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ANTI-VEGF THERAPY FOR DIABETIC MACULAR EDEMA

A roundtable discussion with David S. Boyer, MD; David Eichenbaum, MD; and Victor Gonzalez, MD

Case reports by Franck Fajnkuchen, MD; Neil M. Bressler, MD; and David Eichenbaum, MD

ANTI-VEGF THERAPY FOR DIABETIC MACULAR EDEMA

Clinical data for anti-VEGF agents for treating diabetic macular edema.

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LEVEL 1 DATA ON RANIBIZUMAB FOR DIABETIC MACULAR EDEMA

David S. Boyer, MD: The most exciting paradigm shift that we have experienced in the treatment of diabetic retinopathy has been the advent of the anti-VEGF therapy ranibizumab (Lucentis, Novartis) for diabetic macular edema (DME). Dr. Eichenbaum, can you discuss the significance of the RISE and RIDE trial, and how you use these data to treat your patients?

David Eichenbaum, MD: The most significant effect that the RISE and RIDE data have had on my practice patterns is similar to what occurred when anti-VEGF was available for the treatment of age-related macular degeneration (AMD) and retinal vein occlusion (RVO). I can now tell my patients with center-involving DME that there is a treatment that has a good chance of substantially improving their vision versus what was possible with laser photocoagulation.

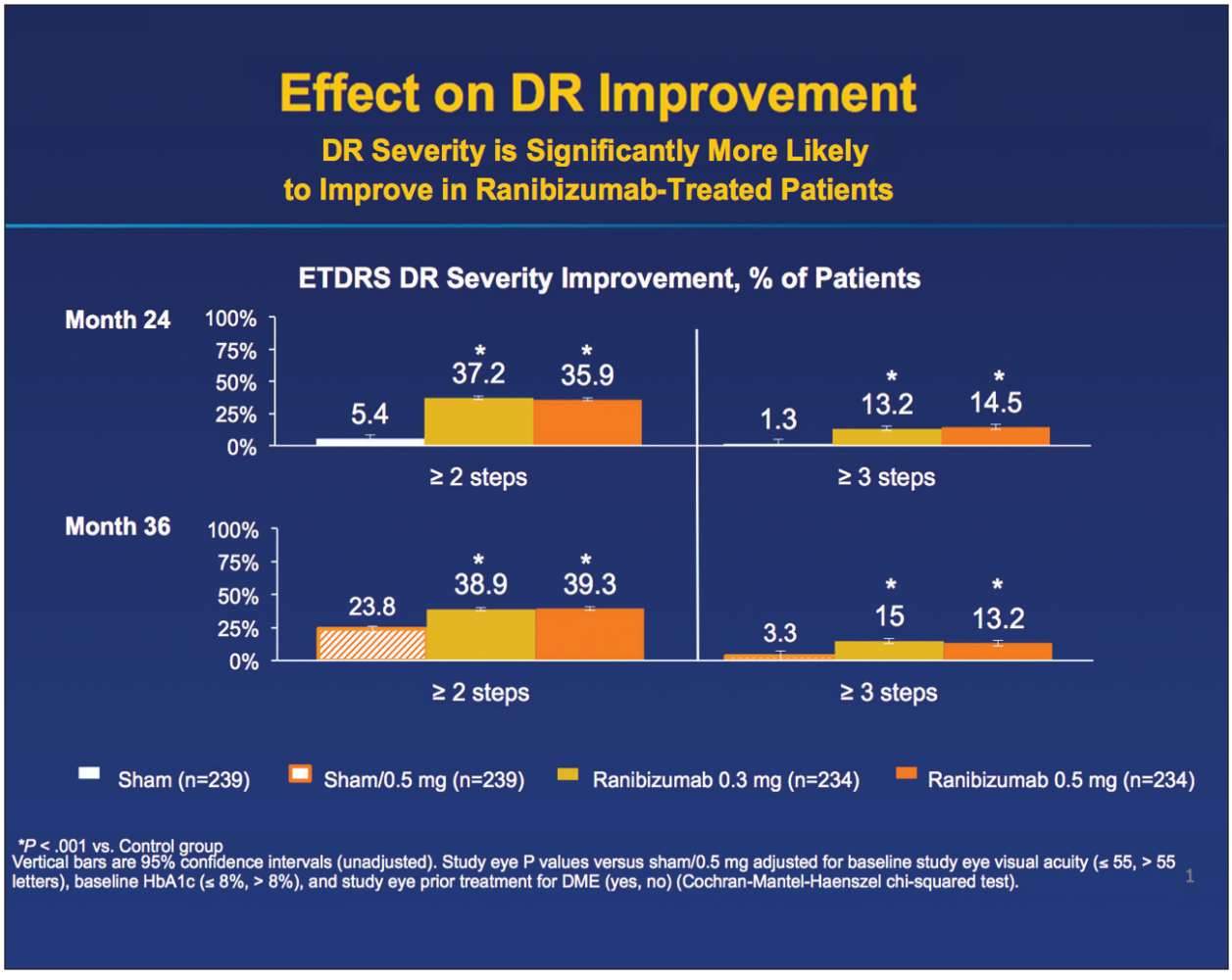

Figure 1. The severity of DME was significantly improved in patients treated with ranibizumab in the RISE and RIDE trials.

Dr. Boyer: Dr. Gonzalez, after reviewing how ranibizumab performed in the RIDE/RISE trials compared with the laser, how does laser fit into your treatment regimens?

Victor Gonzalez, MD: By no means have I stopped using laser for DME. We need to be clear that the data from RISE and RIDE showed us what we could do with edema that involved the central macula.[1] Based on these favorable data for ranibizumab, this anti-VEGF agent is my first-line treatment for center-involving DME.

If I have a patient, however, who presents with localized edema that meets the ETDRS criteria,[2] I will still use focal laser. Additionally, regarding new data on subthreshold laser treatment, until more evidence is available, I will still use standard application for these patients.

Dr. Eichenbaum: I agree. Ranibizumab is my first choice of treatment for center-involving DME. I offer injection therapy first, and then I talk to my patients regarding the addition of laser.

I agree with Dr. Gonzalez that laser is still relevant as first-line treatment for non-center involving edema.

Dr. Boyer: It is also important to point out is that in the RIDE and RISE trials, laser was applied to the anti-VEGF treatment groups in approximately 25% of cases, suggesting that we will still use laser in some of these patients in addition to anti-VEGF. The visual acuity data, however, in the ETDRS study with laser showed that approximately 15% of patients gained 3 lines with laser, and in RISE and RIDE, approximately 40% of patients gained 3 lines with anti-VEGF (Figure 1).

ANTI-VEGF THERAPY VS LASER

Dr. Boyer: There are data from other randomized clinical trials, such as the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I[3] and RESTORE,[4] that show a benefit with ranibizumab. Dr. Gonzalez, how do you interpret these data and how does this information change how you treat your patients?

Dr. Gonzalez: The DRCR.net Protocol I was one of the first studies that truly demonstrated that there was a difference between visual acuity gains with anti-VEGF vs laser. In the active treatment arms, patients were randomized to 1 of 4 treatment groups: sham injection plus prompt laser, 0.5 mg ranibizumab plus prompt laser, 0.5 mg plus deferred laser (deferred by 6 months), and triamcinolone acetonide injection plus prompt laser. The results showed that it did not matter whether laser was prompt or deferred; ranibizumab appeared to provide a significant benefit to patients with center-involving macular edema.[3] This was the first large randomized, controlled study showing that anti-VEGF injection is superior to laser for this indication, but the RESTORE trial was the first to demonstrate the superiority of ranibizumab injection as monotherapy. Patients were randomized either to ranibizumab, laser, or a combination. The results of this study showed that monotherapy with ranibizumab was as good, if not better, than a combination of laser and ranibizumab.[4]

Dr. Eichenbaum: The DRCR.net Protocol I was a well-designed trial, but the protocol is impossible to duplicate in clinical practice. However, there are still some important takeaways. The first is that there is a reduction in treatment burden with injections over time. Data through year 3 shows that, after 2 years of treatment, only 2 to 4 injections out of a possible 13 were required for the ranibizumab plus prompt or deferred laser group.

This is wonderful news for our patients with DME because these patients often have comorbidities, such as kidney disease and nerve disorders, and they are already seeing several specialists. If they can visit the retina specialist less and receive fewer injections to maintain or improve their vision, this is a significant benefit.

The second takeaway from the 3-year data is that there was a slight divergence between prompt and deferred laser, with visual acuity being better for the ranibizumab plus deferred laser treatment. I am curious as to what the 4- and 5-year data will show, but it seems that we can delay laser and use ranibizumab injections as monotherapy. As Dr. Gonzalez notes, injection monotherapy is also supported by data from RESTORE.

Dr. Boyer: If we are going to treat the patient with laser, it is easier and safer when the retina is thinner and we can use less power, inducing less damage to the tissue. All of these studies are indicating superiority of anti-VEGF agents, but as Dr. Gonzalez indicated, we will still laser significant lesions outside the foveal area.

EVIDENCE FOR BEVACIZUMAB FOR TREATING DIABETIC MACULAR EDEMA

Dr. Boyer: In real-world practice, anti-VEGF therapies have begun to be the primary treatment of choice for DME. Many clinicians are using bevacizumab (Avastin, Roche). With regard to off-label use, what information has the BOLT trial provided?

Dr. Eichenbaum: The BOLT trial showed good results for bevacizumab. It was not a head-to-head trial with ranibizumab, but the data show that bevacizumab is a reasonable choice for DME.[5]

Dr. Gonzalez: Although I agree that we need more evidence, it appears that bevacizumab has a beneficial effect for DME when compared with laser.

Dr. Boyer: An important consideration when discussing the BOLT study is that it was a small study, with only 80 patients.

LEVEL 1 DATA ON AFLIBERCEPT FOR DIABETIC MACULAR EDEMA

Dr. Boyer: Regarding aflibercept (Eylea, Bayer HealthCare) for DME, we have had the results of the DA VINCI phase 2 trial for some time, but the results of the VIVID-DME and VISTA-DME phase 3 trials were recently presented. Dr. Gonzalez, what are your opinions of these results?

Dr. Gonzalez: I like that we have seen consistency with the effect of anti-VEGFs on patients with DME. It has been reassuring that, regardless of which anti-VEGF agents, they appear to be superior to laser. The DA VINCI, VIVID, and VISTA trials have demonstrated significant benefits for patients, not only in letters gained, but in the percentage of the patients who gained 3 lines or more.[6,7]

Dr. Eichenbaum: An interesting takeaway from VIVID and VISTA in my opinion is that all of the dosing protocols for aflibercept seem to have a beneficial effect. The more frequent dosing appeared be slightly more beneficial, but similar to the VIEW studies, the results were good in the every-8-week dosing arm, which speaks to the efficacy of aflibercept. Again, we do not know if aflibercept is superior, inferior, or equivalent to ranibizumab or bevacizumab.

Dr. Gonzalez: These studies showed us that there was an improvement in the ETDRS severity gradient with the use of aflibercept, which provide evidence to support that the anti-VEGF agents may modify the long-term outlook for our patients with DME, hopefully resulting in fewer injections once we have controlled the disease.

VEGF LEVELS IN DIABETIC MACULAR EDEMA

Dr. Boyer: So I think it is safe from the comments here that all the anti-VEGF drugs are effective for treating DME. What are the safety concerns in patients with vasculopathy? How do the VEGF levels in our patients who are diabetic differ than those patients with AMD?

Dr. Eichenbaum: The vitreous levels of VEGF are higher in DME, more similar to those in diffuse retinal vascular disease such central retinal vein occlusion (CRVO).[8] The VEGF in AMD is most likely more subretinal and lower in volume than in DME.[9-11] It is a very different disease state than AMD from a VEGF volume perspective.

Dr. Boyer: Although we have no direct information regarding systemic VEGF levels in patients with diabetes, we do have some surrogate information from the IVAN study,[12] and Robert L. Avery, MD, has presented data on the effect of bevacizumab, ranibizumab, and aflibercept on the serum and plasma levels of VEGF in patients with AMD and RVO.[13]

How do you interpret these data? Is this something that should illicit concern for our patients with diabetes?

Dr. Gonzalez: Unfortunately most of our trials are not powered to detect that level of the incidence and frequency of adverse events in particular groups of patient. In order to do this, we would need trials of tens of thousands of patients.

Dr. Gonzalez: Clinically, I do not see a problem with anti-VEGF agents for my patients because I use them on a daily basis, but the potential is there. Theoretically, patients with diabetes have a blood-retinal barrier that is not completely intact. If our patients with AMD have significant systemic levels of anti-VEGF suppression, then, again theoretically, our patients with diabetes should have just as high levels, if not higher. Dr. Avery demonstrated in his study that when 1 eye was injected, there was regression of proliferative in the contralateral eye, which may speak volumes about just how much anti-VEGF agents circulate.[13]

Although we still do not have clear figures in terms of what these percentages truly are, we need to be concerned. There are a few things that we need to keep in mind: We must ensure that we identify individuals who are at high risk, which include patients who are older than 85 years of age; those with a recent history of arterial embolic events; and those who have other cardiovascular conditions.

Dr. Boyer: Dr. Avery's study is important in that it demonstrates that systemic VEGF suppression does vary depending on the anti-VEGF agent. His study showed that bevacizumab results in complete suppression below the LD50 levels in the serum, which could potentially create an effect over a long period of time. There was also a significant decrease in systemic VEGF with aflibercept, although not as prolonged as with bevacizumab. Ranibizumab resulted in the least amount of systemic VEGF suppression; however, it has yet to be determined how this information translates to safety.

BINDING ABILITIES OF ANTI-VEGF AGENTS

Dr. Boyer: How do the binding affinities of the various drugs that are available today affect the results that we can achieve with anti-VEGF agents. Further, how does the binding of an anti-VEGF agent affect systemic levels of VEGF?

Dr. Eichenbaum: Basic science studies have shown that there are differences in binding affinities between ranibizumab, bevacizumab, and aflibercept, but what we

Treat and Extend vs Monthly Dosing Investigator-Sponsored Trial

DAVID EICHENBAUM, MD

Case No. 1: Late responder. Figures 1-6 show the right eye (OD) of a patient of Hispanic descent who had been treated previously with focal laser and bevacizumab. After 1 year of monthly injections with ranibizumab, the edema resolved and the patient responded to once-every-8-week injections in the extension period, guided by OCT.

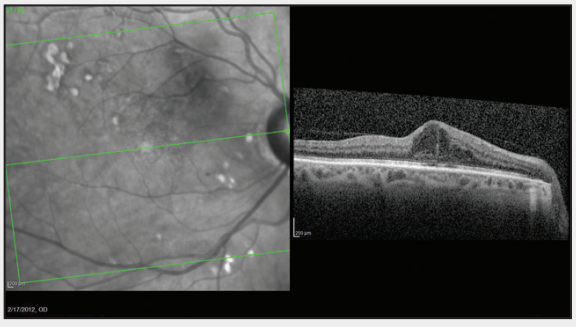

Figure 1. Right eye at study entry (2/17/12); visual acuity: 20/63.

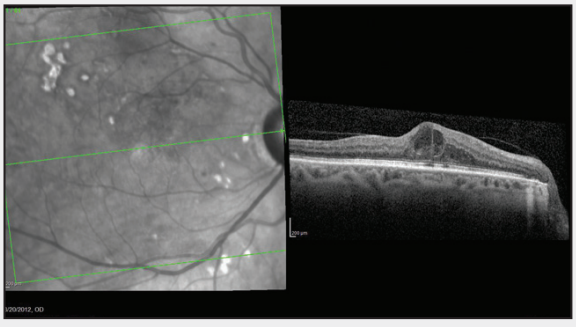

Figure 2. Right eye after 1 injection has no change (3/20/12); visual acuity: 20/63+2.

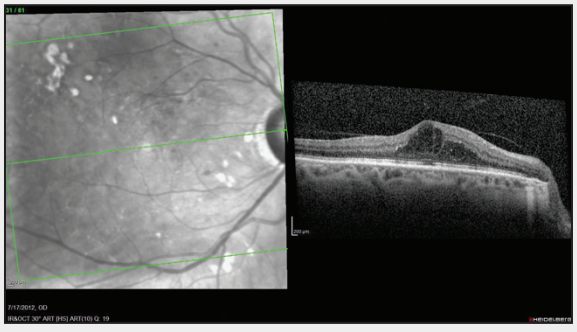

Figure 3. Right eye improves after monthly injections at 5 months (7/17/12); visual acuity: 20/50+2.

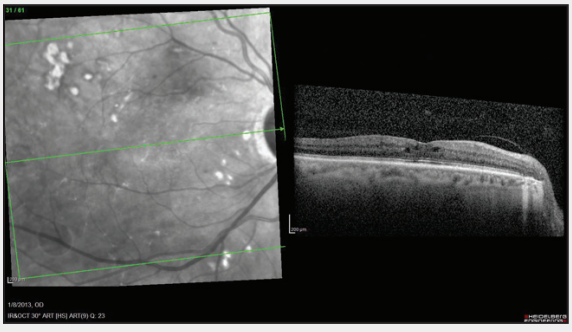

Figure 4. Right eye remains stable after monthly injections over the first year (1/08/13); visual acuity: 20/50-1.

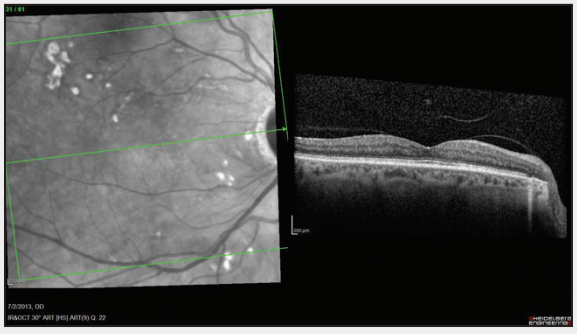

Figure 5. Right eye remains stable in second year with once-every-8 weeks injections (7/02/13); visual acuity: 20/50+2.

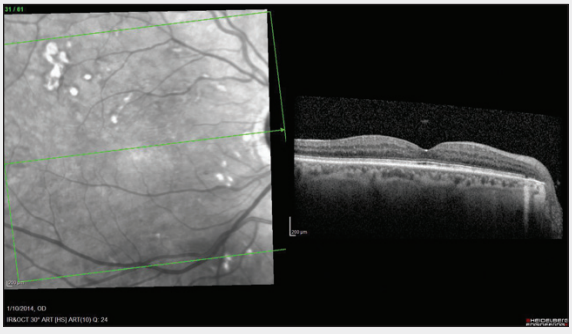

Figure 6. Right eye remains stable in second year with once-every-8 weeks injections (1/10/14); visual acuity: 20/40-2.

Case No. 2: The yo-yo effect. This patient, a 56-year-old white woman who had previously been treated with focal laser and bevacizumab injections in her left eye (Figures 7-11), represents a good example of one who rapidly responds to anti-VEGF treatment but rebounds upon a gentle extension. The visual acuity and anatomy worsen when the time between injections is extended, but this yo-yo effect is reduced over time and with more injections. There is a clear trend in visual improvement, even with the fluctuations on OCT with variable, less-than-monthly dosing.

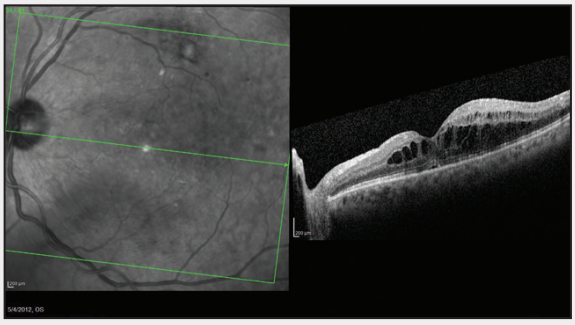

Figure 7. Left eye at study entry (5/04/12); 20/80-2

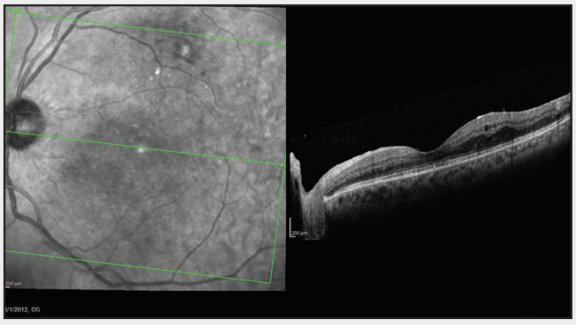

Figure 8. Left eye after 1 injection (6/01/12); visual acuity: 20/50+2.

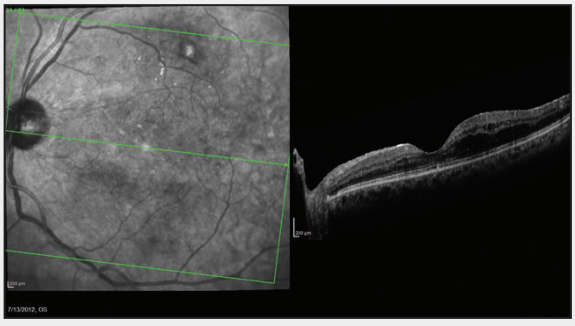

Figure 9. Left eye after extension (7/13/12); visual acuity: 20/50+2.

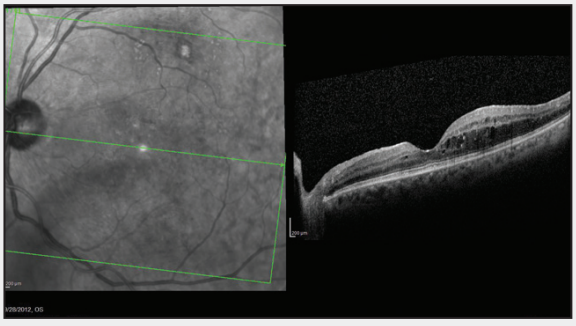

Figure 10. Left eye worsens and the patient receives another injection (9/28/12); visual acuity: 20/32+2.

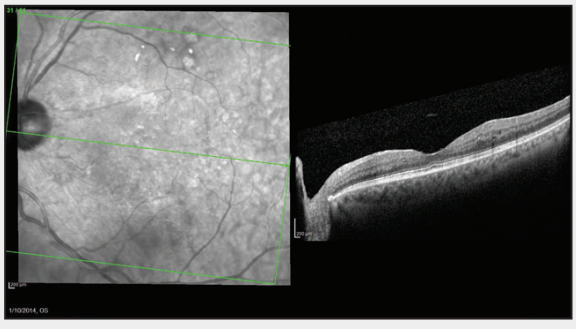

Figure 11. Left eye is dry and the patient is receiving fewer injections (1/10/14); visual acuity: 20/32+2.

do not know is whether there is a significant difference in their effects locally or systemically. It is likely, based on the research from Avery et al,[13] that the FC portion in these anti-VEGF agents affects the duration of systemic presence without changing the local mechanism in the eye. Additionally, different types of molecules may have varying inflammatory roles in the eye due to the presence and absence of longer chain antibody or fusion protein elements.

All of these agents appear to be relatively safe and effective, but there are data pending that may help us to determine whether there is a long-term safety concern with those agents that appear to linger longer systemically.

Dr. Gonzalez: The totality of the data with all 3 anti-VEGF agents, regardless of their binding ability, suggest that they have similar results in terms of resolution of the edema and visual gains.

In regard to safety, it is hard to comment at this point. The binding ability may be different between the drugs, but it does not appear to have a significant effect on efficacy and systemic safety.

Dr. Boyer: It is important to note that drugs with an FC portion may be more likely to trigger an immunologic inflammatory response. Therefore, it would make sense that cases of anti-VEGF induced uveitis would be more prevalent with aflibercept and bevacizumab than ranibizumab.

The other important point involves FC recycling, which keeps drugs that have an FC portion in the body longer to maintain the immunologic effect. We do not yet know if this has a detrimental effect.

INFLAMMATION AND THE ROLE OF STEROIDS FOR DIABETIC MACULAR EDEMA

Dr. Boyer: Where do steroids fit into the treatment arena for DME?

Dr. Gonzalez: A large number of my patients have diabetes and constitute approximately 80% of my practice. Prior to the availability of anti-VEGF agents, I used steroids frequently for these patients and have amassed a lot of experience with benefits and risks associated with their use.

We all know that DME is a multifactorial disease—it is not purely VEGF driven. In DME, I have found that many patients have disease that is either primarily driven by inflammation or VEGF. Other patients are somewhere in between, which is what makes treating them difficult.

I am currently using anti-VEGF agents as my first line of therapy for DME. The recent data that have been presented showing the beneficial effect of the dexamethasone intravitreal implant (Ozurdex, Allergan) for DME did not surprise me.[14] I believe there are important inflammatory cytokines and chemokines, such as interleukin-6 and interleukin-8, that are not affected by anti-VEGF agents but that have a susceptibility to steroids.

I routinely give my patients at least 3 to 4 anti-VEGF injections, and if I do not see an important change in terms of vision and macular thickness, I will immediately add a steroid. Unfortunately, there is no sustainable steroid release device yet available, but if I had the choice, I would use the dexamethasone implant rather than a bolus steroid injection because the data have shown that the intraocular pressure (IOP) rises with this steroid and sustained delivery are not as high. The concerns that we have had in the past with IOP have been mainly with triamcinolone acetonide 4 mg. For example, the SCORE-CRVO trial demonstrated that this dose of steroid was associated with more side effects, particularly high IOP.[15]

Dr Eichenbaum: I agree that steroids are a complementary therapy for DME. Based on the results of the DRCR.net Protocol I, I tend to withhold triamcinolone acetonide when a patient is phakic because of the high incidence of cataract that was shown.[16] The rate of cataract was lower in the dexamethasone data.

I also use anti-VEGF agents as my first line of therapy for DME. If I do not see a response after 3 to 6 injections (pushing more toward 6 injections based on the Protocol I data), I believe it is time to consider another approach. As I noted before I will not use steroids in a patients who are phakic; rather, I will most likely use laser for anti-VEGF nonresponders. In patients who are pseudophakic, I will most likely use triamcinolone acetonide injection, because the vast majority of IOP increases, which, although significant with this drug, can be controlled topically.

Dr. Boyer: My threshold for nonresponse to anti-VEGF agents is lower. I introduce steroids more quickly—after 3 to 4 injections—if there is no response from the patient to anti-VEGF. If, after I have used a steroid, the edema recurs, I will inject the anti-VEGF agent again. The combination of anti-VEGF and steroid appears to work well to control the disease in patients with severe diabetes.

In the DRCR.net Protocol B, which compared triamcinolone acetonide and focal/grid laser photocoagulation for DME, the group of patients who had the best results with steroids had the worst vision and a significant amount of macular edema.[16] Harry W. Flynn Jr., MD, has also demonstrated that patients with large amounts of edema respond well to steroids, after which the response can be maintained with anti-VEGF agents (oral communication, 2013). We would benefit from a steroid delivery, such as a sustained release implant, that is safer than what we currently have available for DME.

Dr. Eichenbaum: Does the patient's lens status change your approach when considering steroids?

Dr. Boyer: If I have a patient who is say, 30 years old and phakic with DME, I will most likely choose the dexamethasone implant when it is available. All steroids are not equal. If you consider what we know about the gene upregulation between fluocinolone, triamcinolone, and dexamethasone in the trabecular meshwork, the upregulation of different genes is unique to each of these steroids.[17]

COUNSELING PATIENTS WITH DIABETIC MACULAR EDEMA

Dr. Boyer: If a patient is 45 years old, diabetic, hypertensive, and overweight, and he or she reports a recent transient ischemic attack (TIA), do these facts alter your course of action for treatment?

Dr. Eichenbaum: I think that if a patient is symptomatic, has symmetric DME, and is taking an anticoagulant to protect against another TIA, it is reasonable and safe to offer them treatment. If, however, a patient presents for treatment and they have had a TIA and no systemic medical evaluation by a primary care doctor and/or neurologist, I would advise him or her to do so and return in 1 month.

Dr. Boyer: Dr. Gonzalez, what is the ophthalmologist's role in counseling patients with diabetes in regard to dietary habits, smoking, and blood pressure control and how it relates to their vision?

Dr. Gonzalez: The ophthalmologist plays an important role in education for patients with diabetes. It is critical that we treat the whole patient, not just the eye because the systemic status will affect the macular edema. Out-of-control hypertension, renal failure, and fluid retention all have an effect. For instance, it is not surprising that when a patient's ankles are 3 times normal in size that the macular edema will also be increased.

The first thing I ask my patients with diabetes is the status of their hemoglobin A1c. Although my newer patients do not know this figure at first, after I ask them at every visit they begin to understand why this is important and to have the information ready. Reinforcement is important.

The DRCR.net's Protocol M, in which our practice is participating, is currently under way. This study is designed to evaluate the effect of patient education by the retina specialist on glycemic control, but I have been using a similar approach to that of the study protocol for many years. When we only had laser and steroids available to us for DME, it was frustrating to try to control the edema only to have the patient come back worse at follow-up. It was not necessarily that these therapies were not effective, but the systemic condition was damaging the blood vessels.

Dr. Eichenbaum: I have a similar approach. I ask about hemoglobin A1c levels—I would estimate that one-quarter of my patients know this on their first visit. I stress to patients that all I can do for them once their diabetes has progressed to the point where it is affecting their eyes is to buy them time. I am pretty blunt about the probability of severe vision loss from ischemia and proliferation. If a patient is presenting with hemoglobin A1c levels of 10% or higher, he or she will do poorly over the long term regardless of how aggressive with treatment I am. Anti-VEGF agents offer the best opportunity to buy this time, but patients have to get their systemic health under control. I tell patients that their diabetes is like a freight train—they have to put on the breaks before they run out of track, and the disease has momentum so the patient will likely worsen for a while even after glycemic optimization. The analogy seems to work and the patients understand that good systemic control is required to slow further damage from occurring to their eyes.

Many of my patients take my counseling to heart and I have remarkable successes in young patients with type 1 diabetes. Patients who have had a vitreous hemorrhage or have lost a toe or part of a foot to diabetes are more likely to change their lifestyles to control their sugars.

The Diabetes Control and Complications Trial (DCCT)[18] and the UK Prospective Diabetes Study (UKPDS)[19] showed that with good control of blood glucose levels, patients can lower the incidences of diabetes-associated complications including retinopathy. Although the tight control that was used in the DCCT and the UKPDS is impossible to replicate, as patients in these trials were checking their blood sugar up to 6 times a day, the use of insulin pumps and modern biphasic insulin units can help simulate that type of tight control. It is important for patients to be engaged in their systemic health.

Dr. Boyer: It is important to consider that it took approximately 26 months of tight control in the DCCT to achieve improvements and that the situation may get worse before it gets better. Patients have to understand that this is not a sprint but, rather, a marathon—it will take time to realize the benefits of controlling their glucose levels to stave off all these complications.

If a 35-year-old patient presents with 20/25 visual acuity and OCT showing a cyst adjacent to the fovea, what would be your approach? A previous examination by an eye care professional found the patient to have 20/20 best corrected visual acuity in both eyes, and the patient would most likely not have noticed any vision loss without examination.

Dr. Eichenbaum: For a young patient with asymptomatic mild visual acuity loss, I discuss treatment but with the caveat that observation is also an option, which is what I would prefer to do, following up 1 to 3 months later.

Dr. Gonzalez: I would also observe this patient, offering treatment if there is progression on follow-up. I prefer to not commit a patient with mild visual acuity loss, minimal retinopathy, and a small cyst to treatment.

I have had success using topical nonsteroidal anti-inflammatory drugs (NSAIDs) for some of my patients. Although there are large, randomized, controlled studies evaluating NSAIDs for macular edema, there are small studies suggesting that these agents may have some efficacy.[20,21]

Younger patients with diabetes are more likely to have a sense of indestructibility, so I also inquire as to whether they have been checking regularly with their general physician or diabetologist and keeping their blood glucose and blood pressure levels under control.

Dr. Eichenbaum: I agree. It is reasonable to assume that a patient with edema and retinopathy is not being compliant systemically, so I will watch this patient more closely than my patients who have less severe ocular and systemic disease.

Dr. Boyer: This is an important point and underlines that we need to communicate with our patients' internist or diabetologist to make sure that they realize that these patients are having complications from diabetes, which may warrant tighter systemic control.

Patient education is particularly important for those with diabetes. I make a point to sit patients down at the fundus camera and show them what their images look like compared to normal eyes. Often this information provides a wake-up call for patients. I tell patients that the eye is a window to the blood vessels, the heart, and kidneys, and that what is happening in the back of the eye is a signal that damage is also occurring in other areas of the body. Patients must be onboard with the treatment plan and education is critical in convincing them to take better care of their systemic health.

Dr. Eichenbaum: Retina images are a powerful educational tool, particularly when explaining to patients with diabetes what is going on with their eyes. In my opinion, if you can show a patient ischemia on an angiogram and compare it to a normal angiogram, this hits home in a striking fashion.

THE FUTURE OF TREATMENT FOR DIABETIC MACULAR EDEMA

Dr. Gonzalez: The availability of new drugs to treat DME has turned the tide on how we treat this disease. I think we've basically summarized, as you pointed out, the paradigm shift that these new drugs have given us. Just 15 years ago we were helping patients in terms of our treatments but we weren't really looking at the total picture. Yes, laser was a great treatment and we're thankful that it was there because it did prevent a lot of blindness. But on the other hand, it also contributed to some of the deficits that some of these patients have. You know, you could have a patient with 20/20 vision and a visual field of 20 degrees and to me that's still, you know, disabling.

Dr. Eichenbaum: I agree that this has been an exciting time in retina, and I believe that the available treatments allow us to treat our patients with greater success than ever before.

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Reducing Injection Frequency Over The Course of Treatment

FRANCK FAJNKUCHEN, MD

CASE NO. 1

A 57-year-old man with type 2 Diabetes Mellitus since 5 years and arterial hypertension was referred for evaluation of diabetic macular edema (DME) in his right eye. He had previously been treated for DME by macular photocoagulation in another center. At baseline, BCVA was 20/100 (49 letters on ETDRS scale) in the right eye and 20/50 (65 letters) in the left eye.

Fundus examination, performed at baseline, revealed macular edema, hemorrhages and hard exudates (Figure 1). Retinography in blue light exhibited retinal cysts (Figure 2). Fluorescein angiography (FA) demonstrated widespread leakage and showed enlargement of the fovea avascular zone related to diabetic macular ischemia (Figure 3). Optical coherence tomography (OCT) confirmed the presence of central macular edema with subretinal fluid. The central retinal thickness (CRT) was 833 µm (Figure 4).

The decision was made to treat DME with an intravitreal injection of ranibizumab (Lucentis, Novartis) for 2 reasons: (1) DME involved the center of the macula, and (2) the recent decrease in BCVA decrease. Due to the presence of a macular ischemia, cautions were taken and it was decided to perform a FA after the third intravitreal injection of ranibizumab.

A month after the first injection, BCVA increased to 20/40 (+20 letters). On OCT, CRT decreased to 457 µm (Figure 5). It was decided to continue injections with 2 consecutive monthly injections. One month after the third injection, BCVA was stable (20/40) and the CRT decreased to 338 µm (Figure 6). FA revealed no worsening of diabetic macular ischemia (Figure 7).

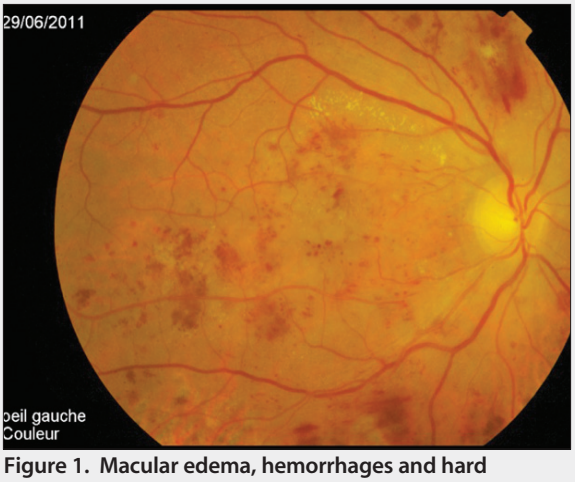


Figure 1. Macular edema, hemorrhages and hard exudates in the right eye. BCVA was 20/100.

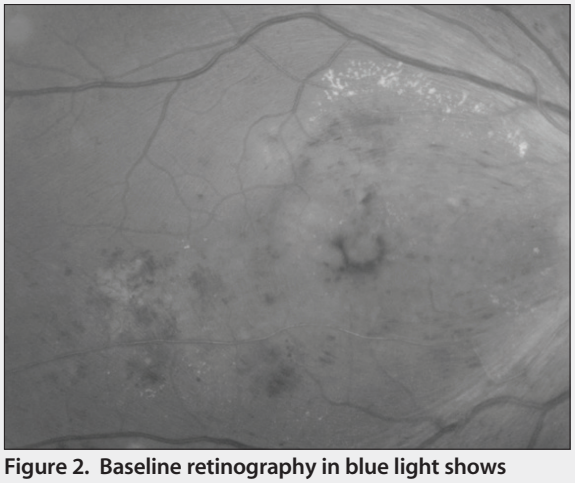


Figure 2. Baseline retinography in blue light shows intraretinal cysts.

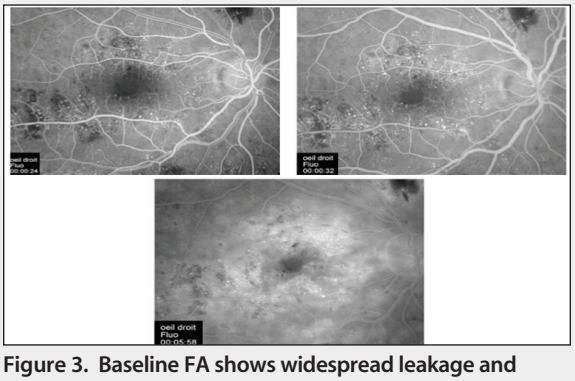


Figure 3. Baseline FA shows widespread leakage and enlargement of the foveal avascular zone.

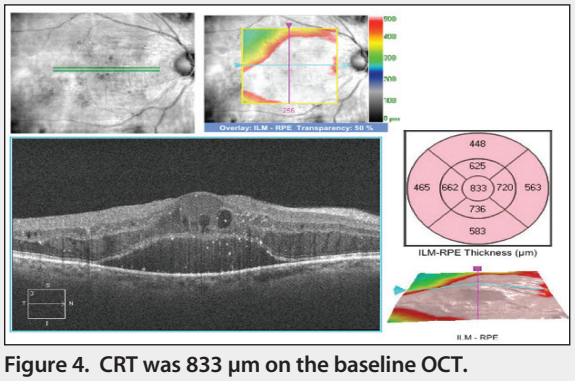


Figure 4. CRT was 833 µm on the baseline OCT.

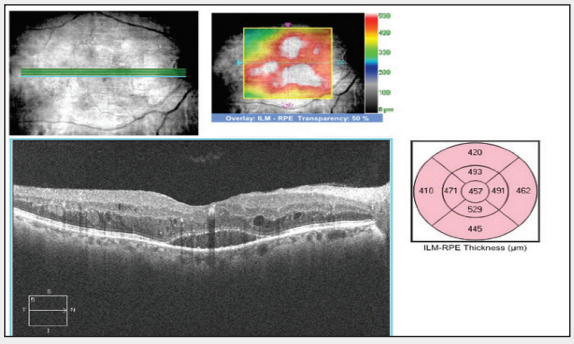


Figure 5. After 1 injection, CRT decreased to 457µm and BCVA improved to 20/40.

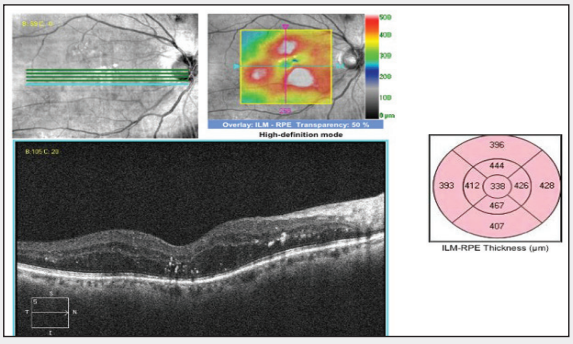


Figure 6. Following the third injection, CRT was 338 µm and BCVA was 20/40.

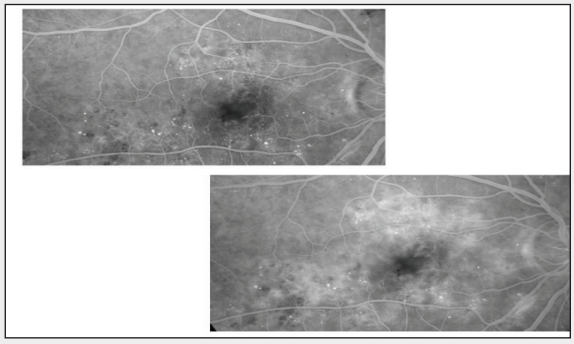


Figure 7. One month after the third injection, FA revealed no worsening of diabetic macular ischemia.

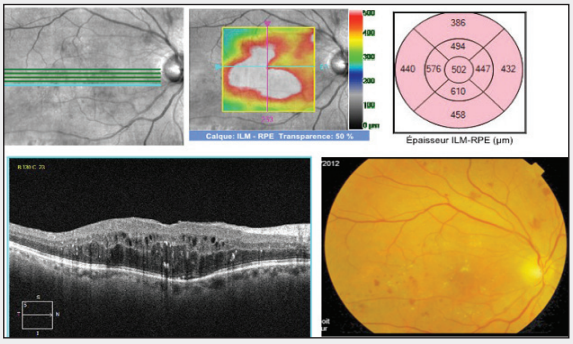


Figure 8. There was a recurrence of DME at month 8, however, BCVA was stable at 20/40.

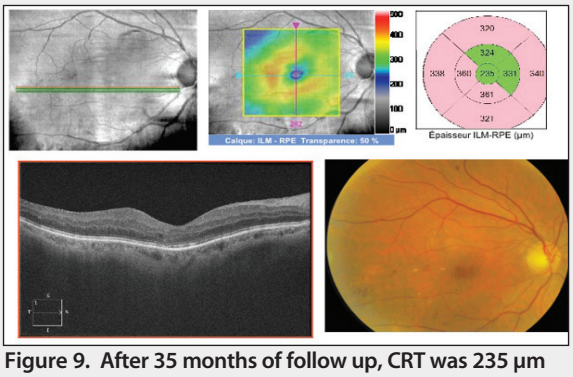


Figure 9. After 35 months of follow up, CRT was 235 µm and BCVA had improved to 20/20.

During the first 6 months of treatment, the patient received 5 intravitreal injections of ranibizumab, after which BVCA was stable and the CRT decreased to 287 µm. At month 8, there was a recurrence of DME, but there was no change in BCVA. CRT was 532 µm (Figure 8). Three intravitreal injections were performed; 1 month after the eighth injection, BCVA increased to 20/25 (79 letters) and CRT decreased to 240 µm.

Over the third year, no injection was performed. At last examination (month 35) BCVA increased to 20/20 (84 letters (+35 letters of visual gain versus baseline)), CRT was 235 µm (Figure 9).

CASE NO. 2

A 60-year-old man with type 2 diabetes mellitus diagnosed at age 15 and arterial hypertension was referred for an evaluation of DME in the left eye. There was no history of a previous laser treatment of DME.

At baseline, the BCVA was 20/50 (66 letters on ETDRS scale) in the left eye and 20/25 (81 letters ETDRS) in the right eye. A fundus examination performed at baseline revealed macular edema, hemorrhages, and hard exudates (Figure 10). FA confirmed the presence of microaneurysms located close to the fovea, demonstrated a leakage, and showed an enlargement of the foveal avascular zone related to diabetic macular ischemia. OCT confirmed the presence of the central macular edema (Figure 11). The CRT was 429 µm, with one large central cyst (Figure 12).

The patient was treated with intravitreal injections of ranibizumab for three reasons: (1) the DME involved the center of the macula; (2) there was a decrease of BCVA; and (3) there were microaneurysms too close to the fovea to be photocoagulated.

One month after the first injection, BCVA remained unchanged and there was a mild reduction of DME

on OCT. The CRT stayed unchanged (428 µm; Figure 13). The decision was taken to continue injections in order to complete a 3 injection loading phase.

One month after the third injection, BCVA was stable but the CRT decreased to 394 µm (Figure 14). During the first 6 months, the patient received 5 intravitreal injections of ranibizumab, then 3 injections during following 6 months. One year after the treatment initiation, visual acuity increased to 72 letters (+6 letters visual gain) and the CRT was 354 µm (Figure 15). A FA revealed no worsening of diabetic macular ischemia (Figure 16).

Over the second year, the patient received 3 injections. At month 18, a foveal depression was detected (Figure 17). Over the third year, no injections were performed. At last examination (month 39), BCVA

Figure 10. Macular edema, hemorrhages, and hard exudates in the left eye. BCVA was 20/50.

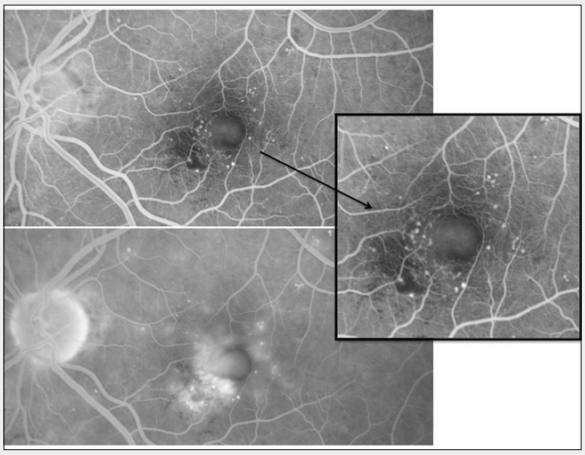


Figure 11. Baseline FA showed a leakage, enlargement of the foveal avascular zone, and microaneurysms located close to the fovea.

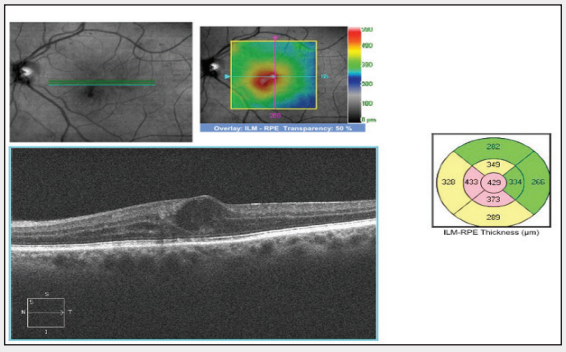


Figure 12. CRT was 429 µm on the baseline OCT.

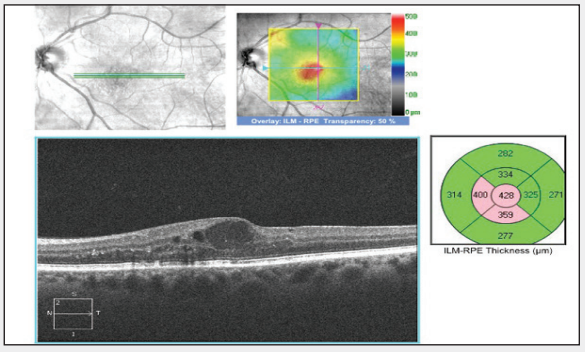


Figure 13. After 1 injection, CRT remained stable.

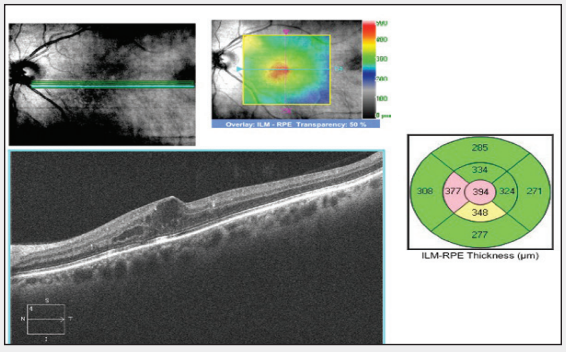


Figure 14. Following the third injection, CRT decreased to 394 µm and BCVA was 20/50.

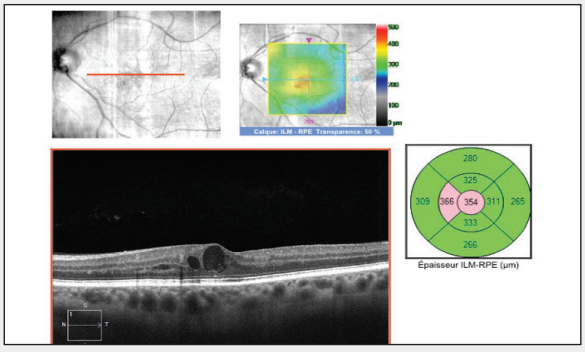


Figure 15. At 1 year, visual acuity increased to 72 letters and CRT was 354 µm.

Figure 16. At 1 year, FA revealed no worsening of diabetic macular ischemia.

increased to 20/25 (80 letters; +14 letters of visual gain versus baseline level) and CRT was 296 µm (Figure 18).

DISCUSSION

Those 2 cases illustrate that an intensive treatment regimen is needed in the beginning (a loading phase) and then the frequency of injection can be decreased. It might take time to achieve anatomical and functional improvements. A rapid visual acuity gain is frequently observed after the first injections followed by progressive gains thereafter over time. The maximum visual acuity level was reached at month 35 in the first case and at month 39 in the second, despite

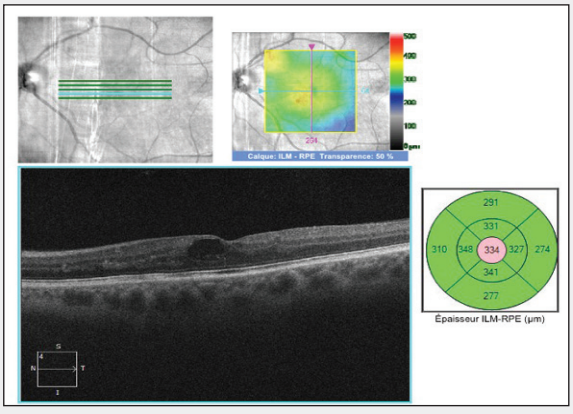


Figure 17. At month 18, a foveal depression was detected.

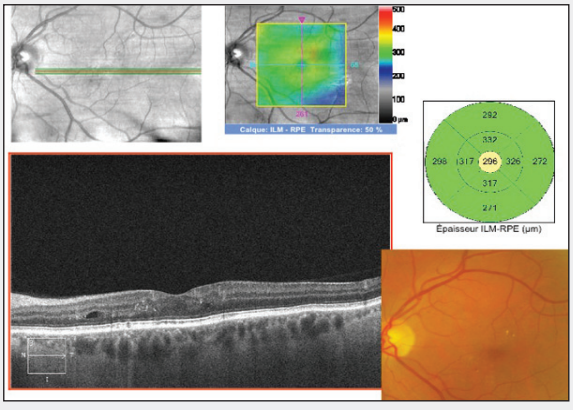


Figure 18. At month 39, CRT was 296 µm and BCVA had improved to 20/25.

a reappearance of a foveal depression starting from month 18. It is important to note that in the 2 clinical cases presented here, ischemia did not progress after initiation of injections.

Fluctuating Central Subfield Thickness

NEIL M. BRESSLER, MD

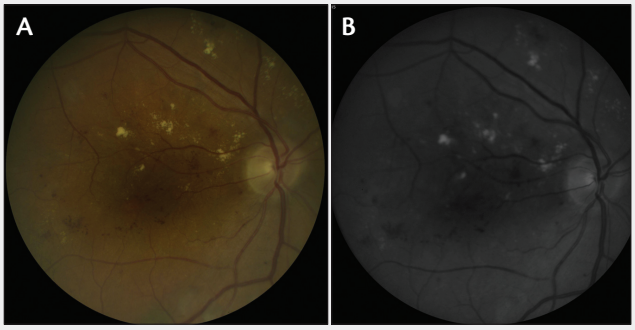
A 64-year-old man presented for evaluation of DME in his right eye. He had previously been followed at another center. His chief complaint was blurriness and decreased vision in the right eye, with BCVA of 20/32. Presenting vision in the left eye was 20/250 due to a central retinal artery occlusion several years ago.

Figure 1 shows the edema in the right eye. Baseline optical coherence tomotraphy (OCT)(Figure 2) shows that the entire macular area was thickened, including the center. This patient could have been included in the DRCR.net trial, but this case is not from the trial.

When treatment with ranibizumab (Lucentis, Novartis) was initiated, macular volume was 13.5 mm^3 and central subfield thickness (CST) was 500 µm (Figure 3). At the next visit 1 month later, the BCVA and CST improved, and according to the algorithm the patient received another injection (Figure 4).

At the next visit, the BCVA was decreased and the CST increased (Figure 5). Our treatment algorithm calls for injection if a patient worsens, so a third injection was given.

Treatment continued every 4 weeks, with BCVA maintained at 20/25 for several months while CST changed from visit to visit—30 µm better, 20 µm worse, (Figures 6-9). The algorithm calls for continuing treatment in the first 6 months, even when improvement is not seen.



Figures 1-3 © 2011 Johns Hopkins University.

Figure 1. Edema in the right eye.

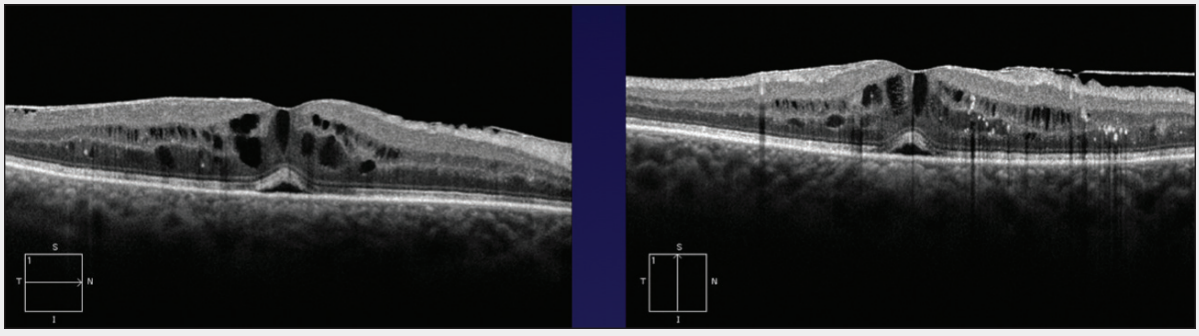


Figure 2. Baseline OCT shows a thickened macula, including the central macula.

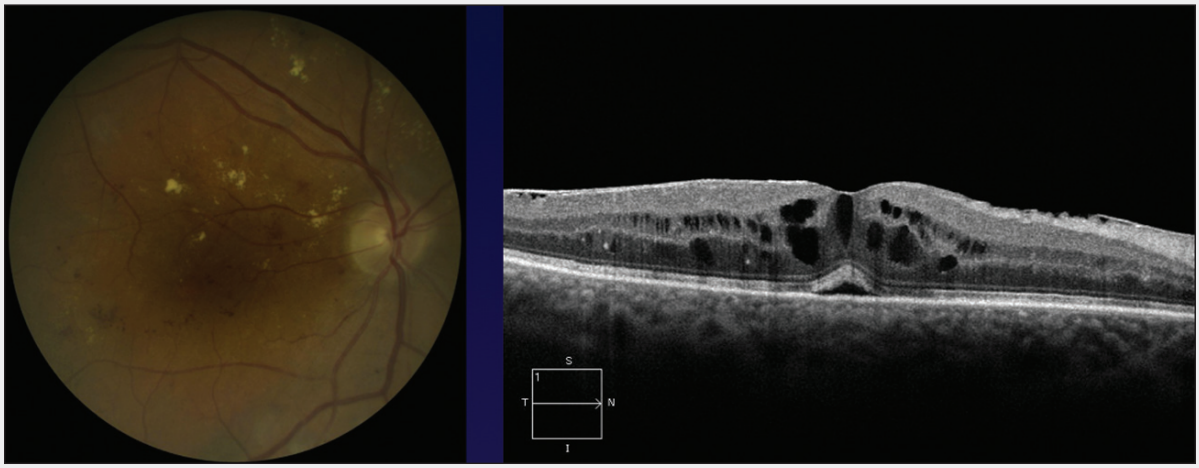


Figure 3. After 1 injection of ranibizumab, macular volume was 13.5 mm^3 and CST was 500 µm.

Following the sixth injection, finally a foveal depression was seen, CST fell to 388 µm, and BCVA improves to 20/20. Once again, as dictated by the algorithm, another injection was given.

The BCVA was then 20/20 in the right eye. The macula was still somewhat thickened, and continued treatment could result in further improvement in CST. At some point, when the BCVA is stable and the OCT is

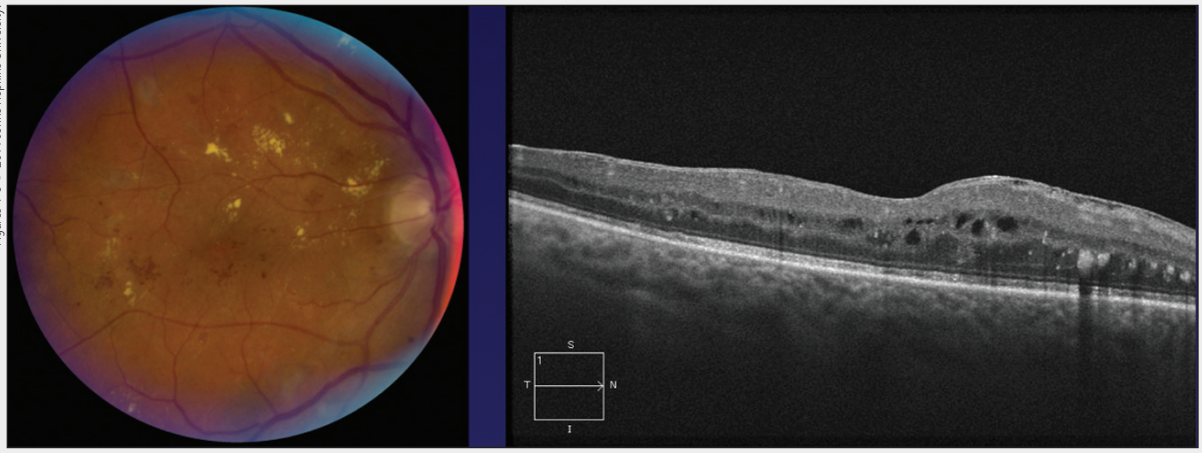


Figure 4. At the next visit 1 month later, BCVA and CST have improved, and according to the algorithm the patient receives another injection.

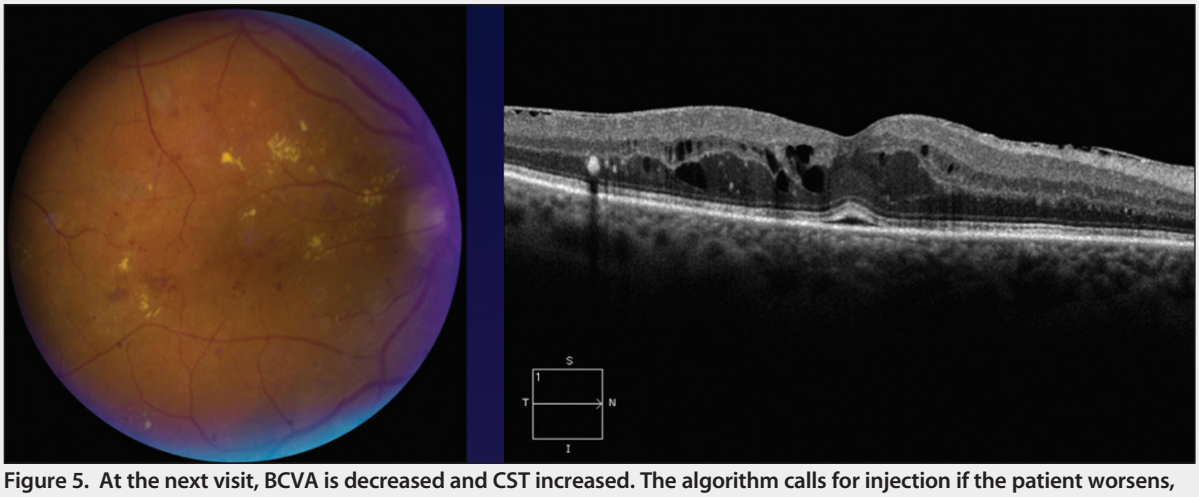


Figure 5. At the next visit, BCVA is decreased and CST increased. The algorithm calls for injection if the patient worsens, so a third injection is given.

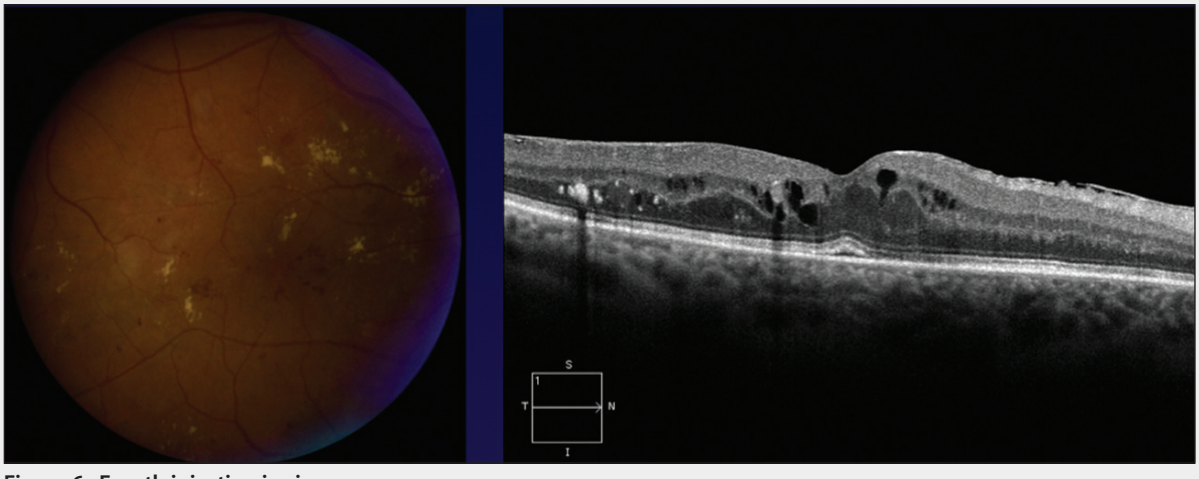


Figure 6. Fourth injection is given.

flat, treatment can be stopped. If the macula is still thickened, because more than 6 injections have now been given, we may choose to add laser.

An important factor, however, in this case is that we continued to treat in the first 6 months when the CST was fluctuating.

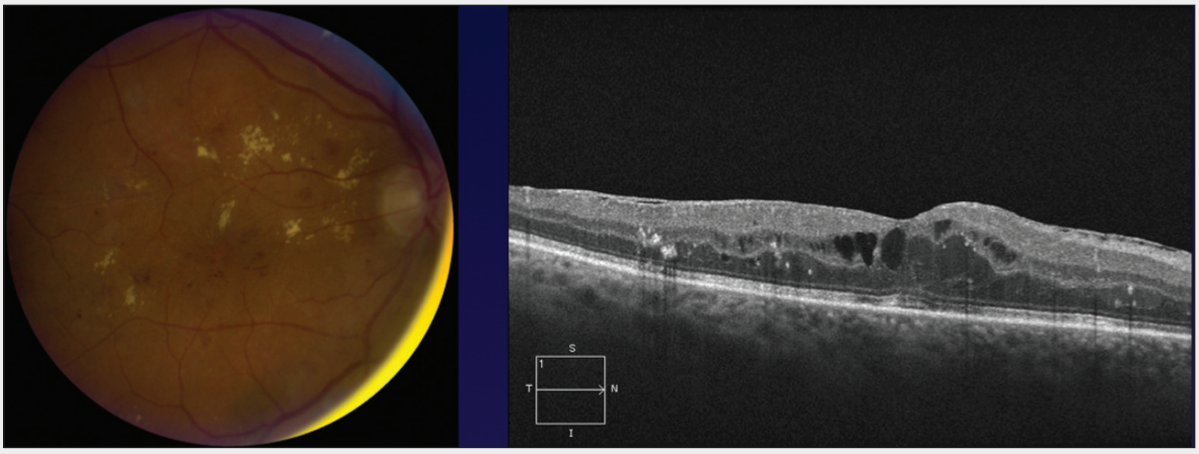


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Figure 7. Fifth injection is given.

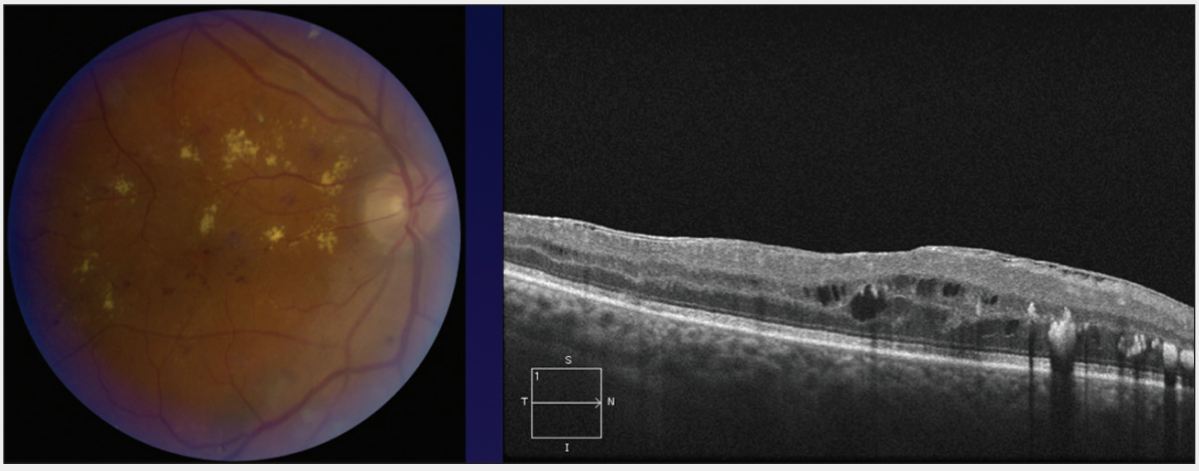

Figure 8. Sixth injection is given.

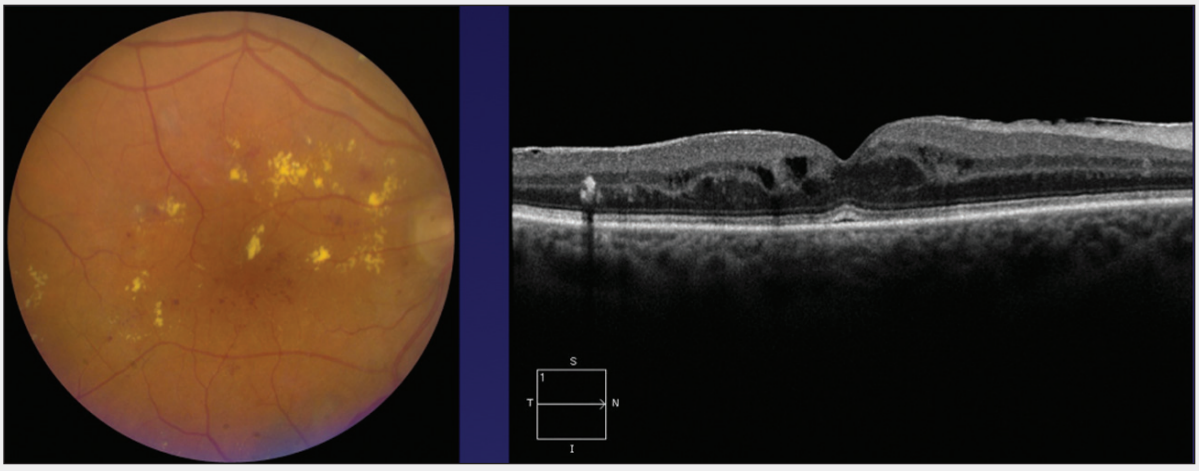

Figure 9. Following the sixth ranibizumab injection, finally a foveal depression is seen, CST falls to 388 µm, and BCVA improves to 20/20. Once again, the algorithm calls for injection.

DRCR.net Protocol M: Effect of Diabetes Education During Retinal Ophthalmology Visits on Diabetes Control

Status: Follow-up
Start Date: 04/04/2011
Clinical Trial ID: NCT01323348

Study Design
The study design is a randomized clinical trial in which investigators or sites will be randomized to provide either intervention (in the form of personalized diabetes education) or usual care to study participants.

Major Eligibility Criteria
- Age ≥18 years
- Type 1 or type 2 diabetes
- Patient is not eligible if patient has a known HbA1c (patient report or available records at time of enrollment) <7.5% within prior 6 months

Treatment Groups
Study participants will be assigned to either the intervention or the control group

1. Intervention Group. The intervention will consist of the following at enrollment and at each follow-up visit (but no more frequently than once every 12 weeks):
    - Measurement of HbA1c in office with immediate feedback
    - Measurement of blood pressure with immediate feedback
    - Assessment of retinopathy risk with immediate feedback
    - Personalized risk assessment reports based on current HbA1c
    - Brief assessment of patient understanding of key issues with immediate feedback
    - Supplemental diabetes management educational materials (provided at baseline only)
    - Feedback to primary care provider
    - E-mail reminder to study participants with e-mail access of individualized risk assessment findings

2. Control Group (Usual care)

Treatment Group Allocation
Investigators or sites will be randomized to provide either intervention or usual care to study participants. A study participant will be assigned to either the control or intervention group according to which treatment group the enrolling investigator is randomized.

Sample Size
At least 2000 study participants with a baseline central laboratory measured HbA1c ≥ 6.0% from approximately 40 sites, each recruiting 50 study participants.

Duration of Follow-up
Duration of follow-up is 24 months with primary outcome at 12 months.

Follow-up Visit Schedule Outcomes
All study participants will have follow-up visits at 12 months and 24 months at which time outcome assessments will be made.
Additional visits will be conducted as needed for the study participant's eye condition.

Primary Outcome Measures
1. Mean change in HbA1c from baseline to 12 months in intervention vs control for study participants being seen for standard care more frequently than every 12 months.
2. Mean change in HbA1c from baseline to 12 months in intervention vs control for study participants being seen for standard care every 12 months.

Information from: Diabetic Retinopathy Clinical Trial Research Network Public web site. Available at: http://drcrnet.jaeb.org. Accessed January 20, 2013.

RETINA TODAY