Treating patients with diabetic macular edema (DME) is a complex endeavor. But for the past 10 years, studies from the DRCR Retina Network have provided clinicians with valuable guidelines and insight into this leading cause of visual loss in working-age adults.

To begin with, the network’s studies were instrumental in establishing anti-VEGF agents as first-line therapy for DME in visually impaired eyes. More recently, the network confirmed that anti-VEGF drugs could be used as rescue therapy following observation or laser for DME with good visual acuity (VA). Moreover, the studies have helped define treatment algorithms for these medications, and they’ve refined the role of optical coherence tomography (OCT) and other imaging devices in evaluating disease.1

“For example, the DRCR Retina Network reported that OCT results do not always reflect vision outcomes,” said Neil M. Bressler, MD, at Johns Hopkins University in Baltimore. “OCT central subfield thickness tells us if there is worsening or stable or improving edema—but it doesn’t necessarily tell us how the vision is doing. Consequently, we realized we should not use OCT as a surrogate of whether the patient is seeing well or not. Instead we need to focus on what the VA testing tells us about the patient’s vision.”

A Revolution Begins

In 2010, the network published primary outcome results from Protocol I, the first large randomized clinical trial demonstrating that intravitreal anti-VEGF was superior to focal/grid laser photocoagulation or intravitreal corticosteroids plus laser for the treatment of DME.2 “This landmark study definitively showed the effectiveness and superiority of a new alternative to laser photocoagulation for DME,” said Dr. Bressler, chair of the network from 2006 to 2012. “Focal/grid laser had been the mainstay of treatment since 1985, when its benefit was reported by the Early Treatment Diabetic Retinopathy Study (ETDRS) Group.”

The revolution didn’t end with Protocol I. Here’s an overview of four subsequent studies—Protocols S, T, V, and U—plus an assessment of potential new treatments.

Protocol S: Anti-VEGF Versus PRP

Rationale. Protocol S3 was designed to compare panretinal photocoagulation (PRP) with anti-VEGF therapy for proliferative diabetic retinopathy (PDR). However, thanks to its structure, the study also revealed insights into the impact of anti-VEGF treatment on DME.

Design. The study compared the safety and efficacy of PRP with intravitreal injections of ran-
ibizumab 0.5 mg (Lucentis) in patients with PDR. Secondary outcomes included changes in visual field, development of DME, and rates of vitrectomy for complications.

Findings. “At two years, we showed that treatment with ranibizumab resulted in VA that was noninferior to PRP treatment,” said Jeffrey G. Gross, MD, at Carolina Retina Center in Columbia, South Carolina. “Secondary efficacy outcomes in the ranibizumab group included decreased need for vitrectomy and better visual fields at two years, compared to the prompt PRP group.”

With regard to DME, fewer eyes in the ranibizumab group developed DME with visual impairment. In addition, for eyes with both PDR and visual loss from DME at baseline, anti-VEGF was given to both the ranibizumab and the PRP groups—yet visual gain appeared to be greater in the eyes receiving anti-VEGF without PRP, suggesting that PRP might diminish the beneficial effects of ranibizumab for the DME.

A follow-up study to Protocol S showed that VA in most of the study eyes remained good at five years and was consistent with the two-year results. However, Dr. Bressler noted that these results should be interpreted with caution since more than one-third of the original participants had died or did not return for the five-year visit.

Nevertheless, the ranibizumab group still had lower rates of DME development with visual loss. They also had less visual field loss at both two and five years, although the difference in visual field loss between the anti-VEGF and PRP groups diminished between the two- and five-year visits.

“These studies also showed that when DME is present in an eye with PDR, it is cost effective, as typically defined in developed nations, to use ranibizumab as an alternative to PRP, since this approach can treat both problems [PDR and DME] simultaneously,” Dr. Gross said.

However, in DME eyes without visual impairment at baseline, anti-VEGF treatment was not cost effective compared with PRP. This finding does not reflect all potential benefits of anti-VEGF therapy in this situation, since there were other advantages to anti-VEGF treatment, including less development of DME with visual loss and fewer eyes undergoing vitrectomy for nonclearing vitreous hemorrhage or traction retinal detachment.

Protocol T: Three Anti-VEGF Drugs
Rationale. Is one anti-VEGF drug more effective than another in treating DME? Protocol T was designed to provide some clarity and treatment guideposts for clinicians on this matter.

Keep an Eye on the Big Picture

In the United States alone, 30.3 million patients have diabetes, and another 84.1 million have prediabetes. Globally, an estimated 463 million adults have diabetes, and this is expected to rise to 700 million by 2045.

Holistic perspective needed. As Dr. Wells pointed out, “Unlike AMD, diabetes is a systemic disease. Glucose and hypertension must be controlled, as it makes a difference in the impact on DR and DME. Consequently, ophthalmologists need to be involved from a holistic perspective.”

Dr. Wells offered a practical example from his own practice: “For example,” he said, “I always look at the ankles of my DME patients to see if they have leg edema and then follow up to see if they are taking diuretics. We often see improvement in DME if the patient’s fluid overload is reduced with diuretic therapy.”

The QoL challenge. And no matter which current or emerging treatment is used, quality of life is a top concern for patients with DME, many of whom are still working, Dr. Grewal emphasized. “This is a key aspect when analyzing the effectiveness of various agents for DME.”

“In developing the study, one of our hypotheses was that there would be differences in efficacy based on VA,” said John A. Wells III, MD, at Palmetto Retina Center in Columbia, South Carolina. Specifically, eyes with worse vision might have thicker maculae as a result of higher intraocular VEGF levels, so a drug with the highest VEGF-binding ability might prove more effective.

**Design.** The study provided a head-to-head comparison between aflibercept (Eyelea), bevacizumab (Avastin), and ranibizumab for the treatment of center-involved DME in patients with a VA of 20/32 or worse. In addition, the researchers designed Protocol T so that if a difference among the groups was noted, a preplanned secondary outcome would determine the impact of baseline VA. Focal/grid laser beyond six months also was applied for eyes with persistent but stable DME involving the center of the macula.

**Findings.** The investigators found that all three agents improved vision in patients with DME, and this improvement was maintained at two years. However, the relative effect depended on baseline VA. In eyes with better baseline vision (20/32 to 20/40) there was no significant difference, on average, among the treatment groups at one and two years. However, at worse levels of initial VA (20/50 or worse), patients treated with aflibercept were, on average, more likely to experience improvement in vision at year 1 compared with those who received either bevacizumab or ranibizumab. In addition, at the two-year mark, those who received aflibercept were more likely to experience improvements in vision than were those who received bevacizumab.

“This study tells us that when you are treating patients with DME-causing visual loss—of 20/32 or worse—in your practice, you should use the (patient’s) VA at the time of initiating treatment to help guide” the choice of agent, Dr. Wells said. “Protocol T also showed us that persistent but stable edema beyond six months is not associated with visual loss, provided that anti-VEGF was resumed if the VA decreased or the OCT central subfoveal thickness [CST] worsened.”

Also of note, in eyes with better baseline vision, bevacizumab reduced edema about 50% less, on average, than the other two drugs through two years. Even so, this did not translate to any less gain in vision for bevacizumab-treated eyes compared with the aflibercept or ranibizumab group when 20/32 to 20/40 at baseline—another example of the potential disconnect between OCT CST outcomes and VA results.

“Yet even through two years, we did not see a lot of severe vision loss” in eyes with chronic persistent edema, Dr. Wells said. “This illustrates that—unlike persistent thickening in neovascular age-related macular degeneration [AMD], where continued anti-VEGF therapy may be necessary to avoid substantial VA loss—such visual loss may not occur in eyes with persistent but stable DME.”

**Protocol V: Aflibercept, Observation, or Laser**

**Rationale.** “Our goal historically has been to intervene earlier in patients with DME to achieve better outcomes,” said Carl W. Baker, MD, with the Paducah Retinal Center in Paducah, Kentucky. That is, he said, “treating an eye at 20/32 is more likely to end up with a better level of VA than treating an eye that walks in at 20/100, even if that 20/100 eye gains 3 lines of vision to 20/50 following anti-VEGF therapy. Yet what should a clinician do if a patient with DME presents with good VA—for example, 20/20? Is anti-VEGF superior to laser or observation for those eyes?”

Dr. Baker added that, in the last 10 years, some clinicians have initiated anti-VEGF treatment in these patients despite a lack of supporting evidence because they were concerned that visual outcomes would be worse if anti-VEGF treatment was deferred. Enter Protocol V, the first large randomized trial since anti-VEGF injections were approved...
to evaluate management strategies for center-involved DME in eyes with good VA.

**Design.** Protocol V was designed to determine whether initial close monitoring of DME patients with good vision or starting with laser is a more viable treatment strategy, provided that anti-VEGF therapy is initiated as soon as vision loss is noted. The study included patients with center-involved DME and VA of 20/25 or better. The patients were initially managed with aflibercept, laser photocoagulation, or observation. For the latter two strategies, aflibercept was initiated as a rescue treatment if VA loss was noted during follow-up.

**Findings.** At two years, rates of VA loss of 5 or more ETDRS letters were not significantly different among the three groups of patients.

“With Protocol V, we have found a paradigm where we can observe some DME patients with good vision and wait on treatment until we see a decrease in vision, thus saving them from unnecessary intravitreal anti-VEGF injections. We are becoming more comfortable monitoring them and initiating treatment only when their vision begins to decline,” Dr. Baker said.

He added, “At the end of the day, we have learned that paying close attention to vision quality is the most appropriate driver of how we treat DME patients with good vision.”

**Protocol U: Persistent DME**

**Rationale.** Protocol U added dexamethasone (Ozurdex) to the mix in an effort to address the persistent DME some eyes experience following anti-VEGF therapy.

**Design.** The phase 2 trial involved patients with a VA of 20/32 to 20/320 who all had received at least three injections of ranibizumab. Eyes that had persistent DME following these injections were randomly assigned to receive dexamethasone or sham as often as every three months. In addition, both groups continued to receive ranibizumab as often as every four weeks.

**Findings.** The addition of dexamethasone was found to be more likely to reduce retinal thickness, but it did not improve VA at 24 weeks more than continued ranibizumab therapy alone. It also increased intraocular pressure.

“A message here is that clinicians should not get frustrated if their patients aren’t experiencing immediate results,” said Dr. Wells. “Persistent DME after six injections is common, but visual loss due to persistent DME is very uncommon.”

He added, “Protocol U showed that switching to steroids, with its attendant risks, does not lead to better vision outcomes than continuing anti-VEGF therapy. I always tell my patients that they can expect on average to require about nine to 10 injections in the first year and five to six in the second year to control the DME, as this was the median number of injections given with all three agents over two years in Protocol T.”

**What’s Next in Treatment?**

While the current anti-VEGF treatment options for DME are effective, they are short-acting, noted Dilraj S. Grewal, MD, at Duke University in Durham, North Carolina. Consequently, patients must come in frequently, which has resulted in a considerable increase in the treatment burden.

One outcome of this burden: loss to follow-up. “This is especially true of patients who do not receive any noticeable improvement after three months of treatment and become discouraged, even though the treatment effects take time,” Dr. Grewal said. “Compliance is a huge challenge.”

**A look at the pipeline.** Drug manufacturers are well aware of the need for longer-acting therapies, Dr. Grewal said. “This is going to be the next big shift in treatment.” He provided an overview of several therapies in the pipeline:

**Faricimab.** In DME, angiopoietin-2 (Ang-2) works synergistically with VEGF-A to drive biological pathways that cause vessel permeability and inflammation. Faricimab (Genentech), formerly known as RG7716, is the first bispecific monoclonal antibody that simultaneously binds to and neutralizes both Ang-2 and VEGF-A. “This drug is designed to affect vascular stability, and its phase 2 trials look promising,” Dr. Grewal said.

**KSI-301.** Kodiak Sciences has developed an

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**Initial Treatment: IRIS Registry Results**

Researchers assessed treatment patterns for DME in 13,410 treatment-naive patients. This chart presents initial treatment provided within 28 days of diagnosis of DME.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% of Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>74.5%</td>
</tr>
<tr>
<td>Anti-VEGF</td>
<td>15.6%</td>
</tr>
<tr>
<td>Laser</td>
<td>8.5%</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>1%</td>
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</tbody>
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* The remaining patients received combination therapy (any combination of anti-VEGF drug, corticosteroid, or laser given within a two-week period).

Adapted from Cantrell RA et al. *Ophthalmology.* Published online Oct. 23, 2019.
antibody biopolymer conjugate (ABC) platform designed to maintain drug levels in ocular tissues for a longer time than is currently available. KSI-301, an anti-VEGF ABC, is designed as a first-line treatment for DME.

**Port Delivery System.** This technology, from Genentech, is designed to dispense ranibizumab through a refillable, surgically placed implant to achieve sustained delivery. “It has been studied in AMD, and the next phase will move toward evaluating its efficacy in DME,” Dr. Grewal said.

AR-13503 SR Implant. This implant, from Aerie Pharmaceuticals, provides sustained release of a small molecule inhibitor of both Rho kinase and protein kinase C. The agent is thought to inhibit angiogenesis, preserve the blood retinal barrier, and reduce retinal fibrosis in DME. It is designed to be administered once every six months via intravitreal injection.

**GB-102.** An injectable depot version of the anticancer drug sunitinib malate, GB-102 (Graybug) “binds to all VEGF receptors and has been targeted for [treatment of] AMD and DME,” Dr. Grewal said. This small molecule receptor tyrosine kinase inhibitor blocks several intracellular receptors associated with angiogenesis, proliferation, vascular permeability, and fibrosis.

**RGX-314.** Gene therapy is also being explored. One example is RGX-314 (Regenxbio), a one-time subretinal treatment. It contains a gene that encodes for a monoclonal antibody fragment; the expressed protein is designed to neutralize VEGF activity. Disease targets include AMD and DR.

**PAN-90806.** This once-daily anti-VEGF eye-drop, from PanOptica, is being evaluated for neovascular eye diseases. Results from an initial dose-ranging phase 1/2 trial released in October 2019 demonstrated a biological response as monotherapy in treatment-naïve patients with wet AMD.8

**Al—and more.** Dr. Grewal also predicted that artificial intelligence will help ophthalmologists evaluate their patients with DME, determine the best treatment strategy, and match this information with insurance coverage restrictions.

“In addition,” Dr. Grewal said, “we will be moving in a more holistic direction, linking patients’ eye treatment with their metabolic profile—all through sophisticated smartphone apps.”


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**Meet the Experts**

**Carl W. Baker, MD** With the Paducah Retinal Center in Kentucky. Financial disclosures: Novo Nordisk: C; Regenxbio: C.

**Neil M. Bressler, MD** The James P. Gills Professor of Ophthalmology at the Johns Hopkins University School of Medicine in Baltimore and Editor-in-Chief of *JAMA Ophthalmology*. Financial disclosures: Bayer: S; Novartis: S; Roche: S; Samsung Bioepis: S. Note: Participation by Dr. Bressler in this activity does not constitute or imply endorsement by the Johns Hopkins University, the Johns Hopkins Hospital, or the Johns Hopkins Health System; nor by the DCR Retina Network; nor by JAMA Ophthalmology.

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See disclosure key, page 11.