Retinal PHYSICIAN
MARCH 2019

A CME ACTIVITY

Diabetic Retinopathy from TRIALS TO TREATMENT

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THIS ACTIVITY IS SUPPORTED BY AN INDEPENDENT MEDICAL EDUCATIONAL GRANT FROM REGENERON PHARMACEUTICALS, INC. AND OPTOS.

RELEASE DATE: 3/1/19 | EXPIRATION DATE: 3/1/20

TARGET AUDIENCE AND GOAL STATEMENT

THIS ACTIVITY IS DESIGNED TO MEET THE EDUCATIONAL NEED OF RETINA SPECIALISTS, COMPREHENSIVE OPHTHALMOLOGISTS, RESIDENTS AND FELLOWS IN TRAINING, AND ALLIED HEALTHCARE PROFESSIONALS INVOLVED IN THE CARE OF PATIENTS WITH RETINAL DISEASES.

LEARNING OBJECTIVES

After completing this activity, the participant should be better able to:

- Accurately diagnose and grade DR using imaging technology
- Treat DME and DR optimally
- Apply insights gleaned from clinical trial data to clinical practice

ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Ultimate Medical Academy (UMA) and KCY Education Group. UMA is accredited by the ACCME to provide continuing medical education for physicians.

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PLANNER DISCLOSURES

The following have no relevant financial relationships to disclose:

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COMMERCIAL SUPPORT

This activity is supported by an independent medical educational grant from Regeneron Pharmaceuticals, Inc. and Optos.

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AN OVERVIEW OF LONG-STANDING AND EMERGING TECHNOLOGIES AND THEIR IMPACT ON DIAGNOSIS AND TREATMENT

Imaging in Diabetic Eye Disease

→ By Justis P. Ehlers, MD

Retina has become an imaging-driven subspecialty. Imaging is the cornerstone of diabetic retinopathy evaluation, and we now manage diabetic macular edema (DME) primarily through image-guided feedback.

Imaging enables us to ascertain overall disease severity, to visualize the extent of vitreoretinal interface abnormalities, and to understand some of the anatomic relationships that we cannot see as readily when looking into the eye.

The goal of this article is to provide a high-level overview across imaging technologies for diabetic retinopathy and to explore some unique opportunities for higher-order image analysis in the future.

FUNDUS PHOTOGRAPHY

Fundus photography provides important objective information about the severity of retinopathy, and it has significant utility for monitoring disease progression. In addition, it's a great tool for educating patients and for facilitating physician-to-physician communication.

Grading the severity of diabetic retinopathy is typically based on the appearance of the fundus on clinical exams or in photographs. A modified system, simplified from those grading systems used in clinical trials, is typically used to grade disease severity in the clinic setting.

OPTICAL COHERENCE TOMOGRAPHY (OCT)

OCT is the primary tool for evaluating anatomic information, including identification of DME and vitreoretinal interface abnormalities. OCT is often used to evaluate any patient who has some level of vision loss with diabetes. Macular edema is often subclinical, and OCT is better at detecting subtle cystic changes compared to clinical examinations.

OCT is noninvasive, widely available, and fast. It also provides quantitative data in terms of macular thickness, which may help us detect changes from visit to visit and guide treatment decision-making.

Retinal thickness maps provide generalized information, but they don't provide direct information on pathologic features or retinal layer integrity. Reviewing the actual B-scans from the OCT enables differentiation of the etiologies of map abnormalities, such as thickening from an epiretinal membrane or from macular edema, which are factors that will influence our treatment decisions.

The retinal thickness and change analysis maps are helpful for tracking disease progression and evaluating treatment efficacy, and may also be used as educational tools to engage patients in their treatment.

OCT ANGIOGRAPHY

OCT angiography (OCTA) is a newer modality that can provide high-level detail around nonperfusion and vascular abnormalities. OCTA enables visualization of vascular alterations, such as microaneurysms, foveal avascular zone

irregularity, capillary nonperfusion, and vascular remodeling.

As this technology advances, there will be more opportunities to quantify various parameters, such as vascular perfusion. Utilizing these quantitative metrics may be particularly useful for evaluating progression over time.

FLUORESCEIN ANGIOGRAPHY (FA) AND ULTRA-WIDEFIELD FA

Fluorescein angiography can help confirm diagnoses and identify microaneurysms and specific leakage patterns — historically described as focal and diffuse — although these have become less important in terms of our treatment decisions as intravitreal pharmacotherapy has become the gold standard for managing this disease.

Fluorescein angiography remains a critical part of diabetic eye disease imaging. It helps to identify underlying ischemia, neovascularization that may not be readily visualized on clinical examination, and overall leakage activity. The panretinal assessment capability of ultra-widefield angiography provides a comprehensive evaluation of retinal vascular disease burden with a single image. This is emerging as a critical tool in the evaluation of diabetic retinopathy.

TOWARD MORE PRECISE MEDICINE

Multiple current and emerging therapies have been shown to improve Diabetic Retinopathy Severity Scale scores, and next-generation imaging provides more information that may help us better understand our opportunities.

Image-guided therapy with OCT has defined our treatment approach for DME, age-related macular degeneration, and retinal vein occlusion. We now have devices that use artificial intelligence to diagnose diabetic retinopathy on fundus photographs.

Emerging opportunities for quantitative metrics may provide new insights into disease activity and for image-guided therapy. Ultra-widefield fluorescein angiography is being employed to identify and quantify microaneurysms, leakage, and ischemia. Many of these quantitative features have been linked to key outcomes in diabetic eye disease, such as diabetic retinopathy progression and the overall risk of DME. Many of these factors can be modulated with current treatments.

New clinical trials, such as Protocol AA, (See "Protocol AA Promises New Insights" above) will help inform the retina community about the role of emerging imaging technologies, including widefield imaging and quantitative metrics.

The future may involve combining imaging technologies and advanced software analysis techniques to detect unique biomarkers that may help us understand risk for progression, as well as predictive image features for optimal therapeutics. ●

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Protocol AA Promises New Insights

One of the great opportunities for the future and one of the great challenges today is that our clinical trial data are limited in regards to the role of ultra-widefield fluorescein angiography in diabetic eye disease. The Diabetic Retinopathy Clinical Research Network Protocol AA is currently examining this issue.[1]

Protocol AA is a prospective, observational 4-year longitudinal study. Investigators are evaluating the impact of peripheral lesions and ultra-widefield imaging on the risk of diabetic retinopathy progression. The primary outcome is the relative risk of worsening of diabetic retinopathy severity over time.

This is a large study examining two groups: those with and those without predominantly peripheral lesions on ultra-widefield images at baseline. Protocol AA will provide tremendous new insights into the importance of the retinal periphery and the distribution of diabetic lesions.

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Update on Managing Diabetic Macular Edema

→ By Diana V. Do, MD

Ongoing research by the Diabetic Retinopathy Clinical Research (DRCR) Network and others continues to inform our treatment decisions for diabetic macular edema (DME). While anti-VEGF is typically our first-line therapy, we are challenged every day to adapt to each individual case, the disease course, and often-unpredictable responses to treatment.

TREATMENT-NAÏVE DME

A 62-year-old man with DME was experiencing blurry vision in his left eye. He had not received any ocular treatments for his DME and he was phakic. His visual acuity was 20/60, and his HbA1c was 8.1%. Imaging showed obvious center-involved edema and diffuse leakage in the posterior pole. What is the most appropriate management strategy for this patient?

DRCR Protocol T found that all three anti-VEGF agents — aflibercept (Eylea, Regeneron), off-label bevacizumab (Avastin, Genentech), and ranibizumab (Lucentis, Genentech) — are effective in improving visual acuity, with aflibercept showing a slight advantage over bevacizumab.[1] Both aflibercept and ranibizumab were more effective in reducing retinal thickness compared with bevacizumab.

Protocol T also found that all three anti-VEGF agents were non-inferior to each other in patients who started therapy with 20/40 or better visual acuity. There was a slight advantage to aflibercept compared to bevacizumab at 2 years in patients who began treatment with visual acuity of 20/50 or worse. These results prompted many retina specialists to think that aflibercept might be more effective than the other two agents.

Following the DRCR Protocol T strict retreatment criteria, most injections were administered in the first year. In year 2, that number declined by almost half.

The conclusion from the 2-year data was that all three drugs were effective and safe. At worse levels of visual acuity, aflibercept was more effective than bevacizumab. Both ranibizumab and aflibercept were noninferior to each other at the year 2 timepoint.

In this patient case, I started with ranibizumab. After two injections, the edema was significantly reduced, and visual acuity was slightly improved. I am continuing to treat with ranibizumab on an as-needed basis.

PERSISTENT DME AFTER INITIAL ANTI-VEGF

A 52-year-old woman who is phakic has a history of proliferative diabetic retinopathy (PDR) treated with laser. She has persistent DME after starting treatment with bevacizumab. Her visual acuity is 20/80.

The patient was unable to adhere to a strict 4-week treatment schedule, so we were treating her every 5 weeks. After two injections, significant edema persisted. Should we continue with the same course of treatment, or should we switch to a different anti-VEGF agent or an intravitreal steroid?

This situation begs the question: How do you define a suboptimal response to anti-VEGF therapy? The majority of our audience (67%) looks for a robust improvement after three anti-VEGF injections. Two of our panelists would switch to aflibercept after two bevacizumab treatments, while one would stay the course for another two or three treatments.

Published evidence has also demonstrated that intravitreal corticosteroids are effective in eyes with DME, but we must be mindful of side effects, specifically, cataract progression and IOP elevation.[2-4]

More recently, DRCR Protocol U studied eyes with persistent edema after therapy with ranibizumab.[5] Patients were randomly assigned to either a combination of the

dexamethasone implant (Ozurdex, Allergan) and ranibizumab or ranibizumab alone. The visual acuity results were similar in both groups. A better reduction in retinal thickness (seen in the combination group) did not necessarily translate to a better improvement in visual acuity.

Also, keep in mind that all steroids are not equal. For example, the dexamethasone implant lasts about 3 to 4 months

> *"Clearly, anti-VEGF therapy is the first-line treatment for DME. And all three anti-VEGF agents are effective."*

in the eye, while the fluocinolone acetonide implant (Iluvien, Alimera Sciences) delivers steroid for up to 36 months.

The USER study, a retrospective review, evaluated real-world use of the fluocinolone acetonide implant.[6] It showed that patients received, on average, one anti-VEGF injection every 3 months. After treatment with one fluocinolone acetonide implant, the retinal thickness stayed reduced and, on average, patients did not need adjuvant therapy for 16 months. If you believe the treatment burden is high with anti-VEGF alone, perhaps the fluocinolone acetonide implant is a good choice in select patients.

The USER study also evaluated IOP changes. Patients were tested for a steroid response prior to receiving the implant. If the patient did not experience an elevation in IOP with a shorter acting steroid (topical or intraocular) challenge test, they were unlikely to develop an IOP increase after the fluocinolone acetonide was implanted. This suggests that ophthalmologists might be able to predict which patients can tolerate ocular steroids without the side effect of elevated eye pressure. These patients would be good candidates to receive a long-acting intraocular steroid, such as the fluocinolone acetonide implant.

In the case mentioned above, I switched the patient to aflibercept because she was having a sub-optimal response to bevacizumab. After starting aflibercept, the DME appears to be decreasing and we are continuing to manage her DME.

KEY TAKEAWAYS FOR DME

Clearly, anti-VEGF therapy is the first-line treatment for DME. And all three anti-VEGF agents are effective. In some eyes, particularly those with worse vision initially, aflibercept may be more advantageous than bevacizumab.

We currently don't have a consensus on the definition of a suboptimal response to anti-VEGF or how to treat these eyes. Certainly, steroids can be a good option for patients who don't experience an increase in IOP when pretested with a steroid.

Fortunately, as retina specialists and ophthalmologists, we have a variety of effective therapies for DME. It's important to aggressively treat DME to prevent vision loss.

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Is Increasing the Dose of Anti-VEGF Beneficial?

READ-3 was a randomized clinical study evaluating high-dose ranibizumab.[1] The current FDA-approved dose is 0.3 mg of ranibizumab for DME. At the time we launched this study, that had not been approved yet, so we used 0.5 mg ranibizumab and compared that with 2.0 mg of ranibizumab, quadrupling the dose.

To our surprise, in a head-to-head comparison, we found no additional benefit to quadrupling the dose of ranibizumab in DME. The visual acuity and OCT retinal thickness outcomes were similar to those with the 0.5 mg dose.

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KEY STUDIES CONFIRM THE ROLE OF ANTI-VEGF AS A FIRST-LINE THERAPY AND EXPLORE PREVENTIVE POTENTIAL

Impact of Anti-VEGF on Treatment and Prevention of Proliferative Diabetic Retinopathy

→ By Jeffrey G. Gross, MD

Panretinal photocoagulation (PRP) has been an effective treatment for proliferative diabetic retinopathy (PDR) for decades. It reduces the risk of vision loss, but it is destructive and can cause peripheral visual field loss, night vision loss, and exacerbation of diabetic macular edema (DME). What's more, 5% of eyes still experience severe vision loss despite adequate PRP.

Anti-VEGF reduces the risk of diabetic retinopathy progression and increases the chance of improving the retinopathy level. In case after case, I have seen neovascularization of the disc regress and resolve, sometimes after a single injection.

My focus here is on three key studies: the Diabetic Retinopathy Clinical Research (DRCR) Network Protocol S, which I consider a great leap in treating PDR; Protocol W, an ongoing study that addresses small steps toward prevention; and PANORAMA, which I call moon-walking or reversing the steps of nonproliferative diabetic retinopathy (NPDR).[1-4]

PROTOCOL S

Protocol S provided evidence supporting the first major advance for the treatment of PDR in 40 years.[1,2] In this multicenter trial of treatment-naïve eyes with or without DME, participants were randomly assigned to either PRP (with ranibizumab [Lucentis, Genentech] as needed for DME treatment) or ranibizumab (with PRP for treatment failure).

In year 1, the PRP group had assessment visits every 16 weeks, while the ranibizumab group had assessments every 4 weeks. Both groups were simultaneously evaluated for DME. In the subsequent years, visit intervals for the ranibizumab group could be extended up to 16 weeks if injections were continually deferred.

In year 2, the mean number of injections administered in the ranibizumab group was 3.3 compared with 7.1 in the first year (all eyes in this group at baseline were required to have 4 monthly injections), and most had 6 injections before there were any deferrals. In subsequent years, the number of injections per year decreased. Most eyes received 4 to 9 injections in year 1. By year 5, almost 40% of patients received no injections, suggesting that anti-VEGF can be a durable treatment.

At 2 years, the ranibizumab group showed a robust improvement in visual acuity, which peaked between 32 and 52 weeks compared to the PRP group. Over the next 3 years, both groups showed improved visual acuity, and by the end of the study, there was almost no difference between the two groups.

Visual field loss was much worse in the PRP group at 2 years, and this group continued to lose ground. The anti-VEGF group began to lose visual field at 2 years, and this was an unexpected finding that requires further investigation.

At 5 years, about one-third of eyes improved from PDR to NPDR; 10% had no diabetic retinopathy and almost 50% improved by 2 or more steps on the Diabetic Retinopathy Severity Scale (DRSS). The median number of visits for the anti-VEGF group was twice that of the PRP group, and there were four times as many injections administered in the anti-VEGF group.

PRP eyes had a much higher incidence of retinal detachments than those in the anti-VEGF group, while vitreous hemorrhage was fairly common and equal in both groups.

The need for vitrectomy was higher in the PRP group. APTC events were similar in both groups.

Protocol S showed that mean change in visual acuity with ranibizumab was noninferior to PRP at 5 years. The ranibizumab group had less visual field loss, required fewer surgeries, and had less DME. In addition, ranibizumab was cost-effective when DME was present. On the other hand, PRP required fewer visits and fewer injections, and it was cost-effective when DME was not present.

This study showed that either ranibizumab or PRP is a viable treatment for PDR, but patient-specific factors — such as anticipated visit compliance, cost, and frequency of visits — need to be discussed.

PROTOCOL W

In the Early Treatment Diabetic Retinopathy Study, more than 50% of eyes developed PDR over 1 year and 60% over 5 years.[5] Investigators showed that early PRP in some patients with diabetic retinopathy significantly reduced the progression to PDR.[5]

Also, in the ETDRS, 15% of eyes developed DME by 2 years, and in Protocol R, 14% developed DME or required treatment by 1 year.[5,6]

We have strong evidence from the RISE and RIDE trials that PDR outcomes are markedly reduced in eyes that are treated with monthly anti-VEGF therapy, and PDR was moderately reduced in eyes that received regular dosing during the first year of treatment in Protocol I.[7,8] In Protocol S, about 47% of eyes treated with anti-VEGF improved by two or more steps at 2 years.[1]

Would an earlier but less frequent dosing regimen result in similar favorable anatomic outcomes? Would favorable anatomic outcomes result in favorable visual acuity outcomes? Protocol W investigators are exploring these questions.

The primary objectives of Protocol W are twofold:

1) to determine the efficacy and safety of intravitreous aflibercept (Eylea, Regeneron) versus sham for preventing PDR or center-involving DME in eyes at high risk for these complications; and

2) to compare long-term visual outcomes in eyes that receive anti-VEGF therapy early in the disease course with those that are observed initially and treated only if high-risk PDR or center-involving DME with vision loss develops.[3]

Protocol W is a 4-year study, with visits at 1, 2, and 4 months and every 4 months thereafter. Injections are required at every visit through 2 years, and subsequently, based on diabetic retinopathy severity. If PDR or DME develops, more frequent anti-VEGF injections are administered.

Findings from Protocol W may help us decide if we should use anti-VEGF therapy early in the course of the disease to reduce the future potential treatment burden, achieve better long-term visual acuity outcomes, and provide a new strategy to prevent vision-threatening complications.

PANORAMA STUDY

PANORAMA is a phase 3 study looking at the efficacy and safety of intravitreal aflibercept in eyes with moderately severe to severe NPDR (DRSS level 47 and 53).[4] Eyes in Group 1 are treated every 16 weeks after three initial monthly doses and 1 q8 interval. Eyes in Group 2 are treated every 8 weeks after five initial monthly doses; after week 52, the treatment schedule is flexible. The primary endpoint is the proportion of eyes improving by 2 or more steps on the DRSS.

This is what I call the anti-VEGF moon-walk. Essentially, we are reversing the steps of NPDR.

At 24 weeks, almost 60% of all treated eyes showed a 2-step improvement in DRSS from baseline compared with 6% in the sham group, and about 9% showed a 3-step improvement compared with less than 1% in the sham group. Visual acuity was improved, and OCT thickness was reduced in all treatment groups. About 25% of eyes in the sham group developed PDR or DME compared with 4.5% in the treatment groups, and the proportion developing vision-threatening complications was much higher in the sham group. No new safety signals were identified.

CONCLUSION

Published studies have confirmed the role of anti-VEGF as a first-line therapy and ongoing studies aim to explore its role as a preventive measure.

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