The incidence and prevalence of diabetes is steadily growing around the world, and retina specialists consequently face the prospect of treating more and more patients with ocular complications of the disease, such as diabetic retinopathy and diabetic macular edema (DME). New treatments continue to emerge, adding to the armamentarium and promising to improve patient outcomes.

With new drugs or drug candidates come new clinical trials to evaluate them. The conclusions derived from these trials may serve as basic guides for physicians, but they are not always useful aids for decision-making, as the patients included in clinical trials do not always reflect the patient population seen in practice. Consequently, real-world outcomes may not always be the same as those in clinical trials.

How can retina specialists practice evidence-based medicine in a real-world setting in which clinical trial data may not apply? Evaluating the merits of a technology or drug requires an understanding of its influence on management strategies in a practical, real-life setting. Patient case presentations can reflect particular insights in patient management. This series explores the evolving landscape of managing patients with DME through the patient cases and experiences of retina specialists. In Part 8 of the series, Michael A. Singer, MD, of Medical Center Ophthalmology Associates in Texas, shares his treatment strategies in two patients with diabetic eye disease.

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Switching Modes of Therapy to Effectively Treat DME

BY MICHAEL A. SINGER, MD

It is common knowledge that, in diabetes, leaking blood vessels in the eye can cause an accumulation of fluid in the macula, a condition known as diabetic macular edema (DME). The treatment protocol for DME varies widely between retina specialists because all patients do not respond similarly. The two cases described in this article demonstrate how switching modes of therapy may be necessary to successfully treat persistent macular edema in diabetic patients.

CASE NO. 1
A 67-year-old woman with a 10-year history of diabetes presented with cataracts in both eyes, DME in her right eye (OD), and previous panretinal photocoagulation (PRP) in her left eye (OS). She was taking a number of systemic medicines, including amitriptyline, low-dose aspirin, sertraline HCl, and losartan-hydrochlorothiazide to treat diabetes and other medical conditions.

On January 19, 2014, her visual acuity was 20/80+2 OD and 20/60+2 OS. OCT showed macular edema with central field thickness (CFT) of 506 µm OD. The patient was given a ranibizumab (Lucentis, Genentech) injection OD (Figure 1). The patient returned on February 17, 2014, and her visual acuity was 20/60-2 OD and 20/70-1 OS. Her CFT had improved to 362 µm, but some residual swelling was seen on optical coherence tomography (OCT). She was given another injection of ranibizumab OD. When she returned on April 17, 2014, her visual acuity had worsened to 20/80 OD and 20/60+ OS, and her CFT had swelled to 615 µm. (Note that more than 1 month had passed since her most recent injection.) She was given another injection of ranibizumab OD. At her next follow-up appointment, on June 1, 2014, she had some improvement in vision and reduction of CFT. The patient’s visual acuities were 20/60 OD and 20/70 OS, and her CFT was 414 µm. These measurements were better than before, but there was still residual edema to necessitate another shot of ranibizumab.

When the patient returned 1 month later, on July 7, 2014, her visual acuity was 20/60+2 OD and 20/80 OS, and her CFT was 528 µm. The decision was still residual edema on OCT, another injection of ranibizumab was given. At her 8-week follow-up 2 months later, she returned with increased edema. Her visual acuities were 20/60-1 OD and 20/100-1 OS, and her CFT was 426 µm. She was given another injection of ranibizumab. On October 12, 2014, the patient’s visual acuities were 20/80+2 OD and 20/80 OS, and her OCT had increased. It was clear that the ranibizumab was no longer helping, as the patient’s CFT was 528 µm, so we decided to switch anti-VEGF drugs and administer an injection of aflibercept (Eylea, Regeneron).

She returned on November 26, 2014, and a reduction in her CFT (409 µm) was noted. The patient’s visual acuities were a little better, at 20/70 OD and 20/60 OS, but there was still residual edema. She received another injection of aflibercept and did not come back until January 18, 2015. At this visit, her visual acuity was 20/70+1 OD and 20/50-2 OS. Since her last visit, she had developed rebound edema, with CFT of 540 µm, so another injection of aflibercept was given. On February 23, 2015, her visual acuity had gotten worse (20/100 OD and 20/50-1 OS), and her CFT on OCT was 565 µm. The decision...
was made to switch gears and inject a dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan).

The patient returned on April 10, 2015, 6 weeks after receiving the dexamethasone implant. Her CFT was markedly improved at 352 µm, and her visual acuity had improved to 20/60-2 OD and 20/60-2 OS (Figure 3). At her next visit on May 19, 2015, her macula was still relatively dry. Her visual acuity was 20/80+2 OD (BCVA 20/50) and 20/100 OS (BCVA 20/40). She returned in July, 5 months after receiving the dexamethasone implant. At this visit, it was noted that the patient’s visual acuity had rebounded (20/100 OD and 20/80 OS), as had the edema (587 µm). She was given another injection of aflibercept OD, and when she returned 2 weeks later on August 5, 2015, her visual acuity had improved (20/50 OD, 20/60 OS). There was a reduction in CFT to 403 µm, but some residual edema, so the patient was injected with a second dexamethasone implant OD. Two months later, on October 9, 2015, the patient’s visual acuity had improved to 20/40+2 and 20/60 OS, which was the best visual acuity she had had for the past year. And, for the first time while she has been under our care, her CFT was less than 300 µm, at 274 µm (Figure 4). A synopsis of the patient’s treatment is summarized in Table 1.

**Discussion**

This case is interesting because it concerns a patient who was relatively resistant to anti-VEGF treatment. She improves somewhat with intravitreal anti-VEGF injections but is never totally dry on OCT. Based on the results of the RISE/RIDE study and VIVID/VISTA studies, multiple anti-VEGF injections were given over time and therapy was changed to stronger anti-VEGF medications with the hope of a better and prolonged anatomic response. Even though the patient was relatively compliant and the intervals between shots relatively short, she still had residual edema that seemed to be, over time, more and more recalcitrant to the anti-VEGF injections. By adding an antiinflammatory medication to her regimen, we were finally able to control her edema to less than 300 µm and allow her to achieve useful driving vision of 20/40 or better.

**CASE NO. 2**

A 61-year-old man with a 24-year history of type 2 diabetes presented to our practice with visual acuity of 20/50 and significant DME OS, with CFT of 438 µm on OCT. We began treating his DME with serial injections of anti-VEGF agents. At his first...
visit on December 3, 2010, he was given an injection of bevacizumab (Avastin, Genentech). When he returned approximately 4 weeks later (December 29, 2010), his visual acuity had improved to 20/30 and CFT had decreased to 293 µm. He was given an injection of sample ranibizumab. At his next visit about 6 weeks later (February 8, 2011), rebound edema was seen. His CFT had increased to 386 µm and visual acuity had decreased to 20/50. He was given another injection of bevacizumab.

His next visit was 2 months later, and by that time, his edema had rebounded even further, with CFT of 675 µm and visual acuity decreased to 20/200.

At this visit, on April 5, 2011, the decision was made to address a different mechanism of action, with use of an antiinflammatory agent instead of an anti-VEGF agent. He was given a dexamethasone intravitreal implant. When he was seen 2 weeks later, his CFT had decreased from 675 µm...
to 250 µm, with a much more normal retinal contour, and his visual acuity had improved from 20/200 to 20/80 (Figure 5). Over subsequent visits as the patient was followed, his visual acuity improved to 20/40. His CFT became normalized, measuring as low as 228 µm. The patient received a second dexamethasone implant 3 months later, and his visual acuity, which had been maintained at 20/40, improved to 20/30. His CFT also improved, to 219 µm. (Figure 6, Table 2).

Discussion
In this case, serial anti-VEGF injections did not control the CFT, and the patient’s visual acuity worsened when the interval between injections was extended to more than 1 month. By adding the dexamethasone intravitreal implant to his treatment regimen, we were able to control his CFT, improve his visual acuity, and increase the duration between injections to 3 to 4 months.

Although the patient in this case was initially treated with intravitreal anti-VEGF medications, over time he became resistant to them, especially when the injection interval was extended from 1 to 2 months. This resistance was manifested by increased CFT on OCT and decreased visual acuity. Once the treatment mechanism of action was changed by switching from anti-VEGF medications to the dexamethasone implant, inflammation was reduced, CFT improved, and visual acuity also improved. This duration of improvement is maintained for approximately 5 months by the use of only one additional dexamethasone implant injection.

CONCLUSION
These two cases illustrate the different ends of the spectrum of how retina specialists practice in the United States today. Case No. 1 represents how many retina specialists approach DME. They start with anti-VEGF injections and continue the course despite the lack of sustained progress, thinking that it is just a matter of time before the anti-VEGF therapy works. They make changes in the type of anti-VEGF after a series of multiple injections (in this case, nine) before considering a different mode of therapy. In Case No. 1, when the patient does receive the dexamethasone implant, there is more improvement when compared with any of the anti-VEGF injections. This improvement was enhanced with a subsequent combination of anti-VEGF and dexamethasone implant.

Case No. 2 is at the other end of the therapy spectrum, which has recently been supported by the EARLY analysis presented by Pravin U. Dugel, MD, and Victor Gonzalez, MD. The EARLY analysis showed that if a patient is going to respond to anti-VEGF therapy, the degree of response is already determined by the third anti-VEGF injection. If the patient is seen to be a suboptimal responder as was the patient in Case No. 2, it might be time to consider a medication that has a mechanism of action other than blocking VEGF.

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**TABLE 2. CASE NO. 2 TREATMENT SUMMARY**

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<th>Date</th>
<th>CFT (µm)</th>
<th>MV</th>
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<th>LogMAR</th>
<th>Treatment</th>
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<td>20/50</td>
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<td>20/50</td>
<td>0.4</td>
<td>bevacizumab</td>
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<td>20/200</td>
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<td>20/80</td>
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Abbreviations: CFT, central field thickness; MV, macular volume

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A video of Dr. Singer presenting these cases can be found on Retina Today’s DME Resource Center: bit.ly/Springer0316.