insulin more than 15 years.[10] Now that we can better assess the retinal vasculature with widefield angiography, however, I believe we see diabetic damage in most patients within 5 to 10 years.

MODIFIABLE RISK FACTORS

DME triples the risk of vision impairment and is associated with a five-fold risk of blindness.[11] Intensive glucose control is associated with a 76% risk reduction in the development of any retinopathy and a 54% risk reduction of retinopathy progression for those who had retinopathy at baseline.[12] The longer someone has diabetes, the higher the risk of DR and DME.[12] The Epidemiology of Diabetes Interventions and Complications trial[13] found that the reduction in the risk of progressive retinopathy and nephropathy resulting from intensive therapy in patients with type 1 diabetes persists for at least 4 years, despite increasing hyperglycemia.

Dyslipidemia is also a modifiable risk factor. Researchers have found a positive association between severity of retinopathy and lipid profiles (total and LDL-cholesterol, LDL/HDL).[14] In addition, high triglycerides and high LDL have been associated with subsequent progression of retinopathy over 2 years.[15] In the Early Treatment Diabetic Retinopathy Study,[16] baseline risk factors for proliferative diabetic retinopathy included high triglycerides.

Hypertension is another modifiable risk factor for DR.[17] In the Barbados Eye Study,[18] antihypertensive treatment halved a patient's risk of developing DR over 9 years. Once a patient has DME, blood pressure control becomes as important as glucose control in the reduction of macular edema.

OTHER SYSTEMIC ISSUES

Renal function and fluid balance can potentially play a role in worsening DR and macular edema.[19] We also know that plasma VEGF increases with poor glycemic control.[20]

Women with type 1 diabetes must be followed closely during pregnancy and through the first postpartum year; however, the effect of pregnancy is usually transient.[21] Pregnancy does not affect the ultimate long-term rate of progression from mild to moderate retinopathy.

LASER THERAPY

Based on the findings of the Early Treatment Diabetic Retinopathy Study,[22] focal laser photocoagulation became the standard of care for most retinal surgeons. The chief

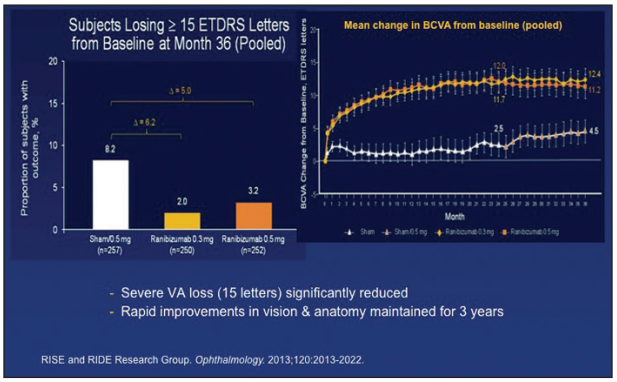


Figure 1. In the RISE/RIDE trial, patients receiving ranibizumab had rapid and sustained improvements in visual acuity and anatomy.

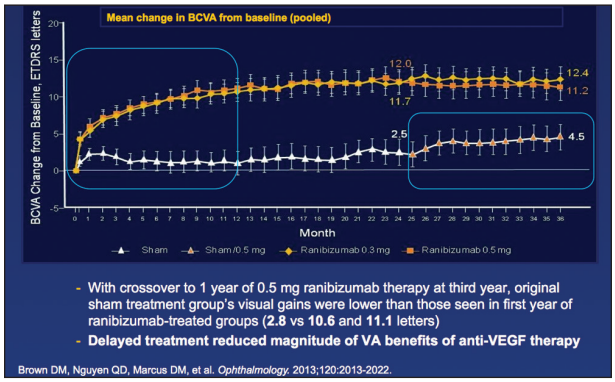


Figure 2. In the RISE/RIDE trial, patients receiving sham treatment who were switched to ranibizumab at 2 years did not achieve the visual gains seen in the original ranibizumab arms.

benefit of laser therapy is that it reduces the risk of vision loss; however, few patients experience vision improvement, and laser therapy has no impact on underlying disease progression.

ANTI-VEGF THERAPY: RANIBIZUMAB

RISE and RIDE[23] were parallel phase 3, multicenter studies designed to assess the safety and efficacy of intravitreal ranibizumab (Lucentis, Genentech) for the treatment of DME. Patients were randomly assigned equally (one eye per patient) to monthly 0.5 mg or 0.3 mg ranibizumab or sham injection. In the third year, patients in the sham group, while still masked, were eligible to cross over to monthly 0.5 mg ranibizumab.[24] Macular laser was available to all patients beginning at month 3; panretinal laser was available as necessary.

As shown in Figure 1, patients receiving ranibizumab had rapid and sustained improvements in visual acuity and anatomy; severe vision loss was significantly reduced. Patients in the sham arm, who could receive laser therapy after 3 months, gained 2.5 letters, while patients in the ranibizumab arms gained more than 2 lines. In the laser arm, about 9% of patients lost 3 lines, while in the ranibizumab arms 2% and 3% lost 3 lines. This is the reason why anti-VEGF therapy has supplanted laser as our standard of care.

Looking at continued treatment to 3 years, as shown in Figure 2, patients receiving sham treatment who were switched to ranibizumab at 2 years did not achieve the visual gains seen in the original ranibizumab arms. Also, consistent with the 2-year data, patients receiving ranibizumab were less likely to develop proliferative DR.

These results point to a key takeaway: Screening is important. If you do not diagnose the DME within 2 years, preferably within 1 year, you lose the ability to achieve that amazing 2- to 3-line gain that was seen in the trials. The burden is on us; no matter what agent we plan to use, we must find DME early. Otherwise, we are leaving 10 letters or 2 lines of visual acuity on the table.

The ocular safety profile at 3 years in RISE and RIDE was consistent with the sham-controlled safety observations from the 24-month analysis. In particular, rates of procedure-related serious adverse events, such as endophthalmitis and traumatic cataract, remained low. The incidence of serious adverse events potentially related to systemic VEGF inhibition was 19.7% in patients who received 0.5 mg ranibizumab compared with 16.8% in the 0.3-mg group, and 13.1% in the sham group. The 0.3-mg dosage was approved.

The patient shown in Figure 3 is a Houston newspaper

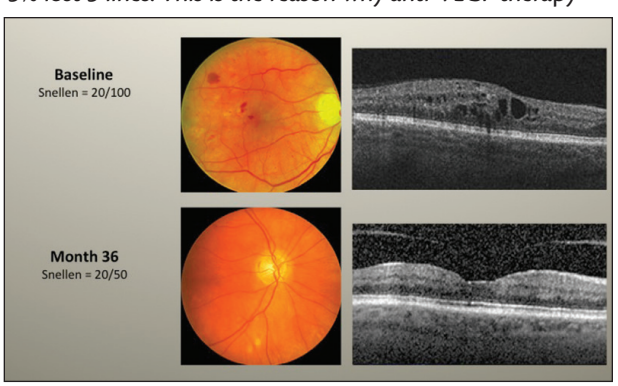


Figure 3. After receiving ranibizumab in the trial, this patient's visual acuity improved to 20/50.

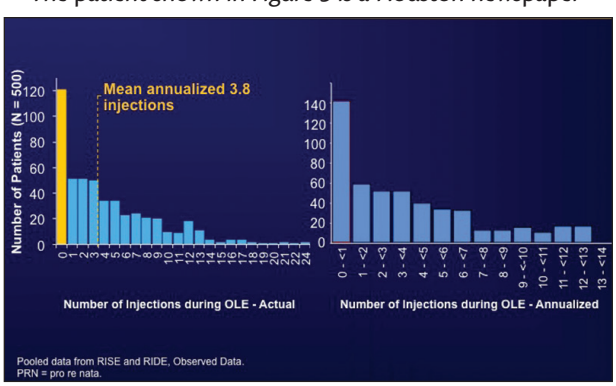


Figure 4. As shown here, 25% of patients did not need another injection in the RISE/RIDE study.

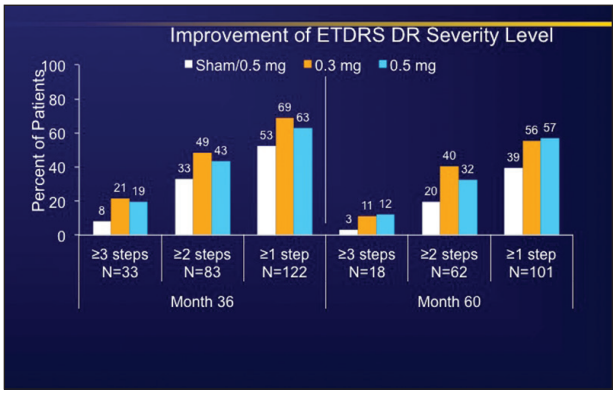


Figure 5. In the RISE/RIDE study, patients continued to demonstrate improvement in diabetic retinopathy with PRN ranibizumab.

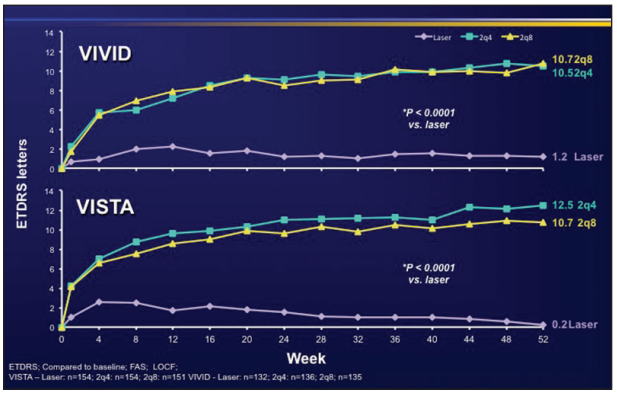


Figure 6. Mean BCVA gains from baseline to week 52 were greater in patients treated with aflibercept group versus laser in the RISE/RIDE trial.

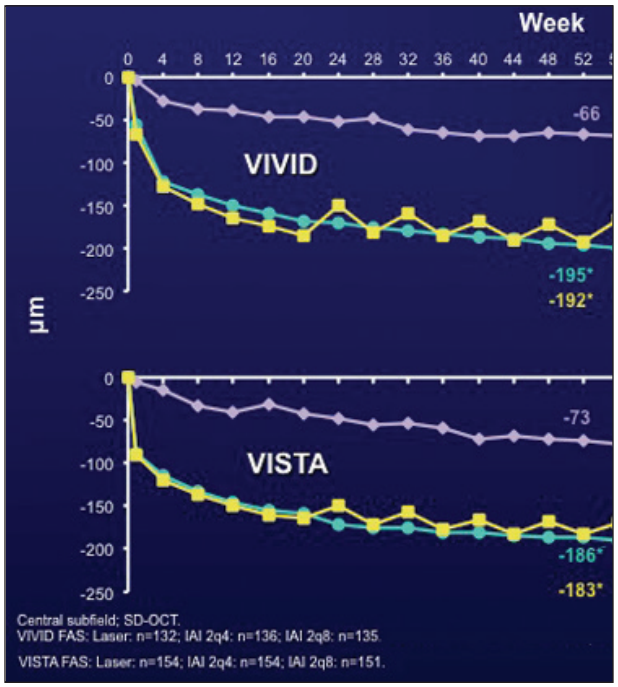


Figure 7. Mean reductions in central retinal thickness were also greater in patients who received aflibercept versus laser in the RISE/RIDE trial.

editor who had to stop working because his visual acuity was 20/100, and he was unable to function. After receiving ranibizumab in the trial, his visual acuity improved to 20/50 and he was able to return to writing op/ed pieces. He is an average patient, someone who improved 2.5 lines. In my opinion, it is an amazing drug, a huge breakthrough in terms of anti-VEGF therapy for DME.

The greatest barrier to delivering treatment that is consistent with study protocols is that working-age patients must receive an injection every month to achieve these results. In an open-label extension of RISE/RIDE, researchers found that visual acuity gains were maintained in patients who were switched to as needed (PRN) ranibizumab.[25]

Note that 25% of patients did not need another injection, and the mean number of injections was 3.8 (Figure 4). There was a bell curve, as some patients still needed injections every month, but the mean and median were both less than 4. These results are very encouraging to me.

Importantly, patients continued to demonstrate improvement in DR with PRN ranibizumab (Figure 5).

Most patients improved to what appears to be their baseline status. In other words, hemorrhaging and vascular tortuosity decreased, and that may be why 25% of the patients did not require retreatment. It may be that the drug took them 2 or 3 years back in their DR progression. This theory has yet to be tested, however.

ANTI-VEGF THERAPY: BEVACIZUMAB

Very few studies of bevacizumab (Avastin, Genentech) have been published. The BOLT study[26] was a prospective, randomized, controlled trial that evaluated intravitreous bevacizumab and macular laser therapy in patients with persistent clinically significant macular edema. At 2 years, patients in the bevacizumab arm showed a mean gain of 8.6 letters, while those in the laser arm showed a mean loss of 0.5 letters.

ANTI-VEGF THERAPY: AFLIBERCEPT

Aflibercept (Eylea, Regeneron), a fusion protein of VEGFR1 and VEGFR2 extracellular domains, binds to VEGF A, VEGF B, and placental growth factor 1 (PlGF1) and PlGF2 with high affinity. In VIVID and VISTA,[27] two similarly designed, double-masked, randomized, phase 3 trials, investigators in 54 centers worldwide performed a head-to-head comparison between aflibercept and laser for treatment of DME.

Mean BCVA gains from baseline to week 52 in the aflibercept 2q4 and 2q8 groups versus the laser group were 12.5 and 10.7 versus 0.2 letters in VISTA, and 10.5 and 10.7 versus 1.2 letters in VIVID (Figure 6). The corresponding proportions of eyes that gained at least 15 letters were 41.6% and 31.1% versus 7.8% in VISTA, and 32.4% and 33.3% versus 9.1% in VIVID.

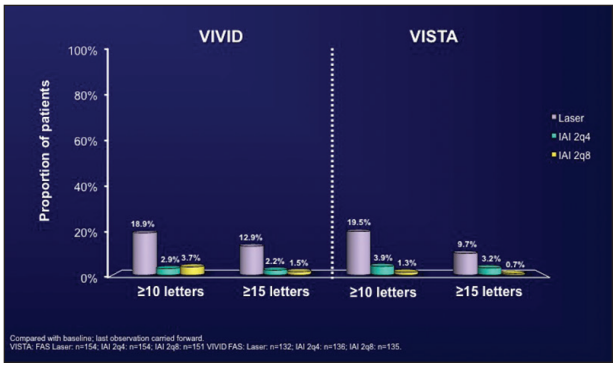


Figure 8. A rate of 10% of subjects in the laser therapy group lost 3 lines of vision, whereas the highest number of lines of vision lost in the aflibercept arms was 3.2%.

IMPORTANT TAKE-AWAY FOR PATIENTS

One of the most important messages we as retina specialists can convey to our patients is illustrated by Figure 1: maintaining hemoglobin A1c within their target range will protect their vision.[1]

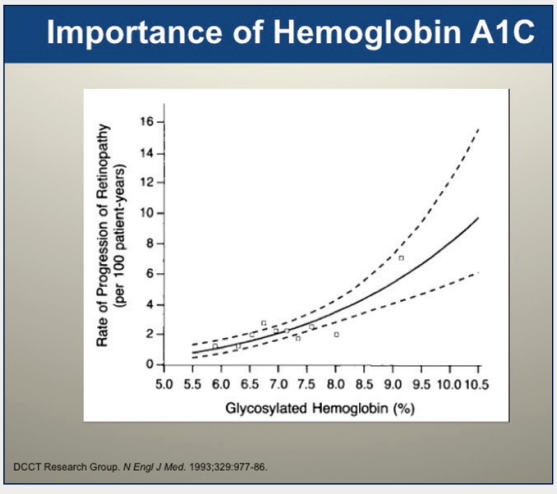


Figure 1. A 1-point reduction in hemoglobin A1c can decrease the incidence of diabetic retinopathy by 28%.

This graph helps me illustrate how beneficial an even a seemingly small change in hemoglobin A1c can be. A 1-point reduction can decrease the incidence of diabetic retinopathy by 28%, and with each subsequent 1-point reduction, the risk is reduced another 28%.

I encourage you to ask patients about their A1c every time you see them and talk to their doctors. Make it a team approach, because managing diabetes is tough. We must be part of the education process to help patients manage their diabetes and prevent end-organ damage all over their bodies.

1. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329:977-986.

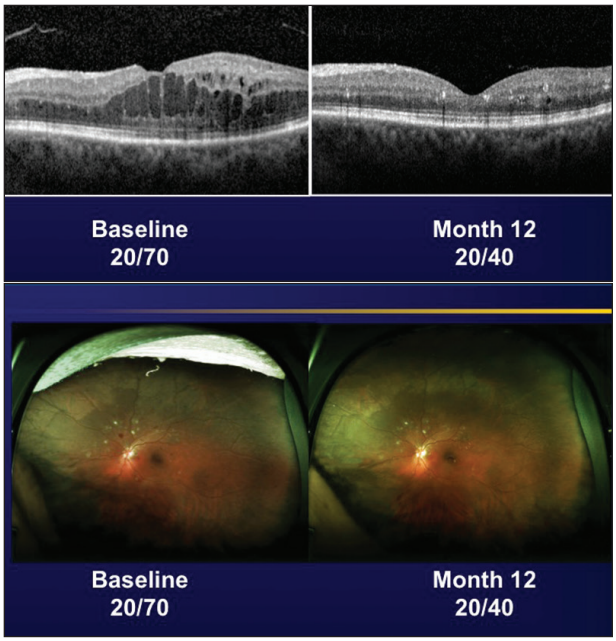


Figure 9. After treatment every other month with aflibercept, this patient's visual acuity improved to 20/50.

I think that anti-VEGF drugs for DME are truly a transformative breakthrough that enables us to do what we have not been able to do before.

Similarly, mean reductions in central retinal thickness were 185.9 µm and 183.1 µm versus 73.3 µm in VISTA, and 195.0 µm and 192.4 µm versus 66.2 µm in VIVID (Figure 7).

Overall incidences of ocular and nonocular adverse events and serious adverse events, including the Anti-Platelet Trialists' Collaboration-defined arterial thromboembolic events and vascular deaths, were similar across treatment groups.

In addition, patients needed fewer injections in this trial, especially in the 2q8 arm. Fewer laser treatments were needed in both arms. In the 2-year results, which includes capped PRN treatment, gains were maintained even with less frequent dosing. These results are not yet published.

In my opinion, Figure 8 illustrates the main reason to use anti-VEGF therapy as first-line agents for DME. In these trials, laser therapy results in a 10% rate of 3-line losers, while in the aflibercept arms, the highest number is 3.2%.

CONCLUSION

I will close with a look at another one of my Houston patients who participated in the VISTA trial. This 54-year-old Hispanic man had baseline visual acuity of 20/70. After treatment every other month with aflibercept, his visual acuity improved to 20/50, and the edema resolved (Figure 9). The patient is working again and he is driving.

I think that anti-VEGF drugs for DME are truly a transformative breakthrough that enables us to do what we have not been able to do before. It is exciting to be part of this revolution where we can treat patients who have a devastating disease and restore functional vision. This is why we went into ophthalmology, to help people see and to prevent blindness. ■

1. Zhang X, Saaddine JB, Chou CF, et al. Prevalence of diabetic retinopathy in the United States, 2005-2008. *JAMA*. 2010;304:649-656.
2. Centers for Disease Control and Prevention. National diabetes statistics report: estimates of diabetes and its burden in the United States, 2014. Atlanta, GA: US Department of Health and Human Services; 2014. Accessed March 18, 2015.
3. Frank RN. Etiologic mechanisms in diabetic retinopathy. In: Ryan SJ, ed. *Retina*, Schachat AP and Murphy RP, eds. vol. 2 *Medical Retina*, St. Louis: Mosby; 1994; 1253-1265.
4. Khurana RN, Do DV, Nguyen QD. Anti-VEGF therapeutic approaches for diabetic macular edema. *Int Ophthalmol Clin*. 2009;49:109-119.
5. Grant MB, Afzal A, Spoerri P, et al. The role of growth actors in the pathogenesis of diabetic retinopathy. *Expert Opin Investig Drugs*. 2004;13:1275-1293.
6. Gardner TW, Antonetti DA, Barber AJ, et al. Diabetic retinopathy: more than meets the eye. *Surv Ophthalmol*. 2002;47(Suppl 2):S253-S262.
7. Funk M, Schmidinger G, Maar N, et al. Angiogenic and inflammatory markers in the intraocular fluid of eyes with diabetic macular edema and influence of therapy with bevacizumab. *Retina*. 2010;30:1412-1419.
8. Boyer DS, Hopkins JJ, Sorof J, Ehrlich JS. Anti-vascular endothelial growth factor therapy for diabetic macular edema. T*her Adv Endocrinol Metab*. 2013;4:151-169.
9. Danis RP. Diabetic macular edema. In: Albert DM, et al., eds. *Albert & Jakobiec's Principles and Practice of Ophthalmology*. 3rd ed. Philadelphia, PA: WB Saunders; 2008:1793-1806.
10. Klein R, Davis MD, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. A comparison of retinopathy in younger and older onset diabetic persons. *Adv Exp Med Biol*. 1985;189:321-335.
11. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IV. Diabetic macular edema. *Ophthalmology*. 1984;91:1464-1474.
12. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.
13. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med*. 2000;342:381-389.
14. Kissebah AH, Kohner EM, Lewis B, et al. Plasma-lipids and glucose/insulin relationship in non-insulin-requiring diabetics with and without retinopathy. *Lancet*. 1975;1:1104-1108.
15. Orchard TJ, Dorman JS, Maser RE, et al. Factors associated with avoidance of severe complications after 25 yr of IDDM. Pittsburgh Epidemiology of Diabetes Complications Study I. *Diabetes Care*. 1990;13:741-747.
16. Davis MD, Fisher MR, Gangnon RE, et al. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study Report #18. *Invest Ophthalmol Vis Sci*. 1998;39:233-252.
17. West KM, Erdreich LJ, Stober JA. A detailed study of risk factors for retinopathy and nephropathy in diabetes. *Diabetes*. 1980;29:501-508.
18. Leske MC, Wu SY, Hennis A, et al; Barbados Eye Study Group. *Ophthalmology*. 2005;112:799-805.
19. Chase HP, Jackson WE, Hoops SL, et al. Glucose control and the renal and retinal complications of insulin-dependent diabetes. *JAMA*. 1989;261:1155–1160.
20. Kakizawa H, Itoh M, Itoh Y, et al. The relationship between glycemic control and plasma vascular endothelial growth factor and endothelin-1 concentration in diabetic patients. *Metabolism*. 2004;53:550-555.
21. Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. *Diabetes Care*. 2000;23:1084-1091.
22. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol*.1985;103:1796-1806.
23. Nguyen QD, Brown DM, Marcus DM, et al; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119:789-801.
24. Brown DM, Nguyen QD, Marcus DM, et al; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120:2013-2022.
25. Brown DM. Ranibizumab PRN for diabetic macular edema: Long-term open-label extension of the phase 3 RIDE and RISE trials. Paper presented at: Annual Meeting of the American Society of Retina Specialists; August 11, 2014; San Diego, CA.
26. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Arch Ophthalmol*. 2012;130:972-979.
27. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept of diabetic macular edema. *Ophthalmology*. 2014;121:2247-2254.

Corticosteroids in DME: A Rapidly Changing Landscape

New formulations and novel delivery devices address the inflammatory component.

By Nancy M. Holekamp, MD

Most discussions about the use of corticosteroids to treat diabetic macular edema (DME) begin with data from the RISE and RIDE trials[1]: 39.2% of patients receiving ranibizumab (Lucentis 0.3 mg, Genentech) gained 3 lines of visual acuity, and 57.2% of patients improved to 20/40 or better. From a different perspective, however, that means 61% of patients in RISE and RIDE did not meet the primary endpoint of a 15-letter gain, and 43% did not achieve 20/40 visual acuity. These data show that anti-VEGF therapy is not solving the entire DME problem. This is our opportunity to discuss the role of inflammation in DME.

INFLAMMATION

In patients with DME, early focal leakage is primarily VEGF-driven, but when it advances to diffuse leakage, leading to fibrosis, pigmentary alterations, and loss of photoreceptors, the equation changes. What was primarily a VEGF-driven process is now primarily inflammation driven, creating a larger role for corticosteroids.

Figure 1 shows the relationship between aqueous cytokine expression and the severity of retinopathy.[2] When the ETDRS retinopathy severity score is 10, the VEGF level is in the 900s. As the score increases to 81, indicating severe diabetic retinopathy probably of longer duration, the VEGF level increases somewhat but is not statistically significant. Meanwhile, the other cytokines—IL-1β, IL-6, IL-8, MCP-1, IP-10—show statistically significant increases when the score is 81. We can conclude that worse diabetic retinopathy is not all about VEGF, again suggesting a greater role for corticosteroids.

DME causes both anatomical and physical changes, but biochemical factors are also involved. As illustrated by Figure 2, anti-VEGF strikes only one aspect in each of these two categories.[3-14] A steroid, however, will strike about half of the biochemical factors and almost half of the anatomical and physical changes (Figure 3). A corticosteroid has many more targets and much more potential to have an impact on chronic, longstanding, or severe DME.

TRIAMCINOLONE

Triamcinolone is available in two forms. Kenalog (Bristol-Myers Squibb) is not approved for treating DME by the US Food & Drug Administration (FDA). In fact, the label states it is not for intraocular use, but ophthalmologists have long-standing experience with it. Triesence (Alcon) is FDA approved for some rare conditions, such as sympathetic ophthalmia and giant cell or temporal arteritis. When we use it for DME, we are using it in an off-label manner.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) looked at 854 eyes in a clinical trial evaluating ranibizumab and triamcinolone with prompt or deferred laser.[15] At the 1-year mark, sham plus laser did not improve visual acuity, while eyes in the ranibizumab groups showed improved visual acuity (Figure 4). In the steroid group, visual acuity improved almost to the level of the ranibizumab

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

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

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

Figure 1. This figure shows the relationship between aqueous cytokine expression and the severity of retinopathy.

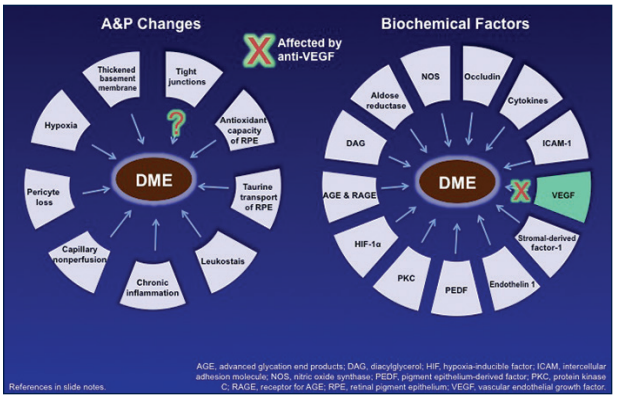


Figure 2. Anti-VEGF strikes only one aspect in each of these two categories.

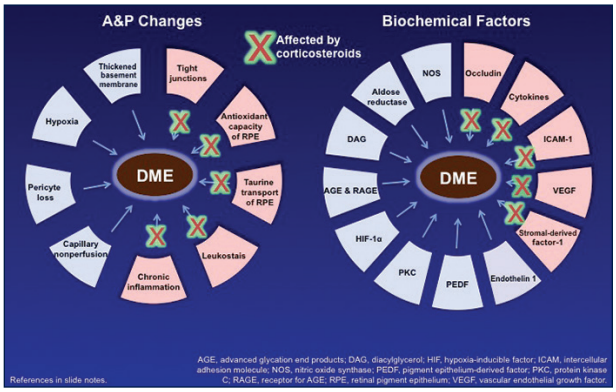


Figure 3. A steroid will strike about half of the biochemical factors and almost half of the anatomical and physical changes.

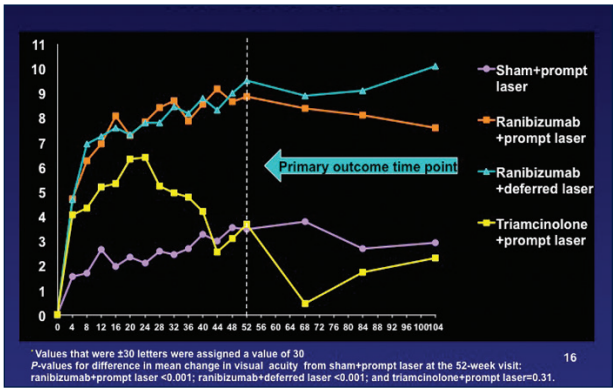


Figure 4. At 1 year, sham plus laser did not improve visual acuity, while eyes in the ranibizumab groups showed improved visual acuity.

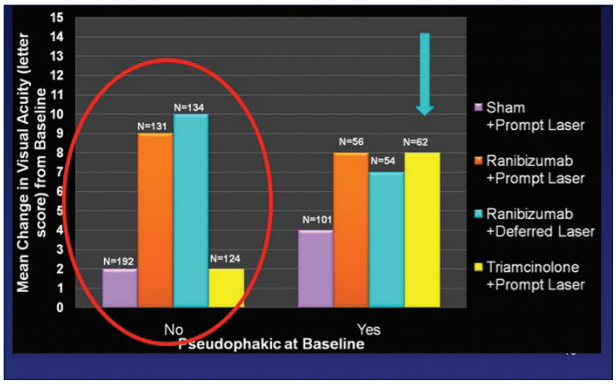


Figure 5. In patients who were phakic, visual acuity was poor, because cataracts developed.

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

*Excludes eyes with IOP lowering medications at baseline
**Includes 2 filter and 2 cilliary body destruction
20

Figure 6. At the 3-year final visit, the dexamethasone implant 0.7-mg group had greater letter gains than the placebo group.

groups at about 4 months, but then declined sharply, never recovering until late in the follow-up period. One of the explanations for this is cataract formation, which is a common side effect of this drug class. While visual acuity is improving and then declining because of cataract, the retina is getting thinner.

The researchers stratified their results by phakic status (Figure 5). In patients who were phakic—about two-thirds of those in the triamcinolone arm were phakic—visual acuity was poor, because cataracts developed. Pseudophakic eyes, however, did as well as eyes in the ranibizumab-treated arms. Pseudophakic eyes treated with triamcinolone in the DRCR. net trial did as well visually as the those in the ranibizumab-treated arms. By the 2-year follow-up, 55% of patients in the triamcinolone/prompt laser group required cataract surgery.

Corticosteroids also have a risk for elevated intraocular pressure (IOP), and in this study, a significant number of eyes in the triamcinolone/prompt laser group had pressure rises that needed to be managed (Figure 6).

In summary, triamcinolone combined with focal grid laser did not result in superior visual outcomes compared with laser alone, but that was likely because of cataract. Pseudophakic eyes treated with triamcinolone and prompt focal laser had outcomes equivalent to eyes in the two ranibizumab arms. The caveat is that we will need to manage increased IOP.

DEXAMETHASONE

The MEAD[16] study was a 3-year, sham-controlled trial in which patients were randomly assigned to the dexamethasone intravitreal implant, either 0.7 mg (Ozurdex, Allergan) or 0.35 mg, or placebo. At the 3-year final visit, the proportion of patients with at least a 15-letter improvement from baseline was significantly higher with the dexamethasone implant 0.7 mg (22.2%) compared with placebo (12.0%) (Figure 7).

In the total study population, visual acuity for the dexamethasone-treated eyes improved but then declined, probably because of cataract formation. In pseudophakic eyes treated with the dexamethasone implant, visual acuity was consistently significantly better than sham over the 3-year study with no loss of treatment benefit. Almost 60% of phakic patients needed cataract surgery by the end of the 3-year study. This is a recurring theme and a trade-off we make to help our patients with DME. There is a benefit, however, to having a steroid "on board" when cataract surgery is performed.

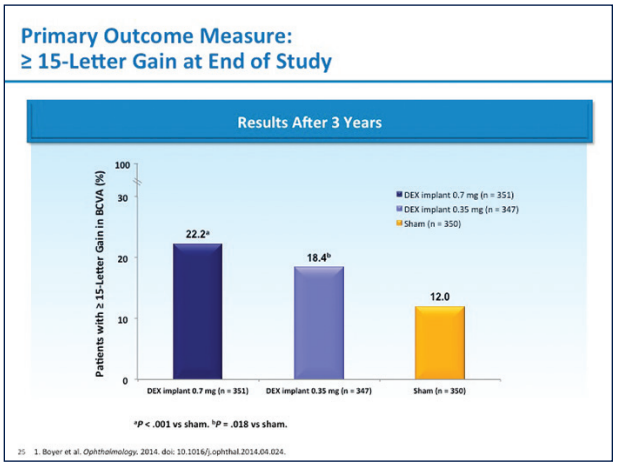


Figure 7. Patients in the dexamethasone group were more likely than placebo patients to have at least a 15-letter improvement from baseline.

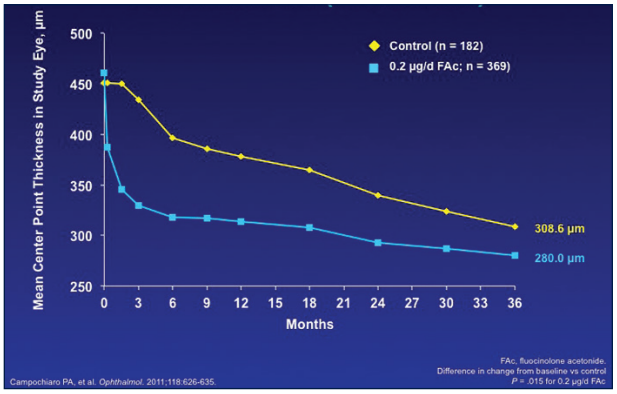


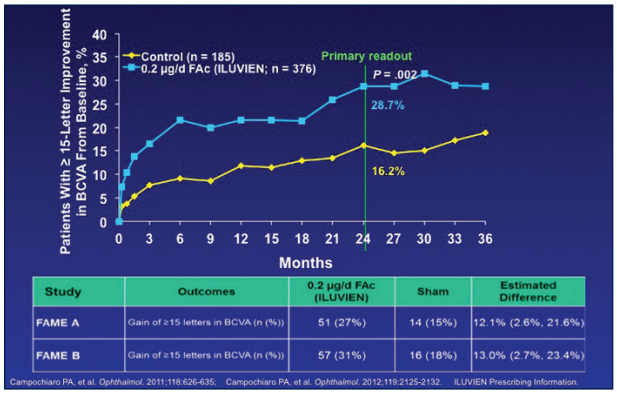
Figure 9. Patients receiving the fluocinolone implant also had an immediate decrease in central retinal thickness.

Intraocular pressure will likely increase when the dexamethasone implant is in the eye, rising upon implantation and then decreasing over time as the implant biodegrades. This pressure rise is reproducible and manageable with topical antiglaucoma drugs. In the MEAD study, about 41% of eyes in the 0.7-mg group needed IOP-lowering drugs.

FLUOCINOLONE

The fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences) is delivered with a self-sealing 25-gauge applicator. Unlike the dexamethasone device, which biodegrades in the eye, the fluocinolone device is not bioerodible. It releases a submicrogram daily dose of fluocinolone for about 3 years.

Two randomized, phase 3 clinical trials, FAME-A[17] (0.2 µg/d) and FAME-B[18] (0.5 µg/d), evaluated the fluocinolone implant. The FDA approved the 0.2 µg/d implant. In these studies, fluocinolone was dosed only once a year, and some eyes did not need it that often. About 28.7% of patients had a 15-letter improvement in visual acuity compared with placebo, regardless of which dose they received (Figure 8), and



Study	Outcomes	0.2 µg/d FAc (ILUVIEN)	Sham	Estimated Difference
FAME A	Gain of ≥15 letters in BCVA (n (%))	51 (27%)	14 (15%)	12.1% (2.6%, 21.6%)
FAME B	Gain of ≥15 letters in BCVA (n (%))	57 (31%)	16 (18%)	13.0% (2.7%, 23.4%)

Figure 8. Patients receiving the fluocinolone implant had a 15-letter improvement in visual acuity compared with placebo.

central retinal thickness decreased immediately (Figure 9).

As with all steroids, fluocinolone will cause cataracts in a large proportion of eyes. In the FAME studies, 82% of eyes developed a cataract, and cataract surgery was performed in 80% of eyes.

In the FAME trials, an IOP above 30 mm Hg was considered an adverse event, and 20% of eyes were in that category. About 38% of eyes were treated with IOP-lowering drugs.

In summary, the FAME clinical trial met its primary endpoint with a 15-letter improvement in best-corrected visual acuity from baseline to month 24. Improvements in vision were sustained over 3 years. Retinal thickness showed a favorable anatomic response. The rate of common complications of this drug class, cataract formation and IOP elevation, may be somewhat higher for fluocinolone acetonide than they were for triamcinolone and certainly dexamethasone.

SUMMARY

Ophthalmologists have used triamcinolone for more than 10 years, and the DRCR Network has studied it in a scientifically rigorous manner; however, none of the formulations is FDA approved for the treatment of DME.

The dexamethasone drug delivery implant is indicated for treatment of adults with DME with no restrictions related to phakic eyes.

Fluocinolone acetonide is indicated for the treatment of DME in patients who were previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP. This is because the eyes with the highest pressure rise in the FAME trials were those that had never been exposed to corticosteroids. When we decide to use a corticosteroid to treat DME, we will not use fluocinolone first, because it remains in the eye for 3 years. We will likely use a shorter-acting steroid, such as the dexamethasone intravitreal implant or triamcinolone to see if the patient's macular edema responds favorably with improved visual acuity and anatomy but without an unfavorable response

(Continued on page 15)

Decision Tree for Treating Diabetic Macular Edema

Our treatment algorithm is evolving.

By Karl G. Csaky, MD, PhD

Our clinical definitions of diabetic macular edema (DME) have evolved since the time when laser was our only treatment option, and foveal center involvement was not required for a diagnosis of clinically significant macular edema. In contrast, recent clinical trials of anti-VEGF agents and steroid therapy have all required retinal thickening of the foveal center and some degree of vision decrease. Therefore, it is important to recognize how our thinking has changed about treating this disease.

The following cases represent my typical approach to DME treatment.

NONCENTER-INVOLVING MACULAR EDEMA

The patient in Figure 1 has 20/20 visual acuity, minimal center-involving clinically significant macular edema, and a few microaneurysms temporal to the fovea. Under certain circumstances, monitoring a patient like this for a short time, especially if there is poor systemic control of the diabetes, may be appropriate. However, if clinically significant macular edema is present, focal laser photocoagulation can be considered. In this case, I treated with laser, and the macular edema resolved.

Although focal laser may still be viable for these types of cases, it is important to note that the background diabetic changes in the retina are not altered by laser photocoagulation. So, as we move forward in our understanding of anti-VEGF treatment, we need to think about the surrounding retina as well as the macular edema.

When researchers with the Diabetic Retinopathy Clinical Research Network looked at anti-VEGF therapy in the context of center-involving macular edema, and the number of injections required, and whether to treat with immediate or deferred laser, they found that deferred laser resulted in slightly better visual acuity at 3 years.[1] These data suggest that too few anti-VEGF treatments may be slightly harmful to vision. Therefore, I believe that in most cases, macular fluid and significant surrounding diabetic retinopathy changes need anti-VEGF therapy to some degree.

CENTER-INVOLVING DME

The patient in Figure 2 has center-involving DME and a visual acuity of 20/50. After four anti-VEGF injections, the visual acuity improved to 20/20, and the fluid resolved. Although it is difficult to appreciate from the fundus photos, many of the diabetic background retinal changes improved.

For center-involving DME, I typically start with an anti-VEGF agent, because the side-effect profile is good, the visual response is usually good, and it also has an effect on the surrounding diabetic retinopathy. In other words,

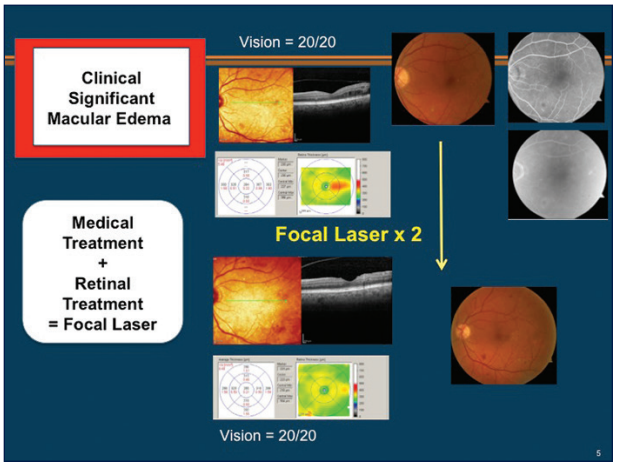


Figure 1. The patient's visual acuity is 20/20 and has minimal center-involving clinically significant macular edema.

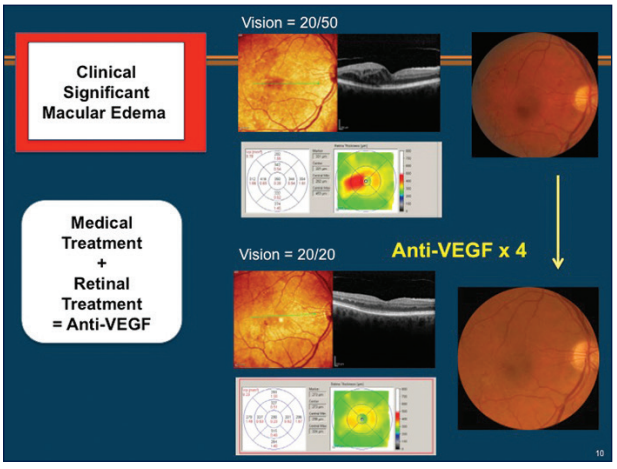


Figure 2. After four anti-VEGF injections, the patient's visual acuity improved to 20/20, and the fluid resolved.

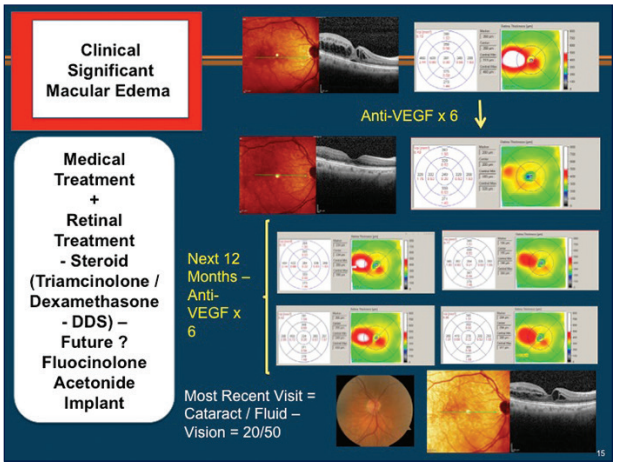


Figure 3. This patient received six anti-VEGF injections, but as shown on OCT, the fluid did not resolve completely.

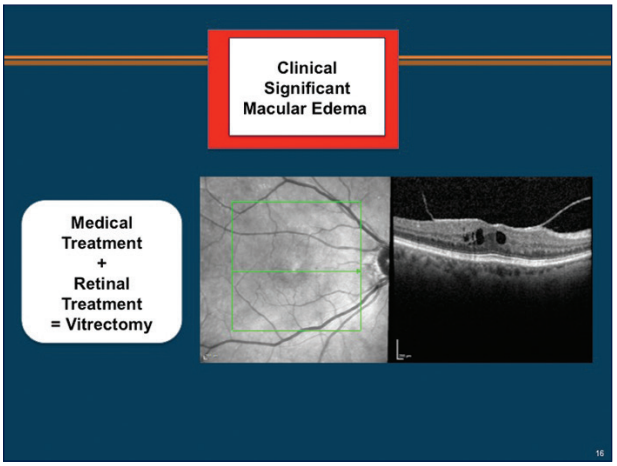


Figure 4. This patient has persistent macular edema despite numerous anti-VEGF injections.

I typically begin treatment with an anti-VEGF agent. If I do not see an immediate response, then I modify my approach.

anti-VEGF treatment appears to be disease-modifying, improving not only the center fluid status but also the underlying diabetic retinopathy diffusely throughout the retina.

POOR OR NO RESPONSE TO ANTI-VEGF

I typically begin treatment with an anti-VEGF agent. If I do not see an immediate response, then I modify my approach. Data suggest there may be differences in the way some patients respond to certain anti-VEGF agents.[2] Therefore, while one approach is to switch to another anti-VEGF agent, I typically try to introduce a steroid. Various steroid formulations are available to us, including triamcinolone, which is used off-label for DME, the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan), and the fluocinolone intravitreal implant 0.19 mg (Iluvien, Alimera Sciences).

Similarly, in some cases, the effect of anti-VEGF therapy is not complete, as in this patient who has center-involving DME (Figure 3). This patient received six anti-VEGF injections, but as shown on OCT, the fluid did not resolve completely.

Over the next 12 months, I continued to treat with anti-VEGF agent, but the response was inconsistent, and I never reached a threshold where I could decrease the number of anti-VEGF injections over time. I believe this patient is exhibiting an inflammatory response in addition to a VEGF overexpression as a cause of the macular edema.

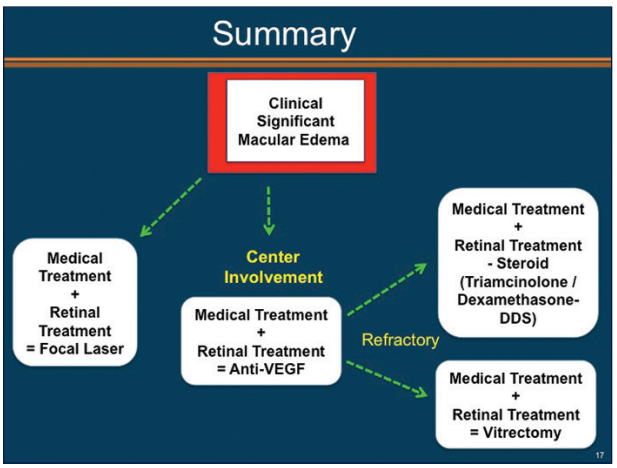


Figure 5. The treatment algorithm used by Dr. Csaky.

The patient underwent cataract extraction and was treated with the dexamethasone intravitreal implant 0.7 mg with subsequent complete resolution of the macular edema.

When a patient has only a partial response to anti-VEGF therapy and/or I cannot decrease the number of injections, I prefer to treat with the dexamethasone intravitreal implant 0.7 mg, particularly because the intraocular pressure (IOP) rise is predictable and controllable. From the clinical trial data, I know that if I need to repeat the dexamethasone implant treatment, the IOP rise will most likely be the same. This response is in contrast to what was found with triamcinolone, which appears to have an additive effect that the dexamethasone implant does not demonstrate.[3,4]

DME WITH VITREOMACULAR TRACTION

This patient discussed in Figure 4 has persistent macular edema despite numerous anti-VEGF injections. The vitreomacular traction is precluding improvement. I would consider vitrectomy for this patient.

In the past, we were somewhat reluctant to perform vitrectomy in patients with diabetes, because we were concerned that patients who had undergone vitrectomy would have a poor response to intravitreal injections. This is primarily because of the low retention of injected agents in the eye when the vitreous is removed. Although its use is off label in this circumstance, I have found that the dexamethasone intravitreal implant 0.7 mg works just as well after vitrectomy. So, we should not be afraid to perform vitrectomy, because we will have treatment options for persistent DME postvitrectomy.[5]

SUMMARY

To date, all of the anti-VEGF trials for DME have considered center involvement and some degree of vision loss as criteria for treatment. This approach may be evolving as we consider the effectiveness of anti-VEGF therapies in controlling both macular edema and background diabetic retinopathy.

Absent center involvement, if the edema is not near the fovea but is clinically significant, focal laser still has a role. As indicated in the treatment algorithm featured in Figure 5, if the DME is refractory to anti-VEGF therapy, I consider a steroid, either triamcinolone, dexamethasone, or fluocinolone. Finally, looking carefully at the possibility of a vitreous traction component or any issues with the vitreous, one should also consider vitrectomy. ■

1. Elman MJ, Qin H, Aiello LP, et al; Diabetic Retinopathy Clinical Research Network. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology*. 2012;119:2312–2318.
2. The Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med.* 2015 Feb 18. [Epub ahead of print].
3. Roth DB, Verma V, Realini T, Prenner JL, Feuer WJ, Fechtner RD. Long-term incidence and timing of intraocular hypertension after intravitreal triamcinolone acetonide injection. *Ophthalmology*. 2009;116:455-460.
4. Boyer DS, Yoon YH, Belfort R Jr, et al; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121:1904-1914.
5. Boyer DS, Faber D, Gupta S, et al; Ozurdex CHAMPLAIN Study Group. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. *Retina*. 2011;31:915-923.

(Continued from page 12)

to the corticosteroid. Fluocinolone's niche is the diabetic patient who has a chronic need for a corticosteroid. ■

1. Brown DM, Nguyen QD, Marcus DM, et al; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120:2013-2022.
2. Dong N, Xu B, Wang B, Chu L. Study of 27 aqueous humor cytokines in patients with type 2 diabetes with or without retinopathy. *Mol Vis*. 2013;19:1734-1746.
3. Iluvien full prescribing information. Alimera Sciences. http://www.alimerasciences.com/wp-content/uploads/2014/09/iluvien-prescribing-information.pdf. Accessed March 12, 2015.
4. Stewart MW. Corticosteroid use for diabetic macular edema: old fad or new trend? *Curr Diab Rep.* 2012;12:364-375.
5. Funatsu H, Noma H, Mimura T, Eguchi S, Hori S. Association of vitreous inflammatory factors with diabetic macular edema. *Ophthalmology*. 2009;116:73-79.
6.Yoshimura T, Sonoda KH, Sugahara M, et al. Comprehensive analysis of inflammatory immune mediators in vitreoretinal diseases. *PLoS One.* 2009;4:e8158.
7. Funk M, Schmidinger G, Maar N, et al. Angiogenic and inflammatory markers in the intraocular fluid of eyes with diabetic macular edema and influence of therapy with bevacizumab. *Retina*. 2010;30:1412-1419.
8. Kern TS. Contributions of inflammatory processes to the development of the early stages of diabetic retinopathy. *Exp Diabetes Res.* 2007;2007:95103.
9. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care.* 2003;26:2653-2664.
10. Tang J, Kern TS. Inflammation in diabetic retinopathy. Prog Retin Eye Res. 2011;30:343-358.
11. Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol.* 2009;54:1-32.
12. Zhou J, Wang S, Xia X. Role of intravitreal inflammatory cytokines and angiogenic factors in proliferative diabetic retinopathy. *Curr Eye Res.* 2012;37:416-420.
13. El-Sherbeny A, Naggar H, Miyauchi S, et al. Osmoregulation of taurine transporter function and expression in retinal pigment epithelial, ganglion, and Müller cells. *Invest Ophthalmol Vis Sci.* 2004;45: 694-701.
14. Sohn HJ, Han DH, Kim IT, et al. Changes in aqueous concentrations of various cytokines after intravitreal triamcinolone versus bevacizumab for diabetic macular edema. *Am J Ophthalmol.* 2011;152:686-694.
15. Elman MJ, Aiello LP, Beck RW, et al; Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117:1064-1077.
16. Boyer DS, Yoon YH, Belfort R Jr, et al; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121:1904-1914.
17. Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118:626-635.
18. Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119:2125-2132.

Challenging Cases in DME

Experts offer their suggestions to treat out of-the-ordinary cases of diabetic macular edema.

Presented by: Raj K. Maturi, MD

Discussants: David M. Brown, MD; Karl G. Csaky, MD, PhD; and Nancy M. Holekamp, MD

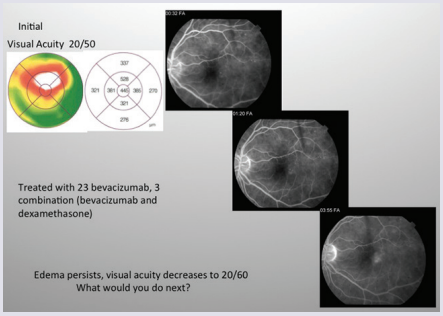
These days, teating diabetic macular edema is becoming more straightforward. When I see a new patient who is phakic and has center-involving macular edema, it makes sense to use an anti-VEGF agent. If a patient has other issues, a foot ulcer, for example, or recent cataract surgery, my first line of treatment is typically a steroid. Despite our expanding armamentarium of treatment options, however, we are often faced with complex cases, usually involving diabetes that is not well controlled. The cases that follow are two of the more difficult cases I have managed during the past few years.

CASE No. 1

This 67-year-old woman has had poorly controlled diabetes for 22 years. She does not monitor her blood sugar. She does not know her hemoglobin A1c target, and she is currently undergoing treatment for significant renal disease. She has a history of hypertension and atrial fibrillation controlled with medication.

The patient, who is phakic, reported increasing difficulty with near-vision tasks. Her visual acuity was 20/50. She had a significant amount of center-involving macular edema and an increased foveal avascular zone (Figure 1).

After numerous treatments with bevacizumab (Avastin, Genentech), as well as three combinations of bevacizumab and dexamethasone solution (custom compounded, not implant), the edema persisted.



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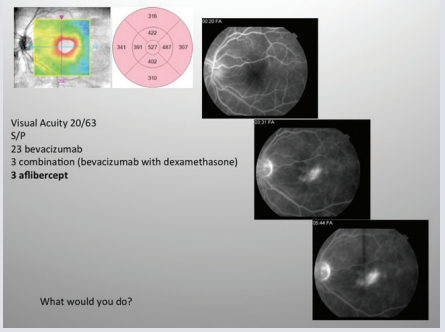

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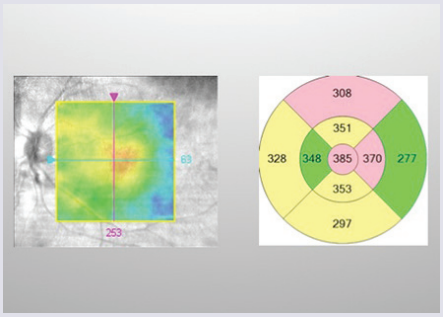

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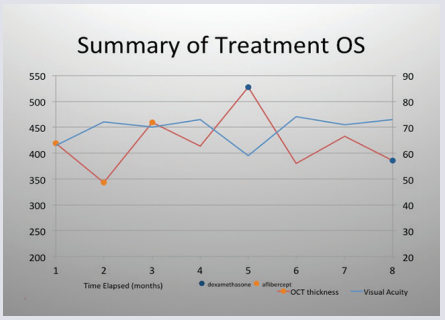


Figure 4.

In a phakic patient with a suboptimal response to initial anti-VEGF therapy, switching to a different anti-VEGF agent may be beneficial, especially if the patient has been treated with one anti-VEGF agent for a long period. So, I switched to aflibercept (Eylea, Regeneron). After three injections, neither the edema nor the visual acuity had improved (Figure 2).

At that point, I treated with the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan). After one injection, the patient's visual acuity improved remarkably, and the edema flattened out, an effect that persisted for 4 months (Figure 3).

Figure 4 summarizes this patient's treatment history. On the left is central subfield thickness, and on the right is visual acuity in letters; the blue represents acuity, and the orange represents the treatment; the orange dots are aflibercept, and the blue dots are dexamethasone 0.7-mg injections.

In this case, there was some benefit in terms of the edema, but the visual acuity improved to only 20/32. Part of the reason for that may be because the patient received many anti-VEGF injections, and when the edema is chronic, a loss of photoreceptors is likely, as well as chronic structural changes that limit maximum visual acuity. Additionally, the presence of hypertension and chronic diabetes causes macular ischemia, which also limits visual gain. It is important not to wait too long to try something different. Although we are not always exactly sure what the different drug should be, it is absolutely important to move on when the response is poor. If we do not, I believe we are leaving some vision on the table, and this case is an example of that.

PANEL DISCUSSION: CASE No. 1

David M. Brown, MD: Dr. Maturi, how long do you think we can wait? Two years is too long. We showed that in RIDE and RISE.[1]

Raj K. Maturi, MD: I think 6 months is a good time frame. If the patient has excellent control systemically and you are seeing improvement, you can continue to treat, but if you stop seeing improvement, if you see continued edema, then it is time to take a new approach. There is no point in doing the same thing over and over again and expecting a different result.

Nancy M. Holekamp, MD: I am assuming you started treating this patient before we had FDA approval of other agents.

Dr. Maturi: Yes.

Dr. Holekamp: Because today you would not give someone 23 bevacizumab injections in a row.

Dr. Maturi: Exactly.

Dr. Holekamp: I am interested in how everyone defines *refractory*? Is it three injections? Is it four injections? Is it 6 months?

Karl G. Csaky, MD, PhD: That is a good question. I think it has to do with both anatomic response and visual acuity response. Our thinking has evolved, because we now have data on DME in terms of how long we can wait to see an effect. We also have several agents that we can use, often in combination. Therefore, I have become more liberal about labeling a patient as refractory. For example, if a patient has a good response, both anatomically and visually, to an anti-VEGF agent but demonstrates a continued frequent need for anti-VEGF injections to maintain those improvements, then, in my opinion, that is also a definition of *refractory*.

Dr. Maturi: That is a good point, Dr. Csaky. The DRCR Network (DRCR.net) Protocol I looked at 250 subjects in the ranibizumab groups.[2] In the first year, they needed an average of nine injections; in the second year, they needed an average of three, and by the third year, they needed only two injections to maintain vision. Visual acuity gains were similar to those achieved in RIDE and RISE with continued monthly injections.

I think we can conclude that patients do not necessarily need monthly injections. They need their diabetes to be treated and their diabetic retinopathy to regress, and we can often decrease the number of injections, but that is not true for everyone. Multiple mechanisms are involved in a significant number of patients. For example, in RIDE and RISE, approximately 40% of patients did not achieve complete flattening, and about half did not achieve visual acuity gains of more than 3 lines. So, obviously, there is more than one mechanism involved, and if one therapy will not treat the whole disease, then we need to try something different.

Dr. Csaky: Dr. Holekamp, what is your definition of *refractory*?

Dr. Holekamp: DRCR.net researchers found that 25% of eyes treated with ranibizumab for DME had a 20% reduction in OCT thickness.[3] Those eyes were considered responders to anti-VEGF therapy. Eyes that did not achieve a 20% reduction were either nonresponders, partial responders, or latent responders.

I administer four anti-VEGF injections, and either it works, or it does not. If it does not work, I move on. Otherwise, I am committing a patient to a chronic path that only becomes more complicated and could permanently damage the photoreceptors. Therefore, in my opinion, anti-VEGF therapy is therapeutic and diagnostic. If eyes respond, I know the disease process is primarily VEGF-mediated and I can continue, and they do very well. If they do not respond or have a suboptimal response, then it is not all VEGF mediated, and I have to switch to a corticosteroid.

Dr. Maturi: At the 2013 meeting of the American Society of Retina Specialists, researchers reported data from anterior chamber fluid and the levels of various mediators for diabetics.[4] Levels of IL-6 and IL-12 were high, and other levels of inflammatory interleukins were high in patients with DME. These are not affected by anti-VEGF treatment. There is definitely a biochemical reason why anti-VEGF therapy may not be enough.

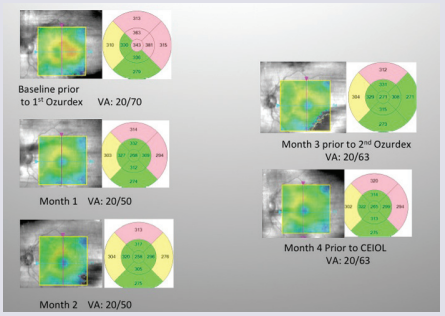
Dr. Csaky: We also need to consider that there may be differences between the anti-VEGF agents. Just because anti-VEGF agents do so well for the surrounding diabetic retinopathy, I do not give them too much time, but if I do not see a response, I may switch to another anti-VEGF agent.

Dr. Brown: I am a strong supporter of anti-VEGF therapy, but for some patients, there is not enough anti-VEGF in my closet to control their edema. Many of these patients need a steroid. I use the dexamethasone 0.7-mg implant. If they need multiple (two or more) implants and there is no pressure rise, I will consider switching to the fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences).

CASE No. 2

This 64-year-old man has a 30-year history of diabetes. He has had DME for 4 years and has been treated with focal laser photocoagulation and multiple anti-VEGF injections. Cataract progression is affecting his visual function.

Even though the edema is mild, it must be completely resolved before cataract surgery is performed. We can infer this from the DRCR.net Protocol I, triamcinolone subgroup in which cataract surgery performed in subjects with macular edema did not result in visual restoration to baseline.[2] In this situation, because cataract surgery will cause inflammatory mediators to be expressed, my treatment of choice is a steroid. Of course, I am not concerned about cataract formation, and I am confident the IOP will be monitored frequently after the cataract surgery.



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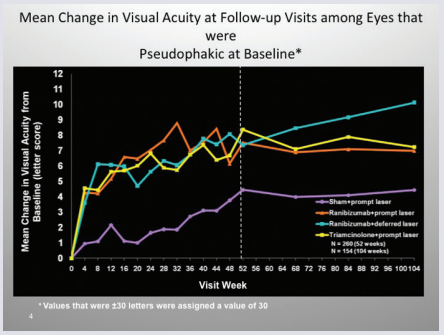

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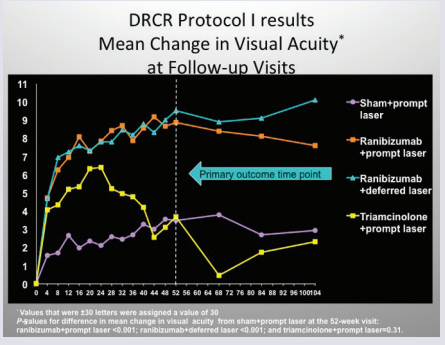

Figure 7.

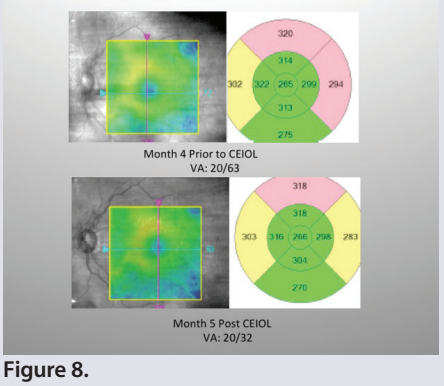

Figure 8.

At month 4, prior to cataract extraction, the patient's visual acuity was 20/63, and he had a small amount of edema. That is when a third or fourth injection of dexamethasone 0.7 mg was given (Figure 5).

Figure 6 represents 2-year data from DRCR.net Protocol I, and the vertical dotted line represents the 1-year time point.[2] This graph includes only pseudophakic patients. The light blue line and the orange line represent the two ranibizumab subgroups. At 1 year, patients in both subgroups gained about 8 letters. The bright yellow line represents steroid, and those patients gained 8 letters, the same amount as the ranibizumab subgroups, even though injections were given only every 3 months. The purple line is the focal laser line. In pseudophakic patients, steroids gave the exact same visual acuity gain as did ranibizumab. Figure 7 shows results for all-comers. So the pseudophakia makes all the difference here.

At month 4, prior to cataract surgery, this patient received another dexamethasone 0.7-mg implant, and after cataract surgery, the edema resolved, and his visual acuity improved to 20/32 (Figure 8).

PANEL DISCUSSION: CASE No. 2

Dr. Holekamp: According to the MEAD study,[5] when the dexamethasone implant is used, these eyes sail through cataract surgery. Whereas, patients who have not been pretreated with dexamethasone are at high risk of worsening DME.

Dr. Maturi: Agreed. As shown in Figure 7, in the first 4 months, the visual acuity of patients receiving the steroid improves just as well as the visual acuity of those receiving the anti-VEGF agent. Their cataracts start to form at about month 5, and visual acuity declines. At about 1 year, the majority of these patients had cataract surgery, but the surgery was not properly timed with the injection because that was not the design. That is something we learned from this study. When edema is present prior to cataract surgery, the vision may not return. The pseudophakic eyes do just as well as the anti-VEGF group out to 2 years, because they did not have, by definition, cataract surgery when edema was present. Of course, steroid-related IOP issues are present that would not be present in the anti-VEGF—alone groups. ■

1. Brown DM, Nguyen QD, Marcus DM, et al; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120:2013-2022.
2. Elman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology*. 2012;119:2312-2318.
3. Bressler SB, Qin H, Beck RW, et al; Diabetic Retinopathy Clinical Research Network. Factors associated with changes in visual acuity and OCT thickness at 1 year after treatment for diabetic macular edema with ranibizumab. *Arch Ophthalmol*. 2012;130:1153-1161.
4. Wong D. A Prospective Study of Anterior Chamber Cytokine Levels and Their Association With Disease Severity in Diabetic Macular Edema. Presented at: Annual Meeting of the American Society of Retina Specialists; August 28, 2013; Toronto, Canada.
5. Boyer DS, Yoon, YH, Belfort R Jr., et al; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121:1904-1914.

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CME QUESTIONS

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1. **According to the Diabetes Control and Complications Trial, which of the following is associated with a 76% risk reduction in the development of any retinopathy and a 54% risk reduction of retinopathy progression for patients who had retinopathy at baseline?**
   a. intensive hypertension control
   b. intensive glucose control
   c. significantly lowered lipids
   d. significantly lowered triglycerides

2. **In the RISE and RIDE trials, what were the outcomes in patients who were switched from sham treatment to ranibizumab at 2 years?**
   a. They did not achieve the visual gains seen in the original ranibizumab arms.
   b. Their visual gains reached the level of those seen in the original ranibizumab arms.
   c. Visual gains were significantly different between the 0.3-mg dose and the 0.5-mg dose of ranibizumab.
   d. Anatomically, sham and treatment arms remained similar.

3. **In the MEAD study, what percentage of patients in the 0.7-mg dexamethasone arm had a ≥15-letter improvement in visual acuity?**
   a. 2.2%
   b. 12.2%
   c. 22.2%
   d. 32.2%

4. **In the FAME trials, what percentage of patients had a 15-letter improvement in visual acuity, regardless of dosage of fluocinolone?**
   a. ~8.7%
   b. ~18.7%
   c. ~28.7%
   d. ~38.7%

5. **Which of the following agents is indicated for the treatment of diabetic macular edema in patients who were previously treated with a course of corticosteroids and did not have a clinically significant intraocular pressure (IOP) rise?**
   a. triamcinolone (Kenalog)
   b. triamcinolone (Triesence)
   c. dexamethasone intravitreal implant 0.7 mg
   d. fluocinolone intravitreal implant 0.19 mg

6. **Studies have shown that any rise in IOP is predictable and controllable for which of the following agents?**
   a. triamcinolone (Kenalog)
   b. triamcinolone (Triesence)
   c. dexamethasone intravitreal implant 0.7 mg
   d. fluocinolone intravitreal implant 0.19 mg

7. **By the third year of the DRCR Network Protocol I, how many anti-VEGF injections, on average, did subjects require to maintain visual acuity?**
   a. 2
   b. 3
   c. 6
   d. 9

8. **In a DRCR Network study, ranibizumab-treated eyes were considered nonresponders, partial responders, or latent responders if they did not show what percentage reduction in OCT thickness?**
   a. 20%
   b. 25%
   c. 30%
   d. 35%

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Discuss the pathophysiology and epidemiology of DME	_____	_____	_____
Differentiate existing DME therapy options from recent primary and secondary treatments	_____	_____	_____
Apply evidence-based medicine when treating macular edema and inflammation	_____	_____	_____
Evaluate the response or nonresponse to treatment: decision tree modeling in treatment decisions	_____	_____	_____
Discuss important conditions to consider in using therapies in patients with significant comorbidities	_____	_____	_____

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