Update on the Diabetic Retinopathy Clinical Research Network

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**Note: Although Dr. Bressler currently is Chair of the Diabetic Retinopathy Clinical Research Network (DRCR.net), Dr. Bressler did not participate in this article on behalf of the DRCR.net but as an individual author.*

Diabetic macular edema (DME) remains is major cause of vision loss in patients with diabetes.[1-5] It is estimated that approximately 28% of individuals with 20 years of known Type 1 and Type 2 diabetes will develop DME.[5] The principal methods of reducing vision loss from DME are intensive glycemic control, systemic blood pressure control, and focal/grid photocoagulation.[6]

The level of glycemic control strongly correlates with the risk of developing diabetic retinopathy (DR) in both type 1 and type 2 diabetic patients, as demonstrated by the Diabetes Complications and Control Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS).[7,8] In a follow-up of the patient cohort in the DCCT, the Epidemiology of Diabetes Interventions and Control (EDIC) trial reported a lower rate of progression to DME requiring laser treatment in the intensive glycemic treatment group vs those in the good control group.[9-11]

In addition to strict glycemic control, blood pressure control has also been demonstrated to reduce vision loss from DME.[12,13] Hyperglycemia has been postulated to cause breakdown of the blood-retinal barrier through compromise of tight junctions between retinal capillary endothelial cells, with resultant fluid flow through capillary walls into retinal tissue, causing retinal edema.[14-16] Retinal edema has also been postulated to become exacerbated by an imbalance of vascular hydrostatic pressure and capillary oncotic pressure between the retinal capillaries and the tissues, clearly implicating systemic arteriole hypertension as an important variable in the development of macular edema.[14]

Macular laser photocoagulation has become the mainstay of treatment for DME. Dilation of the retinal venules and arterioles has been observed prior to the development of DME.[17,18] Macular laser treatment causes arterioles and venules to constrict, reducing the level of edema.[19] This treatment effect is hypothesized to occur as laser treatment reduces oxygen consumption in the outer retina and shifts oxygen flow from the choroid into the inner retina, resulting in arteriole constriction and decreased fluid within the retinal tissue.[14] The Early Treatment Diabetic Retinopathy Study (ETDRS) reported that focal laser photocoagulation reduced the 3-year risk of severe loss of visual acuity by 50% in eyes with macular edema involving or threatening the fovea.[20]

Although macular focal/grid photocoagulation remains the gold standard treatment for DME, several other treatment modalities have been proposed to reduce DME-related vision loss. These treatments include intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab (Avastin, Genentech) or ranubizumab (Lucentis, Genentech), intravitreal or peribulbar injection of steroids such as triamcinolone acetonide, laser photocoagulation treatment in combination with anti-VEGF intravitreal treatment or peribulbar or intravitreal triamcinolone acetonide (IVTA) injection, oral protein kinase C-inhibitors, surgical treatments such as vitrectomy with or without removal of internal limiting membrane, and sustained-release intravitreal fluocinolone acetonide implantation.[6] These therapies have been increasingly utilized in the treatment of eyes with DME, despite a lack of long-term clinical trial data to support their superiority to focal/grid photocoagulation.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a multicenter network funded by the National Eye Institute, designed to facilitate clinical

research and collaboration on diabetic retinopathy, DME, and associated conditions. More than 150 clinical sites have participated in some way with this network, with more than 500 investigators participating in the network including, community-based practices and academic centers. The DRCR.net supports the identification, design, and implementation of multicenter clinical research initiatives focused on diabetes-induced retinal disorders. The network has conducted a series of randomized clinical trials dedicated to finding the most effective therapies for DME. The following is an overview of some of the major DRCR.net trials dedicated to evaluating efficacy and safety of DME treatment modalities.

IVTA AND FOCAL/GRID PHOTOCOAGULATION FOR DME[6]

The safety and efficacy of 1-mg and 4-mg doses of preservative-free IVTA were compared to focal/grid laser photocoagulation for the treatment of DME in a multicenter, randomized clinical trial. Eight hundred forty study eyes of 693 subjects with visual acuity ranging from 20/40 to 20/320 and DME involving the fovea were randomized to focal/grid photocoagulation (n = 330), 1 mg IVTA (n = 256), or 4 mg intravitreal triamcinolone (n=254). Persistent or new edema was re-treated at 4-month intervals. At 2 years, the primary outcome measure evaluated was visual acuity, the secondary outcome measure, retinal thickness as measured by optical coherence tomography (OCT). Safety also was evaluated. At 4 months, the mean visual acuity was better in the 4-mg IVTA group (*P*=.001), but by 1 year there were no differences in visual acuity among all groups. At 2 years, the mean visual acuity was better in the laser group than in the other two groups (*P*=.02, laser vs. 1-mg group; *P*=.002, laser vs. 4-mg group; and *P*=.49 comparing 1-mg and 4-mg group). OCT results generally paralleled the visual acuity results. Intraocular pressure increased from baseline in 4%, 16%, and 33% of eyes in the 1 mg and 4 mg laser treatment groups, respectively, and cataract surgery was performed in 13%, 23%, and 51% of eyes in the three treatment groups, respectively. The benefits appeared similar regardless of whether macular laser had been given before enrollment, or entry visual acuity, or baseline OCT thickness, or whether the eye was pseudophakic at baseline, and the OCT results paralleled the visual acuity outcomes. Investigators concluded that focal/grid photocoagulation is more effective and has fewer side effects compared with to IVTA injection at the 1-mg or 4-mg dose in patients with DME at 2-year follow-up. Of note, these outcomes were similar to those obtained from a subset of eyes enrolled in the ETDRS that were similar to those enrolled in this DRCR.net study, ie, the subset in the ETDRS in which the entry visual acuity was less than 20/32 with central edema on photographs (because OCT was not available). While many ophthalmologists may have believed that focal/grid photocoagulation rarely led to improvement in vision, both the DRCR.net study and this subset in the ETDRS similar to those enrolled in the network study demonstrated that about one-third of the eyes gained 10 or more letters from baseline to 2 years (approximately two or more lines on a standard eye chart). It is possible that this magnitude of improvement was not recognized widely from the ETDRS results because so many subjects participating in the ETDRS started with visual acuities of 20/25 or 20/20, when improvement of two or three lines would be difficult if not impossible to attain for most individuals.

A PILOT STUDY OF LASER PHOTOCOAGULATION FOR DME[21]

This pilot study compared the standard method of focal/grid laser treatment (described as a modification of the ETDRS treatment requiring 50 µm burns and slightly lighter endpoint [mETDRS]) with a milder, more extensive treatment, termed mild macular grid (MMG). Inclusion criteria included eyes with clinically significant DME with visual acuity of 20/400 or better, with a central retinal thickness of 250 µm in the central subfield or 300 µm or more in any one of four subfields directly adjacent to the central subfield on OCT. Eyes were randomized to one of two treatment groups: 1) mETDRS laser treatment or 2) MMG laser treatment. For patients with two study eyes, one eye was randomized to one treatment and the contralateral eye was assigned to the other treatment. The main efficacy outcome was change in retinal thickening from baseline to 1 year as measured by OCT. At 12 months, MMG was less effective than mETDRS in reducing retinal thickening (mETDRS=290 µm, MMG=324 µm, *P*=.03). Twenty percent of eyes undergoing mETDRS treatment with baseline vision 20/40 or worse experienced a 15+ letter gain. Investigators concluded that these results do not support a clinical trial to determine if MMG is superior to mETDRS, and that mETDRS may improve vision better in eyes with decreased vision than previously thought, although DME may not resolve completely.

PHASE 2 EVALUATION OF INTRAVITREAL BEVACIZUMAB FOR DME[22]

This phase 2 randomized, multicenter clinical trial assessed the dose and dose-interval-related effects of intravitreal bevacizumab on central retinal thickness and visual acuity in subjects with DME, the effect of intravitreal bevacizumab combined with macular photocoagulation in DME, and the safety of intravitreal bevacizumab in subjects with DME. This study was not designed to assess the efficacy of bevacizumab in the treatment of DME. The phase 2 study helped

to determine if a phase 3 study was warranted and provided information to help design a phase 3 study. Eligible eyes included those with visual acuity of 20/320 or better with a fellow eye visual acuity of 20/400 or better without anti-VEGF treatment within the past 3 months. The study eye was assigned to one of five groups: 1) laser photocoagulation at baseline, 2) 1.25 mg intravitreal injection of bevacizumab at baseline and 6 weeks, 3) 2.5 mg intravitreal injection of bevacizumab at baseline and 6 weeks, 4)1.25 mg intravitreal injection of bevacizumab at baseline with sham injection at 6 weeks, and 5) 1.25 mg intravitreal injection of bevacizumab at baseline, macular laser photocoagulation at 3 weeks, and intravitreal injection of 1.25 mg bevacizumab at 6 weeks. After 12 weeks (the primary outcome), the main outcomes assessed were central subfield thickening on OCT and ETDRS visual acuity. Safety outcomes assessed included a visual acuity decrease of 20 or more letters at any visit within the first 3 weeks after a bevacizumab injection, ocular inflammation, endophthalmitis at any point, and other reported adverse events (injection-related, ocular, or systemic). At 12 weeks, the 1.25 mg bevacizumab group had a modest increase in visual acuity compared with the laser treated group (+5 letters vs -1 letter, *P*=.01). The 2.5 mg bevacizumab group did not have an appreciably greater effect on DME compared with the 1.25 mg group. This phase 2 study showed that a study arm with combination treatment is feasible, and a larger phase 3 randomized clinical trial is warranted to determine the true clinical benefit.

PILOT STUDY OF PERIBULBAR TRIAMCINOLONE FOR DME[23]

In a phase 2 randomized multicenter clinical trial, peribulbar triamcinolone was evaluated for treatment benefit in DME. Eyes with a visual acuity letter score of 69 or better (approximate Snellen equivalent of 20/40 or better), retinal thickening from DME based on clinical exam, and OCT thickness of 250 µm or more in the central subfield, and without having yet received maximal laser treatment were eligible. One hundred patients were randomized to four groups: 1) focal/grid laser alone, 2) 40-mg posterior peribulbar triamcinolone injection, 3) 20-mg anterior peribulbar injection, 4) posterior peribulbar injection of 40 mg triamcinolone followed by laser 1 month later, and 5) anterior peribulbar injection of 20 mg triamcinolone followed after 1 month by laser. In patients with two study eyes, one eye was randomly assigned to laser and the other eye randomly assigned to one of the other 4 triamcinolone groups. At follow-up, the primary efficacy outcome measured was ETDRS visual acuity, and secondary outcomes included OCT retinal thickening, persistence/recurrence of DME either re-treated or meeting criteria for retreatment during the first 8 months, and change in area of retinal thickening and in threat to/involvement of the center of the macula. The main safety outcomes assessed included elevated intraocular pressure or presence of glaucoma, cataract, ptosis, and any injection-related complications. At 17 weeks, the primary outcome time point, retreatment rates were as follows: 71% for the posterior peribulbar triamcinolone alone group, 64% for the anterior peribulbar triamcinolone alone group, 58% for the laser treated group, 43% for the posterior peribulbar triamcinolone plus laser group, and 38% for the anterior peribulbar triamcinolone plus laser group. The investigators concluded there was no clinically meaningful benefit from peribulbar steroids as a treatment for mild DME, while a treatment benefit for peribulbar steroids in more severe DME was unknown. The investigators concluded there was no justification to warrant a phase 3 trial.

TEMPORAL VARIATION IN OCT MEASUREMENTS OF RETINAL THICKENING IN DME[24]

This multicenter, observational study investigated the diurnal variation in OCT retinal thickness measurements in patients with DME and evaluated intraobserver and interobserver variability of OCT measurements. Inclusion criteria for this study consisted of eyes with DME involving the central macula evaluated on clinical exam with an OCT central subfield ≥225 µm. The main outcome measure reported was reproducibility of OCT-measured central subfield thickness. Reproducibility was better for central subfield thickness than for center point thickness measurements (relative change, 11% vs 17%, respectively, *P*<.001). The study investigators concluded that replicate measurements of central subfield differ by a median of 2% in patients with DME, that a change in central subfield thickness exceeding 11% is likely to be real, and that retinal thickness reproducibility in microns varies according to the degree of retinal thickness.

AN OBSERVATIONAL STUDY OF THE DEVELOPMENT OF CME FOLLOWING SCATTER LASER PHOTOCOAGULATION

Scatter laser panretinal photocoagulation for high-risk proliferative DR or severe nonproliferative DR has been shown to exacerbate DME. The DRCR.net conducted a prospective, multicenter nonrandomized treatment study to determine the incidence and extent of macular edema following scatter laser photocoagulation using OCT in eyes without preexisting macular edema, and to examine whether the incidence and extent of macular edema varies according to the number of panretinal photocoagulation sittings included in the treatment regimen. Eyes with the following characteristics were eligible:

1) OCT central subfield thickness ≤299 µm, and 2) early proliferative or severe nonproliferative DR for which the investigator intended to perform full scatter photocoagulation in either one or four sittings. At his or her discretion, the investigator selected either one sitting of scatter laser photocoagulation with a minimum of 1,200 to a maximum of 1,600 burns, with one burn width separation of burns and scatter extending from the peripheral arcades to beyond the equator; or four-sittings, each separated by 4 weeks, with approximately
300 burns in each of the first two sittings and investigator judgment for the number of burns for the third and fourth sittings for a final four sitting total of between 1,200 and 1,600 burns. The primary outcome measure was retinal thickening by OCT, and the secondary outcome was ETDRS visual acuity at 34-week follow-up. Results were pending at the time of publication of this article.

CONCLUSION

The DRCR.net is a network designed to facilitate collaboration among investigators dedicated to understanding and improving treatments for diabetic retinopathy and diabetic macular edema. At this time, available data suggest that focal/grid photocoagulation remains the most effective treatment for DME and is the benchmark treatment against which all other therapies should be evaluated.[7] The DRCR.net continues to investigate the efficacy and safety of focal laser and the other off-label treatments for DME through large, multicenter, randomized clinical trials, and these future studies will provide valuable information concerning the safety and efficacy of other treatment options for diabetic macular edema. Anyone with ideas for protocols for the network is invited to submit these through the network's web site at www.drcr.net. Ophthalmologists interested in joining the Network also can pursue the possibility of participating as a clinical site through www.drcr.net. ■

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1. Vitale S, Maguire MG, Murphy RP, et al. Clinically significant macular edema in type 1 diabetes. Incidence and risk factors. *Ophthalmology*. 1995;102:1170 –1176.
2. Klein R, Moss SE, Klein BE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. XI. The incidence of macular edema. *Ophthalmology*. 1989;96:1501–1510.
3. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmology*. 1984;91:1464–1474.
4. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care*. 2003;26:2653–2664.
5. Flavio EH, Knudtson MD, Klein BE, Klein R. Clinically significant macular edema and survival in Type 1 and Type 2 Diabetes. *Am J Ophthalmol*. 2008;145:700–706.
6. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology*. 2008;115(9):1447-1449.
7. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1992;329:977–986.
8. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854–865.
9. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med*. 2000;342:381–389.
10. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA*. 2002;287:2563–2569.
11. Danis RP. Diabetic macular edema. In: Albert DM, Miller JW, eds. *Albert and Jakobiec's Principles and Practice of Ophthalmology*. 3rd ed. Philadephia, PA: Elsevier Inc. 2008;1793–1806.
12. Gray A, Clarke P, Farmer A, Holman R, United Kingdom Prospective Diabetes Study (UKPDS) Group. Implementing intensive control of blood glucose concentration and blood pressure in type 2 diabetes in England: cost analysis (UKPDS 63). *BMJ*. 2002;325:860.
13. Stratton IM, Cull CA, Adler AI, et al. Additive effects of glycaemia and blood pressure exposure on risk of complications in type 2 diabetes: a prospective observational study (UKPDS 75). *Diabetologia*. 2006;49:1761–1769.
14. Stefánsson Einar. Ocular oxygenation and the treatment of diabetic retinopathy. *Surv Ophthalmol*. 2006;51:364–380.
15. Harhaj NS, Antonetti DA. Regulation of tight junctions and loss of barrier function in pathophysiology. *Int J Biochem Cell Biol*. 2004;36:1206–1237.
16. Vinores SA, Derevjanik NL, Ozaki H et al. Cellular mechanisms of blood-retinal barrier dysfunction in macular edema. *Doc Ophthalmol*. 1999;97:217:228.
17. Bek T. Diabetic maculopathy caused by disturbances in retinal vasomotion, a new hypothesis. *Acta Ophthalmol Scand*. 1999;77:376-380.
18. Kristinsson JK, Gottfredsdóttir MS, Stefánsson E. Retinal vessel dilatation and elongation precedes diabetic macular oedema. *Br J Ophthalmol*. 1997;81: 274-278.
19. Gottfredsdóttir MS, Stefánsson E, Jónasson F, et al. Retinal vasoconstriction after laser treatment for diabetic macular edema. *Am J Ophthalmol*. 1993;115:64–67.
20. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol*. 1985;103:1796–1806.
21. Diabetic Retinopathy Clinical Research Network. Comparison of modified early treatment diabetic retinopathy study and mild macular grid laser photocoagulation strategies for diabetic macular edema. *Arch Ophthalmol*. 2007;125:469–480.
22. Diabetic Retinopathy Clinical Research Network. A phase 2 randomized trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology*. 2007;1860–1867.
23. Diabetic Retinopathy Clinical Research Network. Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: A pilot study. *Ophthalmology*. 2007;114:1190–1196.
24. Diabetic Retinopathy Clinical Research Network. Reproducibility of macular thickness and volume using Zeiss optical coherence tomography in patients with diabetic macular edema. *Ophthalmology*. 2007;114:1520–1525.