Characterization of Ischemic Index Using Ultra-widefield Fluorescein Angiography in Patients With Focal and Diffuse Recalcitrant Diabetic Macular Edema

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• PURPOSE: To explore the association of angiographic nonperfusion in focal and diffuse recalcitrant diabetic macular edema (DME) in diabetic retinopathy (DR).

• DESIGN: A retrospective, observational case series of patients with the diagnosis of recalcitrant DME for at least 2 years placed into 1 of 4 cohorts based on the degree of DR.

• METHODS: A total of 148 eyes of 76 patients met the inclusion criteria at 1 academic institution. Ultra-widefield fluorescein angiography (FA) images and spectral-domain optical coherence tomography (SD OCT) images were obtained on all patients. Ultra-widefield FA images were graded for quantity of nonperfusion, which was used to calculate ischemic index. Main outcome measures were mean ischemic index, mean change in central macular thickness (CMT), and mean number of macular photocoagulation treatments over the 2-year study period.

• RESULTS: The mean ischemic index was 47% (SD 25%; range 0%-99%). The mean ischemic index of eyes within Cohorts 1, 2, 3, and 4 was 0%, 34% (range 16%-51%), 53% (range 32%-89%), and 65% (range 47%-99%), respectively. The mean percentage decrease in CMT in Cohorts 1, 2, 3, and 4 were 25.2%, 19.1%, 11.6%, and 7.2%, respectively. The mean number of macular photocoagulation treatments in Cohorts 1, 2, 3, and 4 was 2.3, 4.8, 5.3, and 5.7, respectively.

• CONCLUSIONS: Eyes with larger areas of retinal nonperfusion and greater severity of DR were found to have the most recalcitrant DME, as evidenced by a greater number of macular photocoagulation treatments and less reduction in SD OCT CMT compared with eyes without retinal nonperfusion. Areas of untreated retinal nonperfusion may generate biochemical mediators that promote ischemia and recalcitrant DME. (Am J Ophthalmol 2013;■:■–■. © 2013 by Elsevier Inc. All rights reserved.)

DIABETIC MACULAR EDEMA (DME) CONTINUES TO be a common cause of vision loss in patients with diabetic retinopathy (DR) and decreased vision-related quality of life in working-aged Americans.[1] The prevalence of DME among US diabetics approaches 30% in adults who have had diabetes for 20 years or more,[2] and varies with the stage of diabetic retinopathy. It can occur at any stage of diabetes and can predate the appearance of other findings of diabetic retinopathy. In eyes with mild nonproliferative diabetic retinopathy (NPDR), the prevalence of DME is 3%. This rises to 38% in eyes with moderate to severe NPDR and reaches 71% in eyes with proliferative diabetic retinopathy (PDR).[3]

For nearly 3 decades, the standard therapy and only approved therapy for DME has been focal/grid laser photocoagulation.[4] The Early Treatment Diabetic Retinopathy Study (ETDRS) found a 50% reduction in the likelihood of severe vision loss with focal/grid macular laser.[5] The Diabetic Retinopathy Clinical Research Network more recently reported a 10-letter gain in nearly one-third of patients treated with macular photocoagulation, but reported that 19% experience progressive visual loss.[6] The increasing incidence of sight-threatening DME with limited visual improvement following focal/grid laser treatment has challenged clinical researchers to develop more efficient alternatives for the diagnosis and treatment of DME. Several clinical trials, including READ-2[7] and RISE and RIDE,[8] have investigated the use of anti–vascular endothelial factor (anti-VEGF) for DME and have shown rapid, sustained visual improvement. Given the favorable results of these trials, ranibizumab was recently FDA-approved for the treatment of DME.

Diagnostic imaging has played an increasing role in eye care in recent years. Under optimal conditions, traditional angiographic methods employing film or digital fundus cameras can capture 50-degree views. With 7 standard fields, a 75-degree view of the fundus can be obtained. Recent advances in scanning laser ophthalmoscope (SLO)

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technology now allow for consistently reproducible high-resolution angiographic images of the peripheral retina. This development enables panretinal angiographic assessment of retinal vascular perfusion without the need to extrapolate nonsimultaneous angiographic views within a montage. Contact lens–based systems such as the Ocular Staurenghi 230 SLO Retina Lens (Ocular Instruments, Bellevue, Washington, USA) can image out to the 120-degree range. Ultra-widefield fluorescein angiography (FA) using the Optos C200 MA noncontact SLO (Optos PLC, Dunfermine, UK) provides visualization up to 200 degrees.[9]

Researchers (Schwartz SD, et al. IOVS 2005;46:ARVO E-Abstract 4793) have hypothesized the association between peripheral nonperfusion and the presence of neovascularization and macular edema.[10] For patients who have clinically significant DME involving the center of the macula, and high-risk PDR requiring panretinal photocoagulation (PRP), combined focal/grid and PRP laser is recommended by the ETDRS Group[5] and Preferred Practice Pattern (American Academy of Ophthalmology, 2003).[4] Although the ETDRS and other studies provided excellent clinical recommendations, patient management still remains challenging. Despite following current practice patterns, a subset of patients with DME continues to have persistent or recalcitrant DME in spite of several sessions of focal/grid macular photocoagulation or monthly intravitreal injections of VEGF inhibitors and/or intravitreal steroids. A potential explanation for current challenges was nicely reviewed in a recent publication by Wessel and associates[11] showing that peripheral retinal ischemia is significantly correlated with DME in treatment-naïve patients with DR using a clinically practical device.

In this study our main objective was to study patients with focal and diffuse recalcitrant DME and determine the relationship between peripheral nonperfusion assessed with ultra-widefield FA in patients with different severities of DR. We hypothesized that zones of peripheral retinal nonperfusion may generate biochemical mediators such as VEGF and other cytokines that promote recalcitrant DME and cause a suboptimal response to standard therapies.

METHODS

• **STUDY POPULATION:** A retrospective, consecutive, observational case series was carried out at 1 academic institution with the prospective approval of the Illinois Eye Institute Institutional Review Board (IRB), and therefore has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and HIPAA regulations. A chart review was performed on all patients seen with a diagnosis of diabetes mellitus type 2 from September 2, 2010 to March 30, 2012. Approximately 1156 patients diagnosed with diabetes mellitus type 2 were seen in our clinic, of which 76 patients (148 eyes) with recalcitrant DME, who were currently under the care of the University of Chicago Section of Ophthalmology Vitreoretinal Service and met eligibility criteria, were invited to participate in this study. Participants had to be at least 18 years of age or older, have type 2 diabetes, and be diagnosed with recalcitrant DME for at least 2 years. All patients provided informed consent before participation in the study.

Recalcitrant DME was defined as having clinically significant diabetic macular edema (CSDME) with a center macular thickness greater than 300 μm as measured by spectral-domain optical coherence tomography (SD OCT), for a minimum of 2 years duration despite standard therapies. For eyes that met eligibility criteria, the treatment algorithm for CSDME was macular photocoagulation at 3-month intervals only if the study eye had an increase in CMT or decrease in visual acuity ≥5 ETDRS letters. For eyes that met eligibility criteria, the treatment algorithm for PDR was a complete 360 degrees of PRP (between 800 and 1100 spots) at the first visit and then retreatment with PRP at 3-month intervals only if there were any clinical signs of PDR based on ETDRS criteria. Exclusion criteria included diagnosis of ocular disease other than diabetic retinopathy that may produce macular edema (eg, retinal artery or vein occlusion, sickle cell retinopathy, or uveitis) identified by clinical examination, eyes with vitreomacular traction or epiretinal membrane on SD OCT, eyes with tractional retinal detachment identified by clinical examination, eyes that had undergone previous vitreoretinal surgery, eyes that had undergone an anti-VEGF or steroid intravitreal injection within the 2-year study period, eyes with significant media opacities (ie, cataract, vitreous hemorrhage), and eyes with image artifact (eyelids) that precluded photographic evaluation of macular edema and peripheral retinal capillary perfusion status.

• **IMAGING:** All subjects underwent ultra-widefield FA using the Optos C200 MA imaging system (Optos PLC) and SD OCT (Cirrus OCT; Carl Zeiss Meditec Inc, Dublin, California, USA) performed at day 1. All ultra-widefield FA images were obtained with the Optos C200 MA (Optos PLC) after standard intravenous infusion of 5 cc of sodium fluorescein 10%. Images were digitally archived and reviewed using the V2 Vantage Review Software (Optos PLC), allowing high-resolution zoom functionality for the review of all images.

SD OCT images were obtained for each patient to confirm the presence of macular thickening. For each patient, horizontal and vertical SD OCT scans of 6 mm length through the fixation point were obtained for evaluation. An average thickness value was obtained after reviewing both scans. CMT was calculated using the calipers feature on the SD OCT instrument, with manual correction as needed.[12]

• **DATA COLLECTION AND DEFINITIONS:** All ultra-widefield FA images were saved as high-quality jpeg files

and then transferred to Apple Preview software. One trained masked grader (R.D.P.) selected 1 or more images from each angiogram series during the arteriovenous phase (between 45 seconds and 2 minutes) and graded all 148 angiograms for the presence or absence of retinal nonperfusion of ≥1 disc area, neovascularization (defined as focal leakage ≥2 disc diameters), focal macular edema (defined as late hyperfluorescence ≥500 μm diameter covering less than 75% of the macula), and diffuse macular edema (defined as late hyperfluorescence covering ≥75% of the macula).[10,13] The best image was chosen based on the largest field of view and the greatest image clarity. Figure 1 illustrates typical findings encountered when grading.

An ischemic index was calculated using previously described methodology.[10,14] Briefly, the area of capillary nonperfusion seen in the arteriovenous phase image was encircled using the area measurement function and divided by the total image area in pixels (Figure 2). The area of capillary nonperfusion was defined as the area where a dropout of the retinal capillary bed was detected in the ultra-widefield FA image. Retinal vascular leakage was not considered as nonperfusion. Ischemic index has been used in other studies as a marker for retinal nonperfusion.[14]

All eyes were categorized clinically by state of disease, including mild NPDR, moderate to severe NPDR, and PDR according to the international classification proposed by the American Academy of Ophthalmology.[15] Eyes were categorized as quiescent PDR (qPDR) if the patient was clinically diagnosed previously with PDR and had undergone previous PRP and had no clinical signs of proliferative disease for at least 2 years prior to day 1.

SD OCT images were reviewed for all patients to confirm the presence of macular thickening. Only eyes with evidence of angiographic macular leakage and macular thickening documented on SD OCT were considered to have macular edema. Patients were required to have recalcitrant DME with a CMT ≥300 μm by SD OCT and had not received any treatment in the study eye for at least 90 days prior to enrollment.

A chart review was performed for all patients for the following data: sex, age, mean arterial pressure (MAP), hemoglobin A1c, dependence on insulin, and the number of macular photocoagulation and PRP treatments during the 2-year study period. Hemoglobin A1c and MAP measurements were all within a 6-month period from the date of the ultra-widefield FA. SD OCT CMT measurements were recorded at 2 time points: (1) on the day of ultra-widefield FA (day 1) and (2) at a clinic visit at least 2 years prior (baseline). If no macular SD OCT was available exactly 2 years prior to the ultra-widefield FA date, the CMT measurements were taken from a macular SD OCT within 3 months of that date.

All patients referred for evaluation and management of recalcitrant DME and PDR who had undergone laser photocoagulation (focal/grid and/or PRP) within the study period had undergone laser treatment aided with traditional OCT and angiographic techniques, respectively. All patients who had undergone macular photocoagulation treatment followed the modified ETDRS protocol used in the DRCR.net clinical trials.[6]

The term "study period" refers to the time period at least 2 years prior to the date of the ultra-widefield FA. The term "baseline" refers to the first day of the study period. The term "day 1" refers to the day of the angiogram and SD OCT.

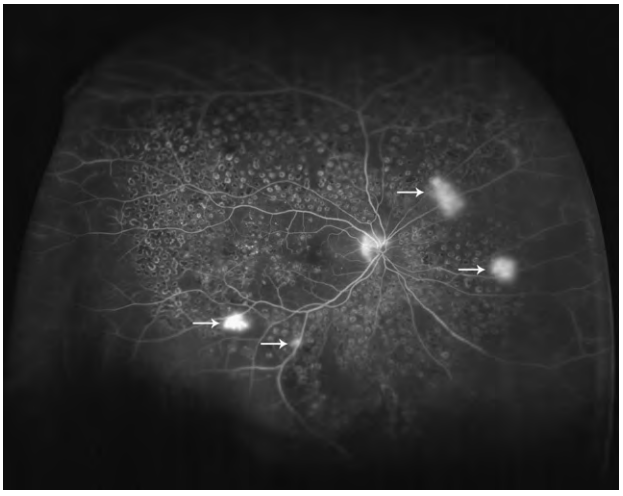

FIGURE 1. Ultra-widefield fluorescein angiography image taken during the arteriovenous phase, demonstrating persistent neovascularization (arrow) at the border between perfused and nonperfused retina despite scatter photocoagulation. This eye was in Cohort 3.

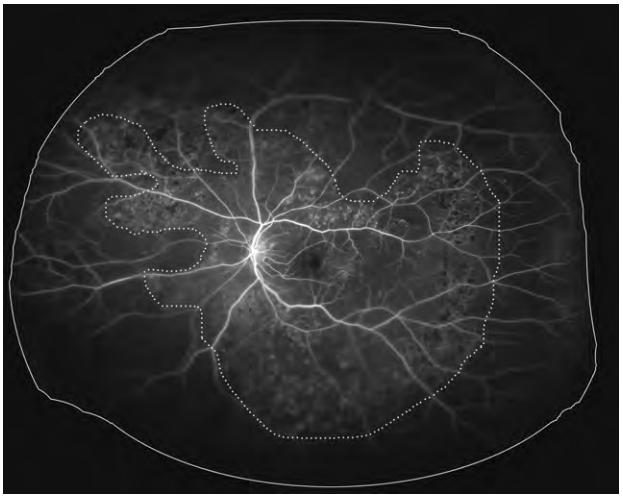

FIGURE 2. An example of the method used in this study for calculating ischemic index. The total fundus area was encircled (solid line) and the area of nonperfusion was delineated (dotted line). Ischemic index was the ratio of the area of nonperfusion over the total fundus area. This eye was in Cohort 4 and had an ischemic index of 59%.

• **STUDY DESIGN:** Four study cohorts were enrolled with eyes that had a diagnosis of recalcitrant DME for at least 2 years. Cohort 1 subjects were diagnosed with mild NPDR and treated with previous macular photocoagulation. Cohort 2 subjects were diagnosed with moderate or severe NPDR and treated with previous macular photocoagulation. Cohort 3 subjects were diagnosed with qPDR and treated with previous macular photocoagulation and PRP. Cohort 4 subjects were diagnosed with active PDR and treated with previous macular photocoagulation with or without previous PRP.

• **STATISTICAL ANALYSIS:** The significance of the differences in the CMT between baseline and at day 1 of the study was analyzed by nonparametric Wilcoxon signed rank test. SPSS version 17.0J for Windows (SPSS Inc, Chicago, Illinois, USA) was used for statistical analyses. A P value of $<.05$ was considered significant.

RESULTS

• **CLINICAL CHARACTERISTICS OF PATIENTS:** The clinical characteristics of the 76 patients (41 men and 35 women) are summarized in Table 1. The mean age of the patients was 48.2 years (range 36-84 years). The mean duration of recalcitrant DME was 32.5 months (range 24-38 months). A total of 158 ultra-widefield fluorescein angiograms from 81 patients initially reviewed. However, 10 angiograms could not be interpreted owing to poor quality, and were therefore excluded. Ultimately, 148 eyes of 76 patients were used in the analysis. Angiographic macular edema was identified in all 148 eyes.

• **CENTRAL MACULAR THICKNESS AND MEAN NUMBER OF FOCAL/GRID TREATMENTS:** The mean baseline CMT in Cohort 1 was 449.4 ± 36.5 μm, which reduced to 336.3 ± 30.5 μm at day 1 after a mean number of 2.3 macular photocoagulation treatments ($P < .01$). The mean baseline CMT in Cohort 2 was 455.6 ± 61.2 μm, which reduced to 368.7 ± 45.3 μm at day 1 after a mean number of 4.8 macular photocoagulation treatments ($P < .02$). The mean baseline CMT in Cohort 3 was 440.6 ± 42.5 μm, which reduced to 389.4 ± 68.4 μm at day 1 after a mean number of 5.3 macular photocoagulation treatments ($P < .02$). The mean baseline CMT in Cohort 4 was 472.3 ± 76.4 μm, which reduced to 438.4 ± 54.8 μm at day 1 after a mean number of 5.7 macular photocoagulation treatments ($P = .28$). The mean number of macular photocoagulation treatments is shown in Figure 3. An inverse relationship was found between mean number of macular photocoagulation treatments and mean percent decrease in CMT in the 4 cohorts. Cohorts 1 through 4 had a mean percent decrease in CMT as follows: 25.2%, 19.1%, 11.6%, and 7.2%, respectively.

• **ISCHEMIC INDEX AND TYPE OF MACULAR EDEMA:** Untreated retinal nonperfusion was calculated using an ischemic index. There were 148 eyes included in the ischemic index grading. The mean ischemic index was 47% (SD 25%; range 0%-99%). The average ischemic index of eyes within Cohorts 1, 2, 3, and 4 was 0%, 34%, 53%, and 65%, respectively (Table 2, Figure 4).

Angiographic evidence of any type of macular edema was present in 100% of eyes (148/148). Focal angiographic macular edema was present in 41% of eyes (61/148) and diffuse angiographic macular edema was present in 59% (87/148). Figure 5 is a scatterplot showing that the mean ischemic index of eyes with focal recalcitrant DME was 41% (SD 21%; range 0%-75%) and the mean ischemic index of eyes with diffuse recalcitrant DME was 64% (SD 26%; range 0%-99%).

TABLE 1. Demographics of Patients With Recalcitrant Diabetic Macular Edema at the Time of Ultra-widefield Fluorescein Angiography (Day 1)

Sex (n)	
Male	41
Female	35
Mean age (y) [range]	48.2 (36-68)
Mean duration (mo) of recalcitrant DME [range]	32.5 (24-38)
Mean glycosylated hemoglobin (± SD)	8.1 (± 1.14)
Diagnosis in study eye (n)	
Cohort 1–mild NPDR with recalcitrant DME	30
Cohort 2–moderate or severe NPDR with recalcitrant DME	43
Cohort 3–quiescent PDR with PRP and recalcitrant DME	33
Cohort 4–active PDR with or without PRP and recalcitrant DME	42
Mean central macular thickness (μm ± SD)	
Cohort 1–mild NPDR with recalcitrant DME	336.3 ± 30.5
Cohort 2–moderate or severe NPDR with recalcitrant DME	368.7 ± 45.8
Cohort 3–quiescent PDR with PRP and recalcitrant DME	389.4 ± 68.4
Cohort 4–active PDR with or without PRP and recalcitrant DME	438.4 ± 54.8

DME = diabetic macular edema; NPDR = nonproliferative diabetic macular edema; PDR = proliferative diabetic macular edema.

DISCUSSION

DIABETIC MACULAR EDEMA IS A CHRONIC DISEASE WITH various clinical manifestations and varying therapeutic response throughout the duration of the patient's life. Therefore, because of this variable nature, a subset of patients with DME are found to be recalcitrant or "suboptimal responders" to macular photocoagulation. Macular photocoagulation is an important treatment modality for

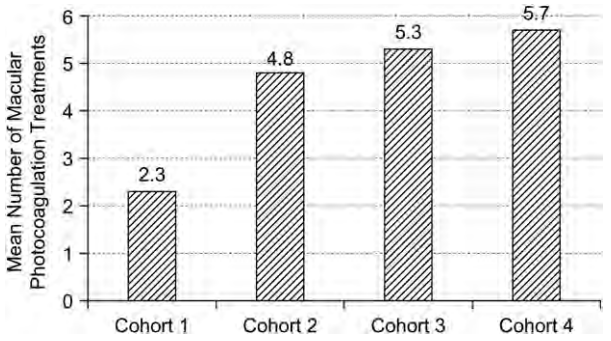

FIGURE 3. Bar graph showing the mean number of macular photocoagulation treatments over the two year study period in the 4 respective cohorts. A direct correlation was seen with the mean number of macular photocoagulation treatments and in eyes with increasing severity of diabetic retinopathy.

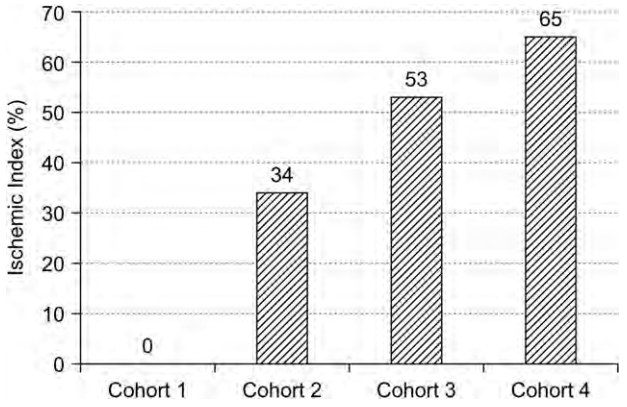

FIGURE 4. Bar graph showing mean ischemic index in patients with recalcitrant diabetic macular edema in the 4 respective cohorts. A direct correlation was seen with ischemic index and in eyes with increasing severity of diabetic retinopathy.

TABLE 2. Number of Patients With Focal vs Diffuse Recalcitrant Diabetic Macular Edema and the Corresponding Average Ischemic Index Using Ultra-widefield Fluorescein Angiography

Cohort Number	Focal Recalcitrant Diabetic Macular Edema, n (%)[a]	Diffuse Recalcitrant Diabetic Macular Edema, n (%)[a]	Average Ischemic Index (SD, %) [range]
1	25 (83%)	5 (17%)	0% [0]
2	19 (44%)	24 (56%)	34% [16-51]
3	11 (33%)	22 (77%)	53% [32-89]
4	6 (14%)	36 (86%)	65% [47-99]

[a]Percentage of eyes in cohort.

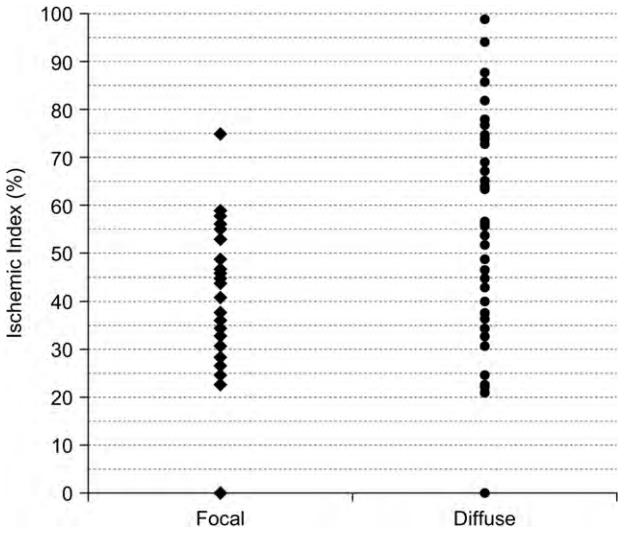

FIGURE 5. Scatterplot showing the distribution of ischemic index in eyes with focal and diffuse recalcitrant diabetic macular edema. A lower mean ischemic index (41% versus 64%) was seen in focal recalcitrant diabetic macular edema compared with diffuse recalcitrant diabetic macular edema.

DME based on the ETDRS, which demonstrated that focal or grid laser photocoagulation reduces the risk of moderate visual loss attributable to clinically significant macular edema by 50%.[16] We opted to include eyes with or without prior PRP for 2 reasons. First, a routine observation noted early in our experience with ultra-widefield FA revealed that significant areas of untreated peripheral retinal pathology remained despite treatment with PRP. Second, because of the retrospective, noninterventional nature of the study, we felt that inclusion of eyes with previous photocoagulation better represented the group we sought to study.

The hypothesis that untreated retinal vascular nonperfusion may be associated with recalcitrant DME is supported by our results, which demonstrated that 80% of patients with recalcitrant DME showed evidence of untreated nonperfusion. To quantify area of nonperfusion, we used a previously described technique.[14] Calculating the ischemic index allowed us to quantify nonperfusion and place a ratio of nonperfused to perfused retina. Our results demonstrate that the most recalcitrant DME existed in patients with the largest areas of retinal nonperfusion. As a result, these patients had the least amount of reduction in CMT, requiring the greatest amount of macular photocoagulation treatments. Of note, the cohort with the highest mean average ischemic index (Cohort 4, 65%) was found to have lowest mean percentage decrease in CMT (7.2%) and required the greatest mean number of macular photocoagulation treatments (5.7) for the study period.

Eyes with untreated nonperfusion (as seen in Cohorts 2, 3, and 4) were found on average to have a higher correlation with diffuse recalcitrant DME (69%) compared to focal recalcitrant DME (31%). There are a number of biologically plausible explanations for this observation. First, the macula's unique anatomy—namely, the manner in which the photoreceptors and associated neural cells of

the Henle layer are configured—makes it especially susceptible to diffuse edema. Second, VEGF is a potent vasodilator produced by ischemic retina that weakens the walls of the macular capillaries. Increasing intraocular VEGF levels enhance vascular permeability, inviting leakage of lipid and diffuse edema.[17]

We noted an inverse association between mean number of macular photocoagulation treatments and the percent decrease in CMT over the study period. A plausible explanation for this observation is that peripheral nonperfusion theoretically produces VEGF and cytokines to perpetuate recalcitrant DME, which as a result causes the need for more therapeutic macular photocoagulation treatments. Aiello and associates[18] demonstrated that PRP results in declining levels of VEGF. In our study, traditional fluorescein angiography–guided PRP during the 2-year study period may have led to an insufficient regression of vitreous VEGF levels, and as a result, several peripheral areas of untreated nonperfusion were seen on ultra-widefield FA in eyes in Cohorts 2, 3, and 4. A direct correlation was found between the mean number of macular photocoagulation treatments and the ischemic index. This observation has led the authors to reevaluate how to treat patients with recalcitrant DME. Traditionally, focal macular laser treatment for DME is usually recommended before PRP, given that DME usually worsens with PRP.[19,20] Paradoxically, PRP seems to have a beneficial effect on severe DME in some situations.[21] Therefore we postulate that patients with recalcitrant DME who are nonresponders to macular photocoagulation and have undergone extensive PRP would benefit first from targeted retinal photocoagulation of untreated retinal nonperfusion. This would be followed by reevaluation of the macular edema and repeated macular photocoagulation. This approach may effectively decrease recalcitrant DME by treating the cause of the disease while decreasing the frequency of therapeutic macular photocoagulation treatments. Furthermore, the implication that recalcitrant DME is directly correlated to ischemic index may be useful to determine injection frequency with anti-VEGF therapies in patients with DME (ie, a patient with low ischemic index may need fewer injections per year compared with a patient with high ischemic index).

We have learned from several clinical trials[7,8] that a significant component of DME is a result of VEGF causing vascular permeability in the macula, and how anti-VEGF treatment suppresses the VEGF load and improves DME. However, as seen in our study in Cohorts 2-4, the peripheral ischemic component of the disease may contribute a considerable VEGF load. Neubauer and associates[22] have previously reported that the benefit of anti-VEGF treatment over macular laser in patients with DME maybe attributable to the medication's treating the areas of peripheral nonperfusion along with improving the vascular permeability status in the macula. By using an antagonist to block existing VEGF and ablating the peripheral areas of nonperfusion to shut down VEGF production, this combination therapy may give us the ability to enhance durability of the targeted laser therapy while drying the macula by suppressing the permeability of the vasculature.

There are limitations to the conclusions that can be drawn from this study. First, as a retrospective review, the sample size and selection bias for patients undergoing ultra-widefield FA are likely significant. Furthermore, the patients in this study were not a traditionally homogenous group, and represent recalcitrant DME in various stages of disease and treatment. We recognize that there are subjective limitations to angiogram interpretation. Despite these limitations, this study represents an important first step in evaluation of peripheral retinal vascular pathology in patients with recalcitrant DME. Randomized prospective studies are needed to confirm the findings of this study. Specifically, future studies are needed to determine the role that treatment of peripheral nonperfusion can play in both the management and prevention of neovascularization and recalcitrant DME.

In summary, this study demonstrates the role ultra-widefield FA plays in visualizing peripheral retinal pathology in DR. Detection and delineation of retinal vascular nonperfusion in the retinal periphery may be of clinical value. The association between retinal capillary nonperfusion and recalcitrant DME demonstrated in this study supports the hypothesis that zones of untreated retinal nonperfusion may stimulate production of biochemical mediators leading to recalcitrant DME and a suboptimal response to therapeutic treatments. Therefore, ultra-widefield FA may be a valuable tool to identify therapeutic target areas for photocoagulation, allowing for efficient treatment of ischemic retina and potentially decreasing the production of VEGF and cytokines that play a role in recalcitrant DME.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST. Dr Messner serves on the Speaker's Bureau for Carl Zeiss Meditec. Dr Hariprasad serves on the Speaker's Bureau for Alcon, Regeneron, Allergan, and Genentech. He also serves as a Consultant for Alcon, Allergan, Bayer, Ocular Therapeutix, Takeda, Leica, Optos, and OD-OS. The authors disclose no funding support. Contributions of authors: design and conduct of the study (R.P., L.M., B.T., K.M., S.M.); collection, management, analysis, and interpretation of the data (R.P., K.M., S.M.); and preparation, review, or approval of the manuscript (R.P., L.M., B.T., K.M., S.M.).

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Biosketch

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