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Targeted Retinal Photocoagulation for Diabetic Macular Edema with Peripheral Retinal Nonperfusion

Three-Year Randomized DAVE Trial

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Purpose: To evaluate the effect of targeted retinal photocoagulation (TRP) on visual and anatomic outcomes and treatment burden in eyes with diabetic macular edema (DME).

Design: Phase I/II prospective, randomized, controlled clinical trial.

Participants: Forty eyes of 29 patients with center-involved macular edema secondary to diabetes mellitus.

Methods: Eyes with center-involved DME and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) between 20/32 and 20/320 (Snellen equivalent) were randomized 1:1 to monotherapy with 0.3 mg ranibizumab (Lucentis, Genentech, South San Francisco, CA) or combination therapy with 0.3 mg ranibizumab and TRP guided by widefield fluorescein angiography. All eyes received 4 monthly ranibizumab injections followed by monthly examinations and pro re nata (PRN) re-treatment through 36 months. Targeted retinal photocoagulation was administered outside the macula to areas of retinal capillary nonperfusion plus a 1−disc area margin in the combination therapy arm at week 1, with re-treatment at months 6, 18, and 25, if indicated.

Main Outcome Measures: Mean change in ETDRS BCVA from baseline and number of intravitreal injections administered.

Results: At baseline, mean age was 55 years, mean BCVA was 20/63 (Snellen equivalent), and mean central retinal subfield thickness (CRT) was 530 μm. Thirty-four eyes (85%) completed month 36, at which point mean BCVA improved 13.9 and 8.2 letters ($P = 0.20$) and mean CRT improved 302 and 152 μm ($P = 0.03$) in the monotherapy and combination therapy arms, respectively. The mean number of injections administered through month 36 was 24.4 (range, 10−34) and 27.1 (range, 12−36), with 73% (362/496) and 80% (433/538) of PRN injections administered ($P = 0.004$) in the monotherapy and combination therapy arms, respectively. Goldmann visual field isopter III-4e area decreased by 2% and 18% in the monotherapy and combination therapy arms, respectively ($P = 0.30$).

Conclusions: In this 3-year randomized trial of 40 eyes with DME, there was no evidence that combination therapy with ranibizumab and TRP improved visual outcomes or reduced treatment burden compared with ranibizumab alone. *Ophthalmology 2017;■:1−8 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Chronic hyperglycemia in diabetes mellitus leads to microvascular damage throughout the body, and the retinal capillary beds often are the first and most severely affected of end organs. Shimizu et al[1] demonstrated in 1980 that the mid-peripheral retinal vasculature was affected profoundly, with marked nonperfusion demonstrated on a montage of fundus fluorescein angiography (FA) images that correlated with diabetic retinopathy levels of increasing severity. This nonperfused hypoxic retina and the surrounding penumbra of underperfused retina is now known to upregulate the hypoxia-inducible factor transcriptional cascade, leading to secretion of a multitude of vasoactive cytokines, including vascular endothelial growth factor A (VEGF) and erythropoietin, which lead to both proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). Although panretinal photocoagulation (PRP) to the mid-peripheral and peripheral retina have been the mainstay for treatment of proliferative disease since the Diabetic Retinopathy Study,[2] PRP in the Early Treatment Diabetic Retinopathy Study (ETDRS) seemed to have adverse effects on vision in the short term, with these effects more pronounced with full scatter than with mild scatter.[3] Indeed, PRP in the era before anti-VEGF therapy more typically was associated with increased DME.[4]

In the management of DME, long-term suppression of VEGF reduces DME and improves visual acuity,[5,6] but most patients require repeated, ongoing anti-VEGF injections for optimal outcomes.[7,8] To decrease VEGF production,

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numerous authors have proposed PRP to the mid-peripheral and peripheral retina,[9–11] and several case series and small, brief studies have implied that targeted retinal photocoagulation (TRP) guided by widefield FA can decrease treatment burden (i.e., decrease the need for ongoing anti-VEGF injections).[12,13] Based on these studies and the widespread belief that substantial VEGF production emanates from the involved nonperfused or adjacent retina, many clinicians advocate peripheral PRP or TRP to nonperfused retina in the setting of DME. To test the hypothesis that widefield FA–guided TRP significantly reduces the number of required anti-VEGF injections, the Efficacy and Safety Trial of Intravitreal Injections Combined with Panretinal Photocoagulation for Clinically Significant Macular Edema Secondary to Diabetes Mellitus (DAVE) was designed to assess the long-term (3-year) effects of combination therapy with ranibizumab injections versus ranibizumab injections alone on visual acuity, anatomic features, and reduction in demand for anti-VEGF therapy.

Methods

The DAVE trial was a phase I/II randomized clinical trial (clinicaltrials.gov identifier, NCT01552408; Food and Drug Administration Investigational New Drug identifier, 113691). Institutional review board/ethics committee approval (Sterling IRB, Atlanta, GA) was obtained for this Health Insurance Portability and Accountability Act–compliant trial that adhered to the tenets of the Declaration of Helsinki. Data were collected at the Retina Consultants of Houston (Houston, Katy, and Woodlands, Texas). Patients older than 18 years with center-involving macular edema secondary to either type 1 or 2 diabetes mellitus, ETDRS best-corrected visual acuity (BCVA) between 24 and 78 letters (Snellen equivalent, 20/320 and 20/32, respectively), and central retinal subfield thickness (CRT) of 250 μm or more as measured by spectral-domain (SD) OCT were eligible for inclusion. All eyes had severe nonproliferative diabetic retinopathy or early PDR. According to the protocol, eyes with high-risk PDR defined by the Diabetic Retinopathy Study criteria were excluded. Only eyes with distinct and extensive areas of capillary nonperfusion outside the vascular arcades on widefield FA (OPTOS 200Tx; Optos, Dunfermline, United Kingdom) that the evaluating investigator believed would benefit from TRP were eligible for enrollment and randomization. The baseline retinal nonperfusion in square millimeters was graded by the Doheny Reading Center.[14] At enrollment, patients were randomized 1:1 to either monotherapy or combination therapy arms and written, informed consent was obtained. For patients who had both eyes enrolled (n = 11), each eye was assigned to a different arm. Pertinent exclusion criteria included any history of PRP, vitrectomy, or other eye conditions that could alter BCVA. A list of major inclusion and exclusion criteria is presented in Table 1.

At all visits, participants underwent ETDRS BCVA testing, slit-lamp and dilated ophthalmic examination, and SD OCT using the Heidelberg Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany). The Heidelberg SD OCT acquisition protocol used volume-per-cube (20 × 20, 49 lines, 768 A-scans per line) with 9-times image averaging. Color fundus photography and widefield FA (200°) were conducted at baseline and repeated every 3 months using the Optos 200Tx. Goldmann visual field (GVF) testing was conducted at baseline and was repeated every 6 months.

All participants received 0.05-ml intravitreal injections of 0.3-mg ranibizumab administered monthly (28±7 days) for 4 treatments starting at baseline. Patients randomized to the combination therapy arm underwent TRP at week 1 with possible re-treatment at months 6, 18, and 25 based on repeat widefield FA results. Peripheral, targeted laser was administered after topical, subconjunctival, or retrobulbar anesthesia, directed to areas of nonperfused peripheral retina plus a 1–disc area margin (Fig 1). At the initial laser treatment, no less than 800 and no more than 2400 applications were applied; at subsequent treatments, the extent of laser was determined by the treating investigator based on areas of nonperfusion identified by widefield FA. Laser was applied with both slit-lamp and indirect laser to achieve consistent coverage to the ora serrata. Afterward, all patients were evaluated monthly and treated on a pro re nata (PRN) basis with re-treatment determined based on the presence of center-involving DME through the end of the trial, month 36. Specifically, ranibizumab injections were administered if DME was demonstrated by SD OCT to involve the foveal depression. The decision for re-treatment was performed in a masked fashion to avoid bias in determining the need for re-treatment.

Sterile technique was followed for every intravitreal injection. Topical anesthetic was instilled and the use of subconjunctival

Table 1. Key Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
>18 yrs of age	Prior panretinal photocoagulation
Center-involving macular edema secondary to type I or II diabetes mellitus	Prior intraocular, subconjunctival, or systemic steroids within 4 months before screening
ETDRS BCVA ≥24 letters and ≤78 letters	
Central retinal subfield thickness ≥250 μm	Prior antiangiogenic drugs in either eye within 2 months of randomization
Decreased visual acuity secondary to diabetic macular edema	Intraocular surgery within 2 months of randomization
Distinct and extensive capillary nonperfusion on widefield fluorescein angiography of the peripheral retina	Concurrent ocular conditions that could require intervention or could contribute to vision loss during the study
	Neovascularization larger than 1/3 disc area within 1 disc diameter of the optic nerve head
	History of rhegmatogenous retinal detachment or stage 3 or 4 macular hole
	Current vitreous hemorrhage
	Uncontrolled glaucoma or history of glaucoma filtering surgery

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.