New data for the management of macular edema and inflammation associated with retinal vein occlusion, diabetes, and uveitis.
STATEMENT OF NEED

Despite new understanding of disease processes and treatments related to inflammatory and edematous conditions of the macula, a significant gap between actual and optimal care persists.

Retinal vein occlusion (RVO) remains the second most common retinal vascular disease after diabetic retinopathy and a common cause of visual morbidity and blindness in the elderly. Specifically, branch retinal vein occlusion (BRVO) is 3 times more common than central retinal vein occlusion (CRVO) and second only to diabetic retinopathy as the most common retinal vascular cause of visual loss. In the Beaver Dam Eye Study, the 15-year cumulative incidence of BRVO was found to be 1.8% and the incidence of CRVO was established at 0.5%. Collectively, retinal vascular occlusive disorders constitute one of the major causes of blindness or seriously impaired vision, and yet controversy surrounds their pathogeneses, clinical features and management. These disorders are characterized by dozens of misconceptions, including a belief that RVOs represent a single clinical entity, that CRVO is 1 disease, that an eye can develop CRVO and central retinal artery occlusion simultaneously, and that estimation of visual acuity provides all of the information needed to evaluate visual function. The major cause of these misconceptions, experts say, is a lack of proper understanding of basic scientific facts related to the various diseases. A major challenge in properly diagnosing and managing these patients is that RVO has a multifactorial etiology with many unclear aspects, including those associated with hypertension, dyslipidemia, and renal dysfunction.

Diabetic retinopathy is the leading cause of new cases of blindness in adults ages 20-74. The estimated prevalence of diabetic retinopathy and vision-threatening diabetic retinopathy was recently found to be 28.5% and 4.4% among US adults with diabetes, respectively. This finding is significant when considered in the context of explosive growth in the incidence of diabetes type 2, which commonly leads to diabetic retinal disease. A gap between optimal and actual care of diabetic eye disease also exists among patients with type 1 diabetes. During a 25-year period, the Wisconsin Epidemiologic Study of Diabetic Retinopathy found relatively high cumulative rates of progression of diabetic retinopathy and proliferative diabetic retinopathy in this population. A separate analysis of more recently diagnosed patients from the same study demonstrated the potential benefit of closing this gap. Improvements in diabetes care were believed to possibly have contributed to a much lower prevalence and less severe retinopathy than expected on the basis of a previous report from the same region of Wisconsin.

Successfully preventing and treating uveitis remains difficult. Uveitis can be caused by any number of infectious diseases, certain autoimmune diseases, reactions to some non-ocular medications, or exposure to toxins. About 50% of cases have no known cause. The disease affects 2.3 million in the United States and is responsible for about 10% of all cases of blindness.

To address these gaps, retina specialists and other ophthalmologists must master new insights on pathogenesis and a proliferation of therapeutic advances spawned by the introduction of new technologies and techniques in recent years.

References

TARGET AUDIENCE

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

LEARNING OBJECTIVES

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

- Recognize various forms of macular edema and inflammation, using the latest developments in medical literature and new insights from case-based learning.
- Make better decisions for patient selection and management with steroid implants.
- Differentiate steroids and their effects in the treatment of macular edema and inflammation.
- Effectively treat various forms of macular edema and inflammation, based on assessment of patient need, latest developments in medical literature and insights from case-based learning.
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 http://www.dulaneyfoundation.org and click “Online Courses.” Upon completing the activity and achieving a passing score of over 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.

ACCREDITATION AND DESIGNATION
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Dulaney Foundation and Retina Today. The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this enduring material for a maximum of 1 AMA PRA Category 1 Credit.” Physicians should claim only the credit commensurate with the extent of their participation in the activity.

DISCLOSURE
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FACULTY CREDENTIALS
David S. Boyer, MD, is a Clinical Professor of Ophthalmology at the University of Southern California Keck School of Medicine, Department of Ophthalmology, in Los Angeles. Dr. Boyer may be reached at vitdoc@aol.com.

C. Stephen Foster, MD, FACS, FACR, FAAO, is a Clinical Professor of Ophthalmology at Harvard Medical School and the Founder and President of the Ocular Immunology and Uveitis Foundation and the Massachusetts Eye Research and Surgery Institution (MERSI), in Cambridge, MA. He can be reached at sfoster@mersi.com.

Michael A. Singer, MD, is the Managing Partner and Director of Clinical Trials at Medical Center Ophthalmology Associates, in San Antonio, TX. He is also Assistant Clinical Professor at the University of Texas Health Science Center of San Antonio. He can be reached at msinger@mcoeyecare.com.

FACULTY/STAFF DISCLOSURE DECLARATIONS
David S. Boyer, MD, has received grant/research support from Alcon Laboratories, Inc., Allergan, Inc., Genentech, and Novartis. He is a consultant and speaker for Alcon Laboratories, Inc., Genentech, Novartis, and Pfizer.

C. Stephen Foster, MD, has served as an advisor or consultant for Abbott, Alcon Laboratories, Inc., Allergan, Inc., Ista Pharmaceuticals, LUX Biosciences, Novartis; as a speaker or a member of a speakers bureau for Alcon Laboratories, Inc., Allergan, Inc., Bausch & Lomb Surgical, Inspire, Ista Pharmaceuticals, LUX Biosciences; has received grants for clinical research from Abbott, Alcon Laboratories, Inc., Allergan, Inc., Eyegate, LUX Biosciences; has received research funding from Genentech, Regeneron, NeoVista, Macusight, Allergan, Alcon, and Thrombogenics; and has been a consultant to, Inc., ISTA, Alcon Laboratories, Inc., and Genentech.

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The Pathophysiology of Macular Edema

BY DAVID S. BOYER, MD

Macular edema occurs when fluid and protein deposits accumulate in the macular region, causing a thickening and swelling of the macula that can be either focal or diffuse. It is believed that a breakdown of the blood-retinal barrier leading to increased retinal vascular permeability is the cause of macular edema, which is major cause of vision loss in a variety of retinal diseases, including diabetic retinopathy, retinal vein occlusion (RVO), uveitis, and Irvine-Gass syndrome.

The pathophysiology of macular edema is complex, with a variety of processes involved in its development. Abnormal retinal capillary permeability or breakdown of the blood-retinal barrier is the underlying etiology. This increased vascular permeability, in which the extracellular spaces expand, causes an accumulation of fluid, which overwhelms the mechanism that maintains the fluid balance, leading to macular thickening and eventual visual loss.

Early vascular and inflammatory changes are most likely secondary to retinal tissue stresses, which can result from hypoxia, altered blood flow, ischemia, toxicity, surgical trauma, and inflammation. These stresses initiate an inflammatory process in the retinal vasculature leading to further alterations in the blood flow and migration of inflammatory cells (leukocytes) to the retinal vasculature. The leukocytes then begin to release inflammatory cytokines. The leukocytes are aided in their targeting of affected tissues by inflammatory adhesion molecules, including intracellular adhesion molecule 1 (ICAM-1), expressed on the inside of blood vessels in the region of retinal stress. These adhesion molecules help the leukocytes roll along and adhere to the interior surface of the blood vessel.

Once a leukocyte adheres to the inside of the vessel, monocyte chemoattractive protein 1 (MCP-1) is secreted to help activate the leukocyte and aid its migration across the vessel wall and into the tissues (Figure 1). Once in the retinal tissue, leukocytes secrete a variety of inflammatory mediators, including interleukin (IL-1), tumor necrosis factor (TNF)-alpha, and vascular endothelial growth factor (VEGF), all of which increase permeability (Figure 2). The presence of inflammatory mediators stimulates the production of more of these molecules and...
leads to amplification of the inflammatory response (Figure 3).

As the condition progresses, the blood-retinal barrier begins to break down, increase vascular permeability that allows fluid to leak from the vessels, and the movement of large molecules out of the vascular compartment (Figure 4). There can also be a loss of pericytes around the capillaries, which can lead to capillary wall weakness, and even the formation of microaneurysms. Endothelial basement membrane thickening can lead to focal closure of some capillaries, which in turn, may increase blood flow through nearby vessels.

Müller cell processes are the principal extracellular matrix tissue of the retina and where most of the fluid begins to form. Cystic spaces have been noted on optical coherence tomography of pathologic specimens, and it appears that the junctions between the Müller cells and neuronal cell membranes become stretched (Figure 5). Müller cells are the only cells that express glucocorticoid receptors in the retina; therefore, it may be advantageous to treat with steroids to eliminate some of this fluid.

Inflammation is a function of both innate and adaptive immunity that spur the body to mount an attack against foreign antigens. Physiological inflammatory cascades eliminate provoking substances and begin to repair affected tissues.

**DIABETIC MACULAR EDEMA**

The pathophysiology of diabetic macular edema (DME) involves intracellular hyperglycemia, which induces free radicals (oxidative stress), protein kinase C (PKC) activation, and formation of advanced glycation end-products (AGE). 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, diabetic retinopathy is now considered to be a state of low-grade inflammation.

In experimental diabetic models, signs of diabetic retinopathy occur as a result of inflammatory reactions secondary to oxidative stresses, proinflammatory cytokines, binding of leukocyte adhesion molecules CD-18 and intracellular adhesion molecules ICAM-1. This leads to the breakdown of the blood-retinal barrier, vascular occlusion, and tissue ischemia.

Inflammatory causes of edema include: an increase of neutrophils in the choroid; increased polymorphonuclear leukocytes in the choriocapillaries associated with loss of endothelial cells; leukocyte aggregation, and capillary
drop-out; elevated CD-4 and CD-6T; cells in the vitreous; elevated macrophages in the vitreous leading to proinflammatory cytokines; and up-regulation of TNF-alpha.

RETINAL VEIN OCCLUSION

In RVO, there is a combination of both increased hydrostatic pressure behind the occlusion, causing the deterioration of the endothelial cell integrity, instigating a secondary inflammation with an upregulation of VEGF and interleukin.6

In several studies a C-reactive protein elevation has been noted.6

The cascade in branch retinal vein occlusion (BRVO) leads to impaired recruitment of lymphocytes and macrophages to the injured area, direct cell death, and again, a weakened blood-retinal barrier, increased lymphocytes in the retina, and further edema.

The rationale for corticosteroid therapy is that inflammation may lead to compression of an arteriosclerotic central retinal artery or primary occlusion of the central retinal vein.7 In one study, chronic inflammation in the area of the thrombus in a branch vein in the vein wall or the perivenular area has been observed in 48.3% (14) of eyes with central retinal vein occlusion (CRVO).8 Further, suppression of VEGF production has been shown to inhibit inflammatory cell activity.9

UVEITIS AND IRVINE-GASS SYNDROME

Macular edema is commonly associated with uveitis. Although the cause of uveitis is often unknown, some cases have been associated with autoimmune disorders, infection, and exposure to toxins. Irvine-Gass Syndrome, also known as postoperative macular edema, is a common complication of cataract surgery.

Uveitis leads to macular edema through an inflammatory process. Uveitis activates the proinflammatory marker, such as VEGF, interleukin, tumor necrosis factor, and interfering gamma, that eventually lead to increased macular edema.

CASE #1

A woman aged 78 years presented with a history of hypertension and a treatment-naive inferotemporal BRVO with 20/30-1 visual acuity. Figure 6 shows her fluorescein angiograms at presentation and Figure 7 shows her optical coherence tomography (OCT) scans. Initially, we did not treat the patient, but when she returned approximately 2 to 3 weeks later, her vision had decreased to 20/40-2 and OCT showed thickening and edema (Figure 8) so we injected the dexamethasone intravitreal implant (Ozurdex, Allergan, Inc.). Approximately 1 month later, her vision improved to 20/25-2 and we observed a reduction of the edema (Figure 9) so at that visit, we did not treat in addition to the sustained release of dexamethasone from the implant. At 2 months post-implant, her vision decreased slightly to 20/30 but OCT did not show swelling of the edema (Figure 10) so we did not treat. We injected a second dexamethasone implant at 4 months because OCT showed some re-accu-

(Text continued on page 11)
Figure 9. Case #1: The patient received the dexamethasone intravitreal implant. One month later, the edema was reduced and vision improved to 20/25-2, and no other treatment was initiated.

Figure 10. Case #1: At 2 months post-implant, her vision decreased slightly to 20/30 but OCT did not show swelling of the edema so we did not treat.

Figure 11. Case #1: We injected a second dexamethasone implant at 4 months because OCT showed some reaccumulation of edema.

Figure 12. Case #1: After the second injection, the patient’s vision was stable at 20/40-1 and there were no signs of reaccumulation of edema on OCT more than 2 months later.

Figure 13. Case #2: After being lost to follow-up, the patient in case #2 presented with 20/400 vision and significant edema.

Figure 14. Case #2: Two weeks after bevacizumab injection, edema did not improve and vision was 20/200.

Figure 15. Case #2: One month after receiving the dexamethasone intravitreal implant, the patient’s vision was still 20/200 but there was complete resolution of edema on OCT.

Figure 16. Case #2: After a 2-month period where resolution of macular edema was maintained with the dexamethasone implant, the edema began to reaccumulate and vision decreased to 20/400, so we placed focal laser.
Macular edema is a common problem in patients with uveitis, often sabotaging good vision. Optical coherence tomography (OCT) studies disclose that macular edema is far more common in these patients than previously thought, even in patients with anterior non-granulomatous uveitis. It precludes good vision even after the uveitis is apparently in remission, for reasons that include retinal pigment epithelial (RPE) dysfunction, vitreomacular traction, and epiretinal membrane (ERM) formation; however, in some cases subclinical inflammation with cytokines effects on the RPE cause macular edema. Figure 1 shows cystoid macular edema (CME) formation on fluorescein angiography (FA) and OCT. It is important to use both FA and OCT for imaging in the long-term care of patients with history of uveitis because these patients often have subclinical vision with edema that does not show on an OCT, but that is evident on FA.

**THE MERSI APPROACH FOR TREATING UVEITIS-ASSOCIATED MACULAR EDEMA**

It is crucial that the phraseology “patients with a history of uveitis” is emphasized when discussing management of macular edema because efforts to treat edema in uncontrolled uveitis are futile. Thus, the approach that I use at the Massachusetts Eye Research and Surgery Institution (MERSI) for treating patients with macular edema associated with uveitis is to first and foremost ensure that uveitis is under control. However, we continue to see many patients who are referred to our institution for uveitic macular edema who, despite having active uveitis, have received multiple injections with either corticosteroids and/or anti-vascular endothelial growth factor agents. This approach is misguided and doomed to fail.

As earlier stated, we take baseline FAs and OCTs and repeat this imaging frequently to document the progress of treatment. When we begin treatment, we have traditionally used a stepwise approach.

**Step 1.** We typically will first inject triamcinolone acetoneide regionally using a lower lid septum approach. The Nozik technique of posterior sub-Tenons injections are less patient friendly, in my opinion, and have proved no more effective in the cases that we have followed.

**Step 2.** Topical nonsteroidal anti-inflammatory drug (NSAID) therapy (off-label use) can also be useful with the selection of an NSAID that shows evidence of penetration to the back of the retina and the choroid, such as bromfenac.

**Step 3.** Additionally, the concomitant use of a systemic NSAID, preferably a COX-2 specific inhibitor, such as celecoxib, has an effect in discouraging a relapse of macular edema.

**Step 4.** For recalcitrant macular edema, systemic acetzolomide at 250 to 500 mg twice daily can be effective. Although there have been reports on the use of higher doses, the additional therapeutic benefit is insufficient in my experience.

**Step 5.** The next step that we take for patients in the presence of persistent edema after obtaining the proper patient consent regarding the complications of endophthalmitis, glaucoma, cataract, and retinal detachment, is to employ an intravitreal injection of preservative-free triamcinolone acetonide.

**Step 6.** We may choose an intravitreal anti-VEGF agent (off-label use), such as ranibizumab (Lucentis, Genentech) or bevacizumab (Avastin, Genentech), after obtaining patient consent regarding the risk of endophthalmitis with intravitreal injections.

**Step 7.** We may also choose to use a combination of both steroid and anti-VEGF injections, as this has proved effective in some patients, when single agent injections have failed.

**Step 8.** The next step is to inject 20 mg intramuscular octreotide once a month (off-label use). There are
octreotid receptors on the retinal RPE, ligation of which help improve RPE pump function.

**Step 9.** Vitrectomy with ILM peeling is appropriate in instances where OCT scanning discloses vitreomacular traction.

**Step 10.** For patients who either refuse frequent injections of steroid of anti-VEGF, or for whom relapse occurs shortly after an injection, we will inject the dexamethasone intravitreal implant.

**CASE #1**
Figure 2 shows the baseline reports for a patient with macular edema and a history of uveitis. The uveitis was put into remission with systemic immunomodulatory therapy with no use of corticosteroids. Intraocular evaluation showed no evidence of active inflammation; however, macular edema was causing visual acuity loss to 20/60 in the left eye.

The choices for treatment include (1) a topical NSAID; (2) a regional corticosteroid injection; (3) a systemic NSAID; and (4) an intravitreal anti-VEGF agent. We chose to employ a regional trans-septal steroid injection along with topical bromfenac twice daily and systemic celecoxib 200 mg twice daily. Although in the past we did not use a multimodal strategy, we found we were already using all of these approaches in a stepwise fashion, so decided to simply start with all three from the beginning.

Over the course of 1 year and long-term maintenance with celecoxib, the visual acuity improved to 20/20 and there have been no relapses of macular edema (Figure 3).

**CASE #2**
Figure 4 shows the FA and OCT scans of a patient who had significant macular edema in the right eye and visual acuity of 20/80.

The patient had been treated previously in a similar manner as Case #1, with a three-pronged approach with regional corticosteroid injection, topical NSAID, and a systemic NSAID, and the macular edema persisted.

The choices for treatment at this point included (1) acetazolamide; (2) intravitreal triamcinolone; and (3) intravitreal bevacizumab. We chose to use intravitreal bevacizumab, because the patient is phakic (steroid has increased risk of cataract). The patient responded to the intravitreal bevacizumab with resolution of the edema, (Figure 5) improvement of the visual acuity to 20/20. We maintained treatment with the topical and systemic NSAID and the patient has had no relapse of macular edema over the course of 2 years.

**CASE #3**
Figure 6 are the FAs and OCTs from a patient in whom uveitis was in remission and who was on systemic immunomodulatory therapy. The left eye had a retinal thickness greater than 600 µm even after we applied topical and systemic NSAIDs, 2 regional injections of triamcinolone, intravitreal triamcinolone, intravitreal bevacizumab, and systemic acetazolamide.

At this point, our options included (1) a vitrectomy with an ILM peel; (2) more intravitreal injections; and (3) dexamethasone intravitreal implant. We chose to inject the dexamethasone intravitreal implant for this patient.
NEW RESEARCH FOR RETINA DISEASE

Figure 4. The FA and OCT scans of a patient who had significant macular edema in the right eye and visual acuity of 20/80.

Figure 5. The patient responded to the intravitreal bevacizumab with resolution of the edema, improvement of the visual acuity to 20/20.

Figure 6. The FAs and OCTs from a patient in whom uveitis was in remission and who was on systemic immunomodulatory therapy. The left eye had a retinal thickness greater than 600 µm even after we applied topical and systemic NSAIDs, 2 regional injections of triamcinolone, intravitreal triamcinolone, intravitreal bevacizumab, and systemic acetazolamide.

and postinjection the patient achieved 20/20 vision and a reduction of macular edema (Figure 7).

DISCUSSION

We have more treatment options for noninfectious posterior uveitis than ever before with off-label use of corticosteroids and anti-VEGF agents, but the dexamethasone intravitreal implant was specifically designed to address intraocular inflammation and macular edema. The purpose of the Huron trial (A Double-Masked, Sham-Controlled, Randomized Study of Dexamethasone Intravitreal Implant for the Treatment of Uveitis) was to evaluate the safety and efficacy of 2 doses of dexamethasone intravitreal implant for the treatment of noninfectious intermediate or posterior uveitis.

The primary outcome measure in this trial was the proportion of patients with a vitreous haze score of 0 at week 8. Additional outcome measures were vitreous haze through week 26, best corrected visual acuity (BCVA),
adverse events, intraocular pressure (IOP), and biomicroscopy/ophthalmoscopy.

The results of the trial showed that a single dexamethasone intravitreal implant was significantly more effective than sham at eliminating vitreous haze. At the primary timepoint of week 8, approximately 4 times more eyes treated with the dexamethasone implant 0.7 mg had complete resolution of vitreous haze compared to sham. Treatment with the dexamethasone intravitreal implant also led to a significant improvement in BCVA by week 3 that persisted through week 26.

In regard to safety, IOP increases were relatively low in the treatment groups. Fewer than 10% of eyes that received the 0.7-mg dexamethasone implant had IOPs greater than or equal to 25 mm Hg at any scheduled visit, and at week 26, the percentage was 0. Seventeen percent of eye with the 0.7-mg dexamethasone implant and 9% of sham eyes were on IOP-lowering medications at week 26. There was no statistically significant difference in rate of cataract surgery between treatment groups and sham, but it is important to note that follow-up was only 6 months for this study.

In summary, the 0.7-mg dexamethasone intravitreal implant appears to be safe and effective for the treatment of noninfectious intermediate and posterior uveitis and its availability will help physicians deal with the under-recognized problem of uveitic macular edema.

In another case, a relatively young woman, aged 59 years, presented with a history of hypertension and diabetes and a BRVO. The patient had undergone previous injections of bevacizumab (Avastin, Genentech), followed by laser at 1 month, and triamcinolone acetonide injection 1 month after laser. After these treatments, the patient had been lost to follow-up before presenting to our office 1 year later with 20/400 vision and significant edema (Figure 13; page 7). We injected bevacizumab and 2 weeks later we saw no decrease in edema on OCT (Figure 14; page 7). We injected bevacizumab and 2 weeks later we saw no decrease in edema on OCT (Figure 14; page 7) and the patient’s visual acuity had only improved to 20/200, so we injected the dexamethasone intravitreal implant. One month later, the patient’s vision was still 20/200 but there was complete resolution of edema on OCT (Figure 15; page 7) that was maintained through 2 months (Figure 16; page 7). At this point, edema began to reaccumulate (Figure 17; page 7) and vision decreased to 20/400 so we placed focal laser. This patient should have been treated earlier, as the under-recognized problem of uveitic macular edema.

In summary, the 0.7-mg dexamethasone intravitreal implant appears to be safe and effective for the treatment of noninfectious intermediate and posterior uveitis and its availability will help physicians deal with the under-recognized problem of uveitic macular edema.

(Continued from page 7)

SUMMARY

The complexity of the inflammatory response suggests that therapies that target more than one part of the process could be of the greatest clinical benefit; therapies that target only one inflammatory mediator may not break the cycle of disease progression. Therefore, it is important to consider a variety of options for patients who present with macular edema caused by DME, RVO, or uveitis.

The vast majority of retina physicians in the world now treat age related macular degeneration (AMD), retinal vein occlusion (RVO), and diabetic macular edema (DME) with anti-vascular endothelial growth factor (anti-VEGF) agents. However, despite the fact that most of these patients respond to treatment, there is still a proportion of patients who are considered nonresponders or who become resistant to this class of medicine. How do we care for these patients and what other options are available to us? The 2 cases below illustrate such patients and offer a potential alternative.

**PATIENT #1: RECALCITRANT WET AMD**

A man aged 65 years presented with a history of retinal detachment and no light perception in his right eye and wet AMD in his left eye. We administered monthly injections of ranibizumab (Lucentis, Genentech) after which his visual acuity improved, vacillating between 20/20 and 20/50, and the retinal thickness on optical coherence tomography (OCT) improved over the course of the first 6 injections, although there was still swelling despite vision being 20/25 (Figure 1).

During months 7 through 9, we continued to inject ranibizumab monthly and we observed some drying of the edema at months 7 and 8 (Figure 2), but the swelling came back at month 9.

We continued monthly ranibizumab injections through month 12, but the patient’s vision and retinal thickness began to fluctuate more widely (Figure 3).

Would you: (1) change from ranibizumab to bevacizumab; (2) increase the dose of ranibizumab; (3) decrease the duration between injections; or (4) add intravitreal triamcinolone?

In the second 12 months, we chose to first alternate between ranibizumab and bevacizumab, but we were unable to maintain 20/20 vision or dry OCTs (Figure 4). We then began to decrease the duration between ranibizumab and bevacizumab injections, and although the vision increases with the injections,
we were still not able to maintain 20/20 vision or a dry OCT (Figure 5).

In months 27 through 33, the patient received intravitreal triamcinolone acetonide and, although he developed pseudo-endophthalmitis, his vision improved to 20/20 at month 28 and OCT shows his eye to almost dry at 304 µm (Figure 6). However, within 6 weeks his vision decreased the retina began to re-swell, despite switching back to ranibizumab only and decreasing the time between injections to every 3 weeks. The vision, however, is good, varying between 20/20 and 20/30 (Figure 7). What would you do now?

Because frequent injections seem necessary with just anti-VEGF agents, at month 37 (Figure 8), we decided to use a combination approach with injecting the dexamethasone intravitreal implant 2 weeks later. After injection with the dexamethasone implant, the cysts that were present in Figure 8 began to resolve, retinal thickness was reduced to 327 µm in spectral domain OCT and vision began to improve to 20/20 (Figure 9). The patient remained dry through month 40 (Figure 11), enjoying a drug holiday at 20/20 for 3 months.

In this case of AMD that was recalcitrant to ranibizumab in regard to mainlining visual acuity improvement and dryness on OCT, combination therapy with ranibizumab and the dexamethasone intravitreal implant worked best.

**PATIENT #2: PROLIFERATIVE DIABETIC RETINOPATHY**

A man aged 44 years presented with proliferative diabetic retinopathy and previous vitrectomy in both eyes. He had multiple fluid-air exchanges postoperatively for recurrent vitreous hemorrhages. When his vitreous hemorrhages did clear, it was revealed that he had bilateral diabetic macular edema (DME) and received monthly bevacizumab injections to control both the DME and to decrease the incidence of re-bleeding and prevent rubeosis.

We gave the patient numerous intravitreal bevacizumab injections, but even after 5 injections, retinal thickness was 886 µm and visual acuity was 20/150 (Figure 12). We then tried adding intravitreal triamcinolone acetonide to prolong the effect. However, because the patient had had vitrectomy, the injected medications had a short duration of effect. In fact, at month 16 and the 12th injection of bevacizumab, the patient’s visual acuity was 20/60 and the retinal thickness was 699 µm (Figure 13).

What would you do? Our choices included: (1) continuing bevacizumab injections; (2) administer a sub-Tenon triamcinolone injection; or (3) applying combination therapy with bevacizumab and the dexamethasone intravitreal implant. We chose combination therapy with bevacizumab and the dexamethasone intravitreal implant because in our experience, we have found that...
this approach produces an increased duration of effect in regard to normalization of OCT contour, increased vision, and decreased need for reinjections.

At month 17, the patient’s visual acuity was 20/40 and the retinal thickness was 540 µm (Figure 14) and we injected the dexamethasone intravitreal implant. After

we injected the dexamethasone implant, the patient’s OCT showed a significant improvement in retinal thickness, which thinned to 251 µm and visual acuity improved to 20/30. The reduced retinal thickness and improved visual acuity was sustained through month 20.

In this patient, in whom drug clearance was more rapid due to previous vitrectomy, a significant benefit was obtained by using combination therapy with an anti-VEGF agent and a sustained drug delivery system.

**SUMMARY**

Macular edema due to AMD, RVO, and DME is due to a cascade of many factors, 2 of which are ischemia and inflammation. By using combination therapy in selected cases, the physician is able to attack the disease with a “one-two punch” and create a drug holiday by minimizing retinal edema and maximizing visual potential.
1. The underlying etiology of macular edema is
__________.
   a. abnormal capillary permeability
   b. unknown
   c. breakdown of the blood-retinal barrier
   d. A and C
   e. none of the above

2. Leukocytes secrete a variety of inflammatory mediators, including:
   a. interleukin (IL-1)
   b. tumor necrosis factor (TNF)-alpha
   c. vascular endothelial growth factor (VEGF)
   d. all of the above
   e. B and C

3. Müller cell processes are the principal extracellular matrix tissue of the retina and where most of the fluid begins to form.
   a. true
   b. false

4. Inflammatory causes of edema include:
   a. an increase of neutrophils in the choroid
   b. increased polymorphonuclear leukocytes in the choriocapillaries associated with loss of endothelial cells
   c. leukocyte aggregation, and capillary drop-out
   d. elevated CD-4 and CD-6T
   e. all of the above
   f. only A and C

5. Proinflammatory markers that are activated in uveitis include the following:
   a. VEGF
   b. interleukin
   c. tumor necrosis factor
   d. all of the above
   e. none of the above

6. Once uveitis is in remission, macular edema no longer is a factor in vision loss in most patients.
   a. true
   b. false
New Research for Retina Disease

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