

# Ultra-widefield Fluorescein Angiography in the Diagnosis and Management of Diabetic Retinopathy

BY IVAN J. SUÑER, MD

**D**iabetic retinopathy is the most common retinal vascular disease. It is also the leading cause of legal blindness in patients 20 to 74 years of age in the United States.<sup>1</sup> Fortunately, we are in the dawn of a new age of pharmacotherapeutic and imaging developments that have better armed us in the diagnosis and treatment of diabetic retinopathy. A particularly fascinating and revealing imaging modality has been ultra-widefield fluorescein angiography (Optos P200MA, Dunfermline, Scotland).

State-of-the-art ultra-widefield fluorescein angiography produces real-time, high-resolution angiographic images of the posterior pole (resmax mode) and approximately 200° of the fundus (standard ultra-widefield mode). This technology, which is based on scanning laser ophthalmoscopy and a novel mirror system, is superior to montaged retinal images, as it provides a true dynamic study of the majority of the retinal vasculature, rather than only snapshots of temporal sequences of different areas of the retina. This not only provides us with excellent resolution for evaluation of the macula, but it also affords us with insights as to the possible role of the peripheral retinal vasculature in the pathogenesis of diabetic macular edema (DME). It also allows us to evaluate the effects of our therapeutic interventions.

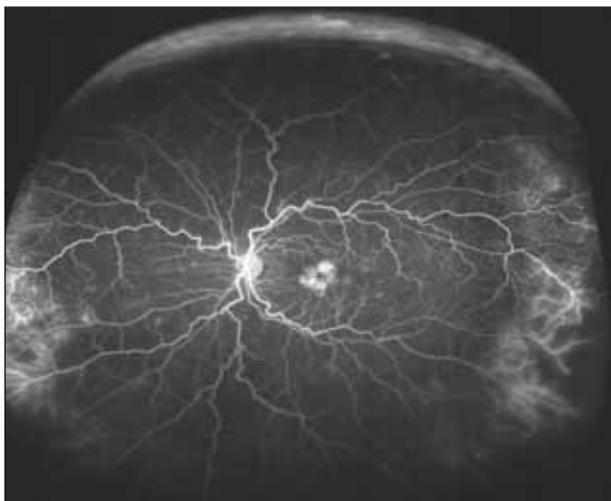
## ULTRA-WIDEFIELD FLUORESCEIN ANGIOGRAPHY IN DME

DME is the most common pathology leading to legal blindness in diabetic retinopathy. Although we now have

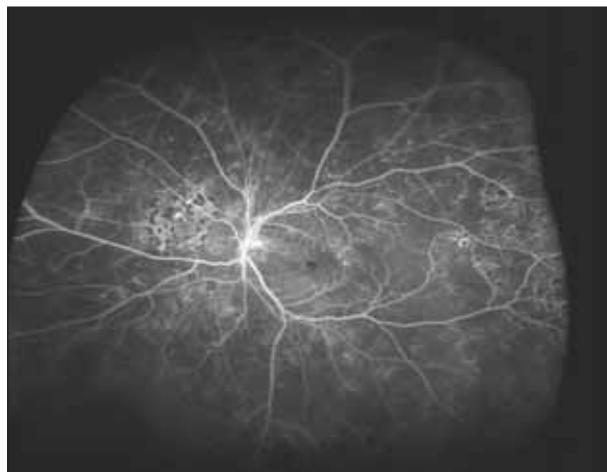
Ultra-widefield fluorescein angiography provides a true dynamic study of the majority of the retinal vasculature.

many available therapies for DME, we cannot always predict which one will be most effective for a particular patient. Macular laser has been the standard, as shown in the Early Treatment for Diabetic Retinopathy Study and Diabetic Retinopathy Clinical Research Network studies. Intravitreal steroids and vascular endothelial growth factor (VEGF) antagonists have also demonstrated therapeutic benefits in smaller studies. Steroids may induce the morbidity of cataracts and glaucoma, however, especially with repeated treatments; and VEGF antagonists are effective in some patients with DME but require repeated injections. These latter treatments are considered off-label, and retina specialists cannot always predict which of these treatments will be most effective for an individual patient before treatment is given.

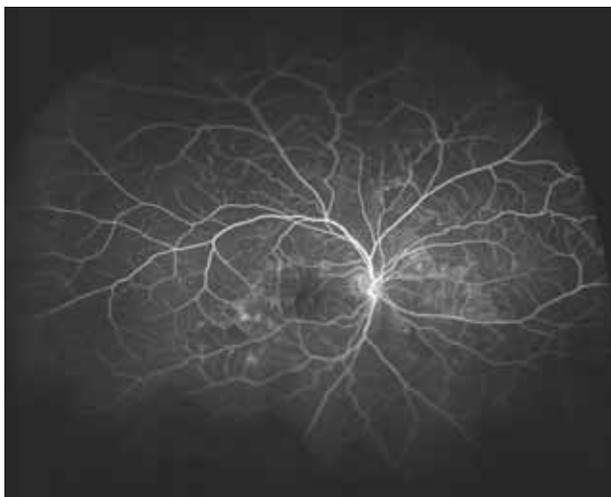
Traditionally, retina specialists have been able to evaluate DME with conventional fluorescein angiography, which provided a view of only the macula. At times, with excellent pupillary dilation, a motivated patient, and an excellent photographer, peripheral sweeps may be available, but certainly not in a standard and reproducible fashion. My experience with ultra-widefield fluorescein angiogra-



**Figure 1.** Ultra-widefield fluorescein angiography of patient with diabetic macular edema and associated peripheral nonperfusion. Note the “brushfire” edge of late leakage demarcating perfused and nonperfused retina.



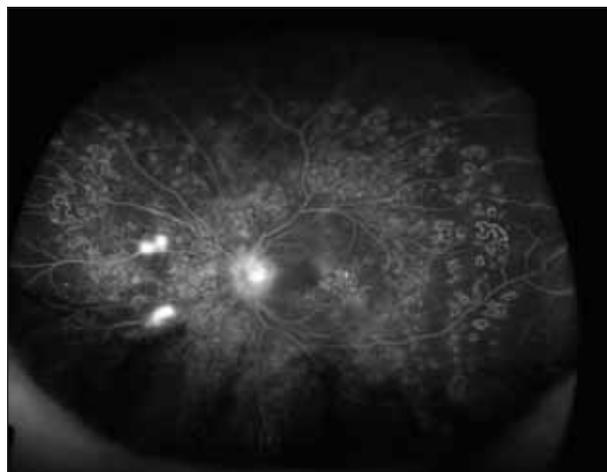
**Figure 2.** Ultra-widefield fluorescein angiography image of patient with diabetic macular edema and associated peripheral nonperfusion. Patient was treated under a research protocol (RaScaL study) with intravitreal ranibizumab and scatter laser treatment to areas of nonperfused retina on ultra-widefield fluorescein angiography.



**Figure 3.** Ultra-widefield fluorescein angiography image of patient with severe peripheral retinal nonperfusion secondary to diabetic retinopathy.

phy using the Optos P200MA for imaging patients with DME has been eye-opening.

We have seen a considerable number of patients with DME associated with profound capillary dropout or nonperfusion in the retinal periphery (Figure 1). The potential involvement of peripheral nonperfusion in DME was a concept espoused by Shimizu in Japan and by Friberg in the United States, among others, decades ago. This relationship is especially relevant today, given the known relationship of elevated levels of VEGF in



**Figure 4.** Ultra-widefield fluorescein angiography image of patient with proliferative diabetic retinopathy. Patient has had panretinal photocoagulation but has residual active neovascularization with leakage.

DME, the potent vascular permeability effects of VEGF on the retinal vasculature, and the demonstrated benefit of VEGF antagonists on many patients with DME. Proof of concept and application of this theory, however, was limited by available imaging technologies. Now, with the availability of ultra-widefield fluorescein angiography, which can easily image the retinal periphery in standard fashion, therapeutic interventions based on this relationship may be explored.

In all likelihood, DME represents a common clinical

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phenotype for multiple pathologies, such as localized vascular leakage, inflammation, vitreoretinal traction, localized macular ischemia, or more diffuse retinal ischemia, which may be present individually or in combination in a particular patient. This represents a fantastic opportunity to marry the novel imaging technologies (optical coherence tomography and ultra-widefield fluorescein angiography) in classifying DME by these features with the therapeutic options that specifically address the findings.

We are currently pursuing such a strategy in a small pilot trial, the RaScaL (Ranibizumab + Scatter Laser) study. We are identifying patients with DME and associated peripheral nonperfusion. We hypothesize that these patients have DME that is driven predominantly by peripheral retinal ischemia. These patients are randomized to either conventional treatment (macular laser plus intravitreal triamcinolone) or a novel treatment strategy of ultra-widefield fluorescein angiography-directed peripheral laser plus intravitreal ranibizumab (Lucentis, Genentech, Inc.). The primary outcomes are vision and recurrence of DME necessitating retreatment at 6 months. In theory, if the DME is driven by the peripheral ischemia, scatter laser ablation of the peripheral retina should stop the drive for VEGF release, and no further interventions should be necessary. The initial ranibizumab injection would block available VEGF in the vitreous cavity. Recruitment is 75% complete, and preliminary results have been encouraging. Many of these patients stabilize with one treatment session of ultra-widefield fluorescein angiography-directed peripheral scatter laser and ranibizumab (Figure 2).

## ULTRA-WIDEFIELD FLUORESCIN ANGIOGRAPHY IN PDR

Proliferative diabetic retinopathy (PDR), although less common than DME, may have more devastating visual consequences. It can result in vitreous hemorrhage, tractional retinal detachment, and combined traction and rhegmatogenous retinal detachment.

The mainstay of treatment is panretinal photocoagulation (PRP) disease. This is extremely effective when performed early in the course. An excellent adjunctive thera-

py has been treatment with VEGF antagonists, which may be effective in turning back the clock on the neovascular process and sometimes aiding in clearance of vitreous hemorrhage, thereby buying time to perform PRP.

However, there are still several lingering issues with PDR. Should we treat earlier than when severely ischemic patients meet high-risk criteria if we can identify those at risk for progression? If we can diagnose patients with severe peripheral nonperfusion on ultra-widefield fluorescein angiography, they may be treated early with PRP and, hopefully, avert later neovascular or perhaps even macular edema complications (Figure 3).

Another controversial question is how much PRP is enough, or, better stated, are we placing excessively heavy PRP treatment, resulting in morbidity from loss of visual field and night vision? Ultra-widefield fluorescein angiography may allow us to treat with a moderate pattern and assess postoperatively for residual ischemia and late leakage from neovascularization. Also, how does one proceed in a patient with progressive proliferation despite initial PRP? Ultra-widefield fluorescein angiography may give us clues if we see areas of untreated nonperfusion or areas of diffuse late leakage in the periphery (Figure 4). These patients may be amenable to additional scatter laser as opposed to vitrectomy surgery.

## FINAL THOUGHTS

We are entering an exciting time in the treatment of retinal vascular diseases such as diabetic retinopathy. Some of these paradigms and concepts are applicable also to branch retinal vein occlusion, central retinal vein occlusion, retinal vasculitides, ocular ischemic syndromes, and ocular tumors (both before and after radiation treatment).

Ultra-widefield fluorescein angiography is an elegant diagnostic imaging modality that has improved our ability to diagnose and classify some of these conditions. Even more exciting for us and for our patients is the potential coupling of this elegant diagnostic imaging modality with novel pharmacologic and laser treatment strategies to provide therapies that target the specific underlying pathobiology of their conditions. ■

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