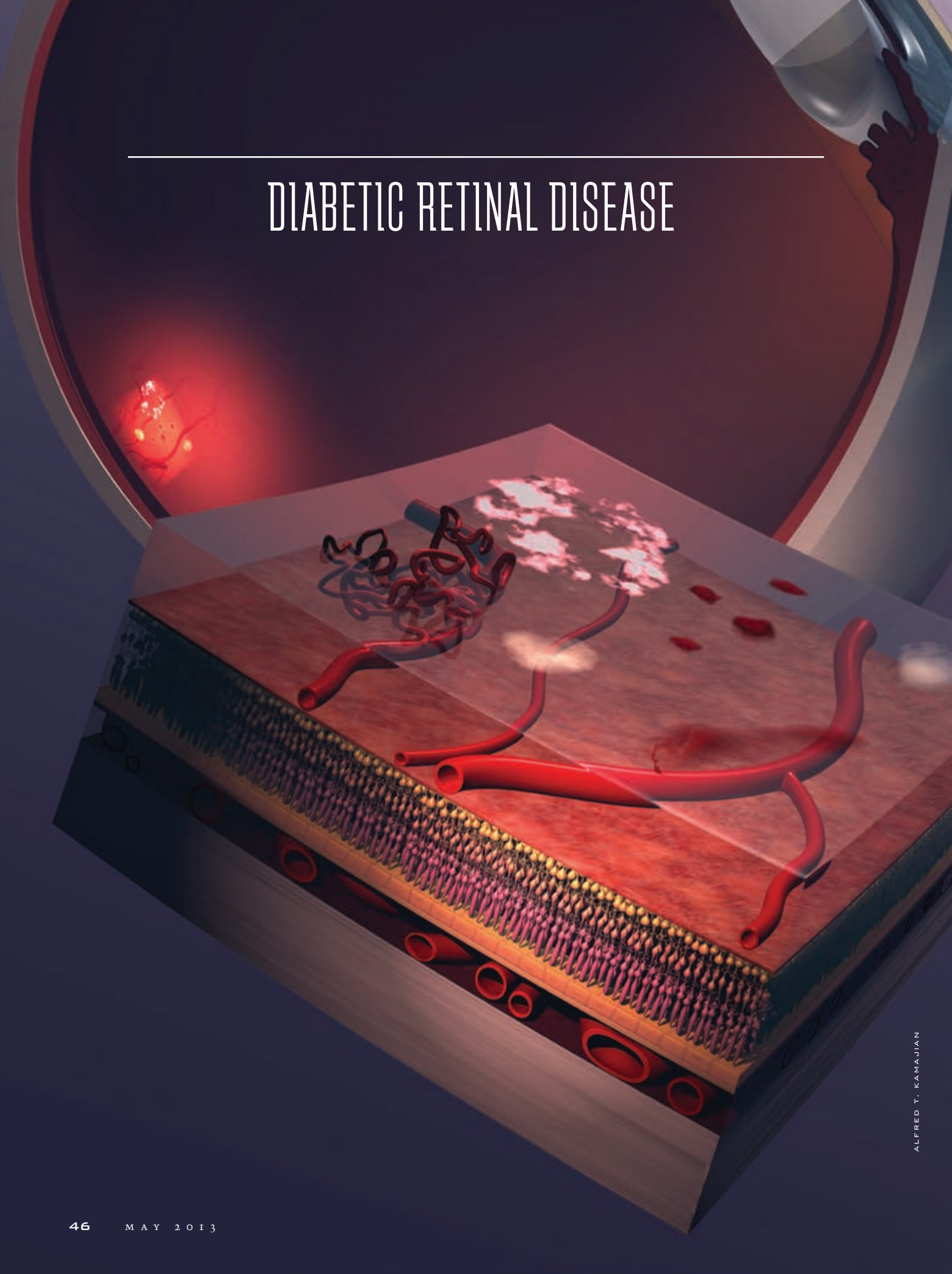
DIABETIC RETINAL DISEASE



ALFRED T. KAMAJIAN

Keeping Up With Evolving Therapies

BY ANNIE STUART, CONTRIBUTING WRITER

For many years, laser was the treatment mainstay for diabetic retinal disease, and some thought corticosteroids held great promise. But, today, anti-VEGF therapies are taking the field by storm, while research continues on novel options and combinations of old standbys. Learn how you can incorporate these new approaches into your practice.

Nearly 26 million Americans have diabetes, and another 79 million have prediabetes.[1] Many are unaware of their condition and the risk it poses to their vision: Diabetic retinopathy is the leading cause of new blindness in Americans aged 25 to 74.[1]

Fueled by factors such as sedentary lifestyles and increased consumption of sugary, high-fat foods, the rising rate of diabetes, particularly among today's youth, is a major global concern, said Abdhish R. Bhavsar, MD, managing partner and director of clinical research at the Retina Center of Minnesota and attending surgeon at Phillips Eye Institute, in Minneapolis. "I'm concerned about what this will mean 10, 20, or 30 years from now. These younger generations may experience diabetic retinopathy at an earlier age. But I'm also hopeful that public education programs on healthier lifestyles will help reduce the rates of diabetes and associated eye disease."

Ophthalmologists have other reasons to be hopeful as well: better tools and strategies than ever before for managing and monitoring the retinal complications of diabetes. Anti-VEGF agents, laser, steroids, surgery, and even systemic therapies are all contributing to the ongoing evolution in treatment for diabetic eye disease.

The Power of Diabetes Management

Despite the growing epidemic of diabetes, Carl D. Regillo, MD, sees a silver lining. Better systemic diabetes care, he said, can stave off progression of retinopathy for a longer period of time. He offers some anecdotal evidence—a reduction in the numbers of problems related to diabetic retinopathy that he sees in his patients.

"Ten or 15 years ago, the average person with diabetes who came to see me either didn't know their A_{1c} or they quoted levels that were so high, I cringed," he said, referring to the glycated hemoglobin test that helps monitor blood sugar levels. "Nowadays, I much more commonly see A_{1c} levels that are fantastic."

TIGHT GLUCOSE CONTROL. It could be that the findings from the Diabetes Control and Complications Trial (DCCT) and other major prospective studies from the 1990s are bearing fruit, said Dr. Regillo, director of the retina service at Wills Eye Institute and professor of ophthalmology at Thomas Jefferson University in Philadelphia.

These trials proved that tight control of blood sugar helps patients in many ways, including reducing the rates of diabetic retinopathy–related complications. In fact, every percentage point drop in A_{1c} can reduce the risk of microvascular complications by 40 percent.[1]

DIABETIC MACULAR EDEMA. (1A) Fundus photo and (1B) OCT of nonproliferative diabetic retinopathy with DME before treatment; VA is 20/80. (1C) After three ranibizumab injections, edema has resolved; VA is 20/50.

"In general, a target A_{1c} of below 7 is recommended, although this can vary for individual patients and should be discussed with the patient's primary care provider," said Lee M. Jampol, MD, professor of ophthalmology at Northwestern University in Chicago.

MANAGING OTHER RISKS. Additional factors known to affect visual outcomes in patients with diabetes include high blood pressure and, possibly, lipid profiles, Dr. Jampol said. "These should be optimized to provide the best chances of preventing visual loss from diabetes. Ophthalmologists should counsel patients strongly in this regard when indicated."

SYSTEMIC MEDICATIONS. Certain systemic medications used to treat risk factors such as high blood pressure may also have a beneficial effect on the progression of diabetic eye disease. For example, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have shown preliminary promise in preventing the onset or slowing the progression of early diabetic retinopathy.[2] However, more study is needed to prove their effectiveness, said Dr. Jampol.

Fenofibrate is a drug used primarily to reduce cholesterol, and some studies, including FIELD (Fenofibrate Intervention and Event Lowering in Diabetes)[3] and ACCORD (Action to Control Cardiovascular Risk in Diabetes),[4] suggest that it may also be beneficial in reducing diabetic retinopathy. However, the studies were not designed specifically to test that, raising some methodological issues.[5] At this time, said Dr. Jampol, the ophthalmology community has not embraced this treatment as a way of managing diabetic retinopathy.

Monitoring Visual Changes

Patients with type 1 diabetes should have an ophthalmic evaluation within five years of diagnosis or once they have passed puberty, said Dr. Jampol, and patients with type 2 diabetes should have an initial ophthalmic evaluation shortly after diagnosis.

FOLLOW-UP EXAM SCHEDULE. The frequency of repeat screening is a function of what you've found and what you've learned about the patient, said Susan B. Bressler, MD, the Julia G. Levy, PhD, Professor of Ophthalmology at the Wilmer Eye Institute. "For example, if this is a very sick individual—meaning that the diabetes is poorly controlled or there are multiple comorbidities—even if there is no apparent retinal disease, you might repeat screening at a closer interval than with a well-controlled, healthy person with diabetes."

IMAGING. To help monitor signs of the disease, fluorescein angiography can delineate hyperfluorescent microaneurysms and neovascularization as well as other intraretinal microvascular abnormalities, said Dr. Bhavsar. B-scan ultrasonography is useful for cases in which vitreous hemorrhage interferes with visualization of the retina.

More countries are using digital imaging to evaluate diabetic retinopathy, said Dr. Jampol. "Given a validated system, this can be effective in identifying advanced cases of eye disease. However, this does not replace the need for a full ophthalmic evaluation."

Use of optical coherence tomography (OCT) in clinical trials has changed the way ophthalmologists make treatment decisions, said Dr. Bhavsar. The cross-sectional images generated by OCT help the physician evaluate retinal thickness and swelling, thus adding an extra parameter to the standard clinical exam.

WHEN TO REFER. Prompt referral to a retina specialist should be considered at least by the time a substantial amount of diabetic retinopathy is present and treatment options are being considered, said Dr. Jampol.

A Complex Disease Process and Treatment

Over the last several years, a great deal of knowledge has been gained about the pathophysiological mechanisms underlying diabetic retinal disease.

CARL D. REGILLO, MD

MULTIPLE MECHANISMS. Although the exact mechanism remains unclear, growth hormone, hypoxia and vasoproliferative factors, and other cytokines, as well as hematologic abnormalities, have all been implicated in the development of the disease.

Vascular endothelial growth factor (VEGF), in particular, has become a prime target, said Dr. Regillo. "VEGF makes the normal vasculature leaky and can also promote abnormal vascular growth. Microaneurysms form, tight junctions break down, and fluids, lipids, and other plasma products leak into the retina, causing swelling, particularly in the macula." Diabetic macular edema (DME), in fact, is the most common cause of vision loss in patients with nonproliferative diabetic retinopathy (NPDR), and it may also occur in proliferative disease.[6]

THERAPY IN FLUX. "With the identification of VEGF as a key mediator of both diabetic macular edema and proliferative diabetic retinopathy," said Dr. Jampol, "the most common approach for diabetic macular edema now involves VEGF inhibition, and it is being considered for proliferative diabetic retinopathy as well."

With the knowledge gained from recent studies, treatment regimens are changing rapidly, particularly for patients with DME, said Dr. Bhavsar. Also, due to the systemic nature of the disease, in part, individual patients' choices are in flux and in regular need of reevaluation, he added.

A wide range of factors influence treatment choices, said Dr. Jampol. They include costs, treatment burden, side effects, complications, binocular or monocular status, condition and treatment response of the fellow eye, and concomitant conditions such as pregnancy, hypertension, cardiovascular disease, stroke, or the need for cataract surgery.

Dr. Bressler added other questions to consider in formulating management strategies: Is it a treatment-naive eye? Does edema involve the foveal center? Is vision impaired? "My approach is tailored to the individual. For example, I will consider how symptomatic the patient is from any existing macular thickening, even if vision on the eye chart is recorded as normal, such as 20/20 to 20/25," she said.

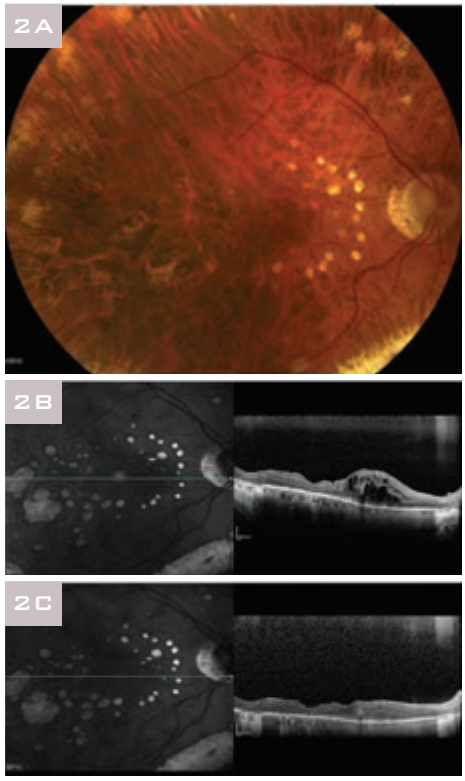
Laser—A Demotion From Gold

In 1985, the landmark Early Treatment Diabetic Retinopathy Study (ETDRS) found that laser therapy reduced moderate vision loss by 50 percent in patients with clinically significant DME.[7] Laser proved to be more effective than intravitreal corticosteroid injection, as was demonstrated in the Triamcinolone vs. Laser Trial conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net). Triamcinolone had a more rapid onset of action, but at two years, laser had produced better visual acuity.[8]

MORE LIMITED ROLE. However, laser now plays a more limited role, after being the decades-long mainstay of treatment for DME, said Dr. Jampol, current chair of the DRCR.net. What changed?

Among other studies, a DRCR.net comparative effectiveness protocol evaluating laser, corticosteroids, and anti-VEGF therapy for DME (Intravitreal Ranibizumab or Triamcinolone Acetonide in Combination with Laser Photocoagulation for Diabetic Macular Edema; NCT00444600) found in 2010 that ranibizumab-treated groups achieved superior results over laser alone.

"Whether added promptly at the initiation of anti-VEGF therapy or deferred for at least six months after anti-VEGF therapy was initiated, focal/laser treatment did not have a substantial effect on the visual outcome or the number of injections," said Dr. Bressler, who formerly served as vice-chair of DRCR.net. "Through two or three years of follow-up, approximately 40 percent of participants assigned to the ranibizumab and deferred laser treatment arm in the network study ever needed laser," she said. "We've reduced not only the number of patients who receive laser but also the number of laser encounters they are exposed to."



MULTIPLE THERAPIES. (2A) Fundus photo and (2B) OCT of a patient with diabetic retinal disease who has had pars plana vitrectomy, panretinal photocoagulation, and focal laser; VA is 20/100. (2C) One month after treatment with 4 mg of intravitreal triamcinolone, VA is 20/60.

STILL STANDARD IN SOME CONDITIONS. Laser panretinal photocoagulation (PRP) of the peripheral retina is still the standard of care for proliferative diabetic retinopathy, said Dr. Bhavsar. In addition, focal laser, which treats the area surrounding the macula, is still the standard for patients with DME not involving the center.

UNRESOLVED QUESTIONS. But what is the gold standard for the person who has good vision and center

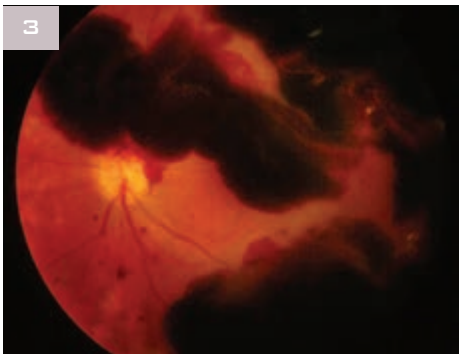
CARL D. REGILLO, MD

involvement? "Should we treat these patients with anti-VEGF therapy, or should we start with laser and only consider anti-VEGF if, over time, they have a less desirable course?" asked Dr. Bressler. Controversy persists, she said, and more studies are needed to confirm the best course.

How Anti-VEGF Tx Affects Management

The use of anti-VEGF therapy in patients with diabetes initially produced some predictable results—reducing blood vessel leakiness and edema, for example. But studies such as the pivotal phase 3 trials RISE and RIDE and the DRCR.net protocols also brought some surprises. Anti-VEGF therapy was clearly superior—above and beyond other treatments, including the prior gold standard, said Dr. Regillo.

VISUAL ACUITY MAINTAINED OR IMPROVED. "These trials demonstrated that anti-VEGF therapy for DME can double the number of people who will have moderate improvement in visual acuity and further reduces the number of people who will have additional vision compromise," said Dr. Bressler, adding that the evidence thus far is largely derived from ranibizumab (Lucentis), which is FDA approved for DME.



VITREOUS HEMORRHAGE. PDR with neovascularization of the disc and vitreous hemorrhage.

In the RIDE and RISE trials, ranibizumab was injected monthly for the treatment of DME, said Dr. Regillo. "Over the course of two years, not only did the rate of progression slow but the levels of diabetic retinopathy on average also improved. Even with the best of blood sugar control, this just doesn't happen."

FEWER INJECTIONS THAN FOR AMD. In clinical practice, however, the approach to anti-VEGF therapy is more individualized than this. "No one uses it in a cookbook fashion," Dr. Regillo said, adding that good outcomes can be obtained with as-needed treatment.

In fact, part of what differentiates the age-related macular degeneration (AMD) cohort from the DME cohort, said Dr. Bressler, is that patients with AMD are dependent on anti-VEGF treatment for years to sustain any early vision benefits. "What we're seeing with diabetes is completely different," she said. "Over time, the need for a large number of injections falls off enormously. With [DRCR] Protocol I, the median number of injections was eight or nine in the first year, two or three in the second year, and one or two in the third year."

MORE MONITORING THAN WITH EARLIER REGIMENS. But the use of anti-VEGF therapy for diabetic retinopathy and DME has drastically altered follow-up schedules, said Dr. Bhavsar. "In the past, we would treat patients [with laser] and see them four months later. Now the timing of interventions is tighter, which means we're seeing patients back almost every month to consider the need for treatment. This is the single most important recent change."

However, said Dr. Jampol, it's important to note that in the DRCR.net study, by the second year of management when edema had resolved or stabilized, many participants had follow-up extended to every 16 weeks unless resumption of anti-VEGF therapy was indicated.

TREATING CENTRAL INVOLVEMENT. Dr. Bressler's first choice for the treatment-naive patient with visual impairment and central involvement is intravitreal anti-VEGF monotherapy—with deferred laser. "This means you deliver anti-VEGF monotherapy and continue this strategy unless the person is having a suboptimal response, defined as persistent edema that is not improving with successive injections, along with continued visual impairment." She waits to consider adding laser to the management strategy until at least six months have elapsed or six consecutive monthly injections have been administered.

USE IN ADVANCED STAGES. Anti-VEGF therapy can address bleeding in advanced stages, including neovascular glaucoma, said Dr. Regillo. "We also sometimes use it when there's vitreous hemorrhage from proliferative disease, and we need the neovascularization to regress quickly." Dr. Regillo exercises caution, however, in situations where anti-VEGF therapy might exacerbate tractional retinal detachments.

CAUTIONARY NOTES. "It's important to remember that patients with diabetes may be more predisposed than other patients to vascular disease and other systemic complications," said Dr. Jampol. "Therefore, ongoing trials with anti-VEGF therapy are paying close attention to cardiovascular and cerebrovascular adverse events." Dr. Bressler noted that, thus far, after three years of data, no serious systemic safety risks have emerged.

LOOKING AHEAD. DRCR.net has several trials under way, including one comparing intravitreal aflibercept, bevacizumab, and ranibizumab in eyes with DME. This study will be completed in about two years.

Dr. Bressler also looks forward to seeing whether anti-VEGF therapies will retard progression of diabetic eye disease in general. "I can potentially envi-

ABDHISH R. BHAVSAR, MD

LANDMARK DRCR.NET TRIALS

Formed in 2002 with funding from the National Eye Institute, DRCR.net is a multicenter clinical research consortium that focuses on diabetic retinopathy, diabetic macular edema, and associated conditions.

With more than 385 physicians participating, the network currently encompasses more than 120 active sites, including community-based practices and academic centers in 39 states. As of December 2012, more than 8,500 subjects had been enrolled in 20 multicenter DRCR.net research protocols.

DRCR.net's contributions to research include providing methodological clarity on issues such as the use of OCT imaging for monitoring DME, managing endophthalmitis risks linked with intravitreal injections, and creating large pools of data for optimizing multiple therapies.

Here's a snapshot of some early lessons learned from DRCR.net trials. More studies are ongoing. Visit www.drcr.net to see all of the protocols and to read full texts of articles from the network's studies.

DIABETIC MACULAR EDEMA TREATMENT

Protocol B Focal/grid photocoagulation is more effective, with fewer side effects over two years, than 1-mg or 4-mg doses of intravitreal triamcinolone.

Protocol E In cases of DME with good visual acuity, peribulbar triamcinolone, with or without focal photocoagulation, is unlikely to be of substantial benefit.

Protocol H Intravitreal bevacizumab reduced DME in some eyes, but the study was not designed to determine whether this treatment was beneficial.

Protocol I For DME involving the central macula, intravitreal ranibizumab with prompt or deferred (24 weeks or more) focal/grid laser was more effective through two years in increasing visual acuity than focal/grid laser treatment alone.

Protocol K Sixteen weeks after focal/grid laser for DME in eyes with definite reduction but no resolution of central edema, 23 to 63 percent are likely to continue to improve without additional treatment.

DIABETIC RETINOPATHY TREATMENT

Protocol F Whether PRP is applied in one session or four sessions is not likely to result in clinically meaningful differences in OCT thickness or visual acuity.

Protocol J In eyes with DME and proliferative diabetic retinopathy receiving focal/grid laser and PRP, adding one intravitreal triamcinolone injection or two intravitreal ranibizumab injections is associated with better visual acuity and decreased macular edema by 14 weeks compared with eyes treated with focal/grid laser and PRP without intravitreal therapy.

OCT IN THE MEASUREMENT OF RETINAL THICKNESS

Protocol C *Study 1:* Despite slight decreases in retinal thickening during the day, most eyes with DME have little meaningful change in OCT central subfield (CSF) thickening or visual acuity between 8 a.m. and 4 p.m.
Study 2: Reproducibility of OCT measurement of retinal thickness in DME was better for CSF thickness measurements than for center point measurements. A change in CSF thickness exceeding 11 percent is likely to be real.

Protocol G *Primary outcomes:* CSF thickness on Stratus OCT in people with diabetes and minimal or no retinopathy are similar to thicknesses reported from a normative database of people without diabetes. CSF thickness is greater in men than in women.
Secondary outcomes: Although subclinical DME is uncommon, approximately one-quarter to one-half of eyes with subclinical DME may progress to more definite thickening or may be judged to need treatment for DME within two years after its identification.

Protocol O Mean CSF thickness is approximately 70 µm greater when measured with Heidelberg Spectralis OCT than with Stratus OCT among individuals with diabetes in the absence of retinopathy or with minimal nonproliferative retinopathy and a normal macular architecture. Diabetic macular edema involving the CSF is likely to be present at the gender-specific thicknesses of greater than or equal to 320 µm for men and 305 µm for women as measured with Spectralis.

SOURCE: Information adapted from www.drcr.net.

sion a world in which a few doses given with some regularity—yet to be defined—may stop a large proportion of people from ever developing visually impairing diabetic eye disease."

Corticosteroids: Benefits and Risks

Currently, corticosteroid treatment of DME involves injecting 2- or 4-mg doses of triamcinolone suspension into the vitreous. Dr. Bhavsar was among those who initially thought corticosteroids would be a big piece of the puzzle for this disease.

Although it does work, the downside is promoting cataract or raising intraocular pressure—two conditions that are already more prevalent in patients with diabetes, said Dr. Bhavsar. "However, there may be some subsets of patients who benefit," he said, "such as those who are pseudophakic and refractory to other treatment."

In a subset of pseudophakic patients in Protocol I of the DRCR.net, intraocular triamcinolone acetonide in conjunction with focal laser produced a response similar to that in the anti-VEGF group. "The reasons for this result are unclear," said Dr. Bressler. "Nevertheless, 50 percent of those patients still had intraocular pressure issues."

NOT A FIRST-LINE APPROACH. "I'm generally not enthusiastic about intraocular steroids to manage DME," added Dr. Bressler, "mainly because I don't like producing cataracts, which will eventually happen in 100 percent of phakic individuals; and cataract surgery in the setting of DME invites other issues. Even if the individual is pseudophakic, however, I must monitor for and manage any resulting glaucoma. Given those adverse effects, steroids are, in my mind, never a first-line therapy."

Dr. Regillo may use a steroid if, after several injections of anti-VEGF therapy, the edema is not improving. "Or I may use it if I am getting a good effect, but the patient needs anti-VEGF therapy very frequently over a long time. The steroid has a longer duration of action, so fewer injections are needed. If it is well tolerated and there is no increase in intraocular pressure, it can be a good alternative to anti-VEGF therapy."

SUSTAINED-RELEASE IMPLANTS. Several studies suggest that low-dose, long-acting steroid delivery will likely be a future option for treating DME, said Dr. Regillo. One prospect is Iluvien (Alimera), a sustained-release fluocinolone acetonide. "But this was derailed a bit when Iluvien did not get FDA approval for this indication," he said.

Ozurdex (dexamethasone intravitreal implant 0.7 mg, Allergan), a biodegradable, injectable rod-shaped implant that lasts an average of four months, is currently approved for noninfectious posterior uveitis and macular edema resulting from retinal vein occlusion. "It has a chance of winning FDA approval [for the DME indication] sometime in the future," said Dr. Regillo.

Sustained-release options have the benefit of reducing the number of injections, said Dr. Bhavsar, and the rate of cataract and glaucoma development may be reduced with Ozurdex. However, cataracts and glaucoma are still significant risks, added Dr. Regillo. "These side effects will continue to limit steroid use in this setting to second-line or back-up therapy."

Vitrectomy: Conflicting Data

As with other methods of treatment for diabetic retinopathy, vitrectomy has seen its role evolve. "Once upon a time, we thought vitrectomy might be a generalized answer for diabetic macular edema," said Dr. Bhavsar. "It, too, can help in a subset of patients, but there is no great evidence for using it across the board on a regular basis."

According to Dr. Regillo, vitrectomy remains a good option for treating the complications of proliferative diabetic retinopathy, such as vitreous hemorrhages or progressive tractional retinal detachment that is threatening or affecting vision.

For DME, the data are conflicting, and the role of vitrectomy is less clear cut, said Dr. Regillo. "However, when there is evidence of vitreoretinal traction or an epiretinal membrane that's exacerbating DME, vitrectomy with membrane peeling may provide some benefit." The only downside of performing this procedure for DME, he said, is that anything injected into the eye after removal of the vitreous gel clears faster.

RESOURCES FOR YOUR PATIENTS

In their homes. Make sure that all your patients with diabetes know about EyeSmart, the Academy's online source for public information about eye health and disease (www.geteyesmart.org).

By clicking on "Diabetic Retinopathy" in the list of eye conditions, your patients can open the door to a suite of expert—yet easily understandable—presentations in the form of text, pictures, and video animations. Topics include the symptoms, causes, progression, and medical and surgical treatment of diabetic retinopathy and diabetic macular edema.

And at your office. Patient education materials can help reinforce the information and advice you give during appointments. Visit the Academy Store (www.aao.org/store) for brochures, handouts, and videos, available in English and Spanish.

"So if you are relying on anti-VEGF therapy after vitrectomy, the anti-VEGF effect doesn't last as long."

BENEFICIAL COMBINATION? Some believe that anti-VEGF agents given before or during vitrectomy may improve surgical results and decrease early postoperative complications, said Dr. Bressler. "But this hasn't been tested in a controlled way," she said, adding that making inroads in surgical management has been more limited, in part, due to the challenges of conducting surgical studies.

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MEET THE EXPERTS




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