EVIDENCE-BASED DATA IN THE TREATMENT OF DIABETIC RETINOPATHY*

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ABSTRACT

There is a wide array of research into the pathophysiology and treatment of diabetic retinopathy (DR) and diabetic macular edema (DME). Many new compounds are currently in or entering clinical trials. Panretinal (scatter) and macular focal photocoagulation (direct laser to microaneurysms within thickened areas and grid laser to other areas of retinal thickening) are established treatments for proliferative DR and DME, respectively, and are currently considered the gold-standard therapies for these conditions. Despite the availability of promising new treatments for DR and DME, laser photocoagulation should remain the first consideration for patients in many situations. New laser techniques that may offer less discomfort to the patient are also under development and evaluation. This article discusses some of these newer laser techniques in addition to agents designed to inhibit vascular endothelial growth factor (VEGF). Anti-VEGF therapies have shown promising early clinical study results for treatment of DME and robust anecdotal clinical effects in proliferative DR. Other treatment strategies discussed include agents that target second-messenger systems and intravitreal steroids. It is likely that future treatment of DR and DME will involve a variety of approaches, independently addressing the different mechanisms and multiple therapeutic targets underlying the complex pathophysiologic processes of diabetic ocular complications. (Adv Stud Ophthalmol. 2008;5(1):22-29)

Diabetic retinopathy (DR) is the leading cause of blindness in the working age population, and one of the major microvascular complications of diabetes. Previous large-scale epidemiologic studies have demonstrated that over 90% of patients with diabetes will develop DR given 15 or more years’ duration of diabetes mellitus (DM). Although proliferative DR (PDR) is usually not observed in the first 5 to 10 years of DM (Figure 1), more than 60% of patients with diabetes eventually develop PDR.12

The World Health Organization estimates that in 2030, the number of people worldwide with diabetes will total 370 million.3 To place the associated clinical care burden in perspective, even if none of these individuals had significant DR complications and thus only required an ophthalmic examination once a year, a total of nearly 24 eyes would need to be examined every second of the entire year in order to adequately manage the worldwide diabetic population.

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Many studies are under way worldwide to examine improvements in care for diabetic eye disease. In an effort to address the need for more efficacious therapies and more rapidly evaluate novel potential therapeutic interventions in the United States, programmatic approaches such as the Diabetic Retinopathy Clinical Research (DRCR) Network, have been implemented. The DRCR Network is a National Institutes of Health-sponsored program dedicated to multicenter clinical research of DR, macular edema, and associated disorders (see www.DRCR.net). Begun in September 2002, it now encompasses over 100 study sites in 33 states, including participation of nearly 1 in every 4 retinal specialists in the United States. Several studies discussed below have been performed by the DRCR Network, and such network approaches to diabetes eye care are likely to take on additional importance worldwide as the burden of diabetes and its associated ocular complications expand.

**Laser Photocoagulation: The Current Standard**

Laser photocoagulation is an established treatment for DR and diabetic macular edema (DME) and is currently considered the gold-standard therapy for both conditions. Two large, randomized, controlled clinical trials—the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS)—demonstrated a clear long-term visual benefit after timely treatment with panretinal laser photocoagulation, especially in the presence of PDR with high-risk characteristics. High-risk characteristics (HRC) include new vessels at the optic disc (NVD) that cover at least 25% to 33% of the disc area (DA), any NVD with vitreous or preretinal hemorrhage, or new vessels elsewhere (NVE) that cover at least 50% of the DA that are also associated with vitreous or preretinal hemorrhage. DR with neovascularization not meeting these criteria is considered PDR with less than HRC. In general, scatter photocoagulation is not recommended for mild-to-moderate nonproliferative DR (NPDR). However, the ETDRS demonstrated that scatter photocoagulation can be remarkably effective in reducing long-term visual loss in severe NPDR or any severity PDR if performed in a timely manner. Patients with type 2 DM, in particular, should be considered for photocoagulation at the severe NPDR stage. The ETDRS also showed that, for eyes with clinically significant macular edema (CSME, defined as thickening of the retina located ≤500 μm from the fovea, hard exudates within 500 μm of the fovea with associated thickening, or retinal thickening ≥1 DA within 1 disc diameter of the fovea), macular focal photocoagulation is effective in reducing moderate visual loss, increasing the chance of visual improvement, and decreasing the frequency of persistent macular edema.

When creating a treatment plan for a patient with DR, there are 2 important points to remember. First, although there is much excitement regarding new treatments for DR (discussed in the next section), laser photocoagulation remains a safe and effective therapy and should still be considered first-line treatment in most cases. Recent and current clinical studies use laser therapy as the comparator arm and are demonstrating that this technique may be even better than generally appreciated for patients. Second, as noted previously, the patient’s diabetes type should be factored into the treatment decision process. Subgroup analysis of the ETDRS data showed that for patients with type 1 diabetes, the difference in outcomes (ie, reducing severe visual loss or need for vitrectomy) between early and deferred treatment was insignificant, whereas for patients with type 2 diabetes, scatter photocoagulation of eyes with severe or very severe NPDR or PDR without HRC results in a 50% reduction of the rate of severe visual loss or vitrectomy, and a 50% reduction in the subsequent risk of

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**Figure 1. The Epidemiology of DR**

DR is a nearly universal consequence of diabetes. Although proliferative DR is usually not seen in the first 5–10 years of the disease, essentially all patients with diabetes will have some degree of retinopathy after approximately 15 years and >60% will develop proliferative DR over time. DR = diabetic retinopathy. Adapted with permission from Klein et al. Arch Ophthalmol. 1984;102:520-526 and Frank. Etiologic mechanisms in diabetic retinopathy. In: Ryan et al (eds). Retina. 4th ed. St. Louis, MO: Mosby; 2006.
PDR with HRC. Thus, patients with type 2 diabetes need to be followed closely as they approach more advanced levels of NPDR and considered for treatment earlier than patients with type 1 diabetes.

**New Laser Treatments for DR**

Advances in laser technology continue. One of these advances, the Pattern Scan Laser (PASCAL), is approved by the US Food and Drug Administration (FDA) for treatment of DR. It is gaining widespread use, and several studies are currently evaluating its benefit in terms of discomfort and postlaser edema. Most recently, the DRCR Network approved amendments to one of its study protocols to allow investigators to use PASCAL photocoagulation as an alternative to treatment with traditional argon laser. The PASCAL system incorporates a diode laser that allows photocoagulation of the retina using a single spot or a predetermined pattern array of up to 56 spots. Because PASCAL allows delivery of multiple spots with a single depression of the foot pedal, and because the individual burn durations are substantially shorter than with single spot applications, it has several potential advantages over traditional argon laser treatment. With PASCAL, individual spot burn durations are generally only 20 milliseconds, which should be associated with less burn spread and less discomfort to the patient. In addition, because multiple burns are delivered at each firing, PASCAL treatment session times are substantially shorter overall than standard laser treatment sessions.

Another laser treatment that has recently been evaluated in a randomized, clinical trial is mild macular grid (MMG) laser photocoagulation, a milder (but potentially more extensive) laser technique for treatment of patients with CSME. With MMG, microaneurysms are not treated directly and small mild burns are placed throughout the macula, whether or not edema is present. In a study conducted by the DRCR Network, MMG was compared with the more traditional modified ETDRS focal/grid photocoagulation technique in 263 subjects. The main outcome was the change in retinal thickening as measured by optical coherence tomography (OCT) central subfield measurement at 12-months’ follow-up. An additional objective was to determine whether treatment with MMG as compared with modified ETDRS focal/grid photocoagulation technique achieved similar visual outcomes at 1 year. The results demonstrated that both laser techniques were effective in reducing retinal thickening (Table). However, subjects treated with standard ETDRS photocoagulation experienced a statistically significant greater decrease in central subfield thickening, weighted inner zone thickening, maximum retinal thickening, and retinal volume than did subjects treated with MMG photocoagulation. In addition, there was no significant difference in visual acuity outcomes with the MMG treatment. At 12 months, the mean change in visual acuity was 0 letters in the modified ETDRS group and 2 letters worse in the MMG group (adjusted mean difference, 2 letters; 95% confidence interval, -0.5 to 5 letters; \( P = .10 \)). Because of the possible inferiority of the MMG technique in treating retinal thickening without any clear benefit in terms of visual acuity outcome, this laser technique is not being pursued in more extensive studies within the network. Modified ETDRS focal photocoagulation continues to be the gold-standard approach for treating CSME.

**Anti-VEGF Therapies for Diabetic Macular Edema**

As discussed by Dr Bandello earlier in this monograph, vascular endothelial growth factor (VEGF) is a key molecular target for new treatments for DR and DME. Three anti-VEGF therapies have current safety and efficacy data for DME: pegaptanib, ranibizumab, and bevacizumab. All 3 have completed phase II studies and are currently in ongoing phase III studies for DME. Highlights of these clinical trials are presented here.

**Pegaptanib**

Pegaptanib is an anti-VEGF aptamer (an RNA molecule that binds specifically to and inhibits 1 of the 4 human VEGF isoforms). It is intravitreally injected approximately every 6 weeks and is approved in the United States for use as treatment of wet age-related macular degeneration (AMD). In a phase II trial, pegaptanib was shown to be safe, with a modest, statistically significant effect on reducing macular thickness and improving visual acuity. This phase II study was an international, randomized, sham-controlled, double-masked, parallel, dose-ranging study conducted across 39 centers (United States, Canada, Europe, and Australia). Patients were stratified based on study site, area of retinal thickening (≤2.5 vs >2.5 DA), and visual acuity (<58 vs ≥58 ETDRS letters) to receive 1 of 3 pegaptanib doses (0.3 mg, 1 mg, or 3 mg) or sham. The main outcome measures were best-correct-
ed visual acuity, central retinal thickness as assessed by OCT measurement, and additional therapy with laser photocoagulation between weeks 12 and 36. The results are summarized in Figures 2 and 3; statistically significant improvement was observed with regard to visual acuity and retinal thickening outcomes with the 0.3-mg pegaptanib dose.8 Moreover, photocoagulation was deemed necessary in fewer subjects in the pegaptanib arms as compared with the sham-treated group (0.3 mg vs sham, 25% vs 48%; \(P = .04\)).8

RANIBIZUMAB

Ranibizumab is a humanized, modified, monoclonal anti-VEGF antibody fragment, which has extremely high affinity for all isoforms of VEGF. Like pegaptanib, ranibizumab is intravitreally injected, although it has a more frequent dosing schedule than pegaptanib with injections performed every 4 weeks. Two small phase II studies have been completed and published.9,10 Both studies were single-center, nonrandomized clinical trials in 10 patients with chronic DME. In both studies, there was evidence of visual gain and reduction of retinal thickness. In one study of 10 eyes with DME involving the center of the macula, the mean ± standard deviation decrease in retinal thickness of the center point of the

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* \(P\) values were obtained using repeated-measures least squares regression models adjusting for baseline values and accounting for the correlated data from subjects with 2 study eyes; †measurements include only eyes with a central subfield thickness of ≥250 µm at baseline; \(P = .05\) for log-transformed 12-mo data; ‡maximum thickening of central and 4 inner subfields; \(P = .46\) for log-transformed 12-mo data; ††maximum thickening of central and 4 inner subfields; \(P = .06\) for log-transformed 12-mo data; ‡‡maximum thickening of central and 4 inner subfields; \(P = .04\) for log-transformed 12-mo data.

ETDRS = Early Treatment Diabetic Retinopathy Study; MMG = mild macular grid; OCT = optical coherence tomography.

Adapted with permission from Writing Committee for the Diabetic Retinopathy Clinical Research Network et al. Arch Ophthalmol. 2007;125:469-480.7

In a randomized, sham-controlled, double-masked, dose-ranging, phase II study, patients were stratified based on area of retinal thickening (≤2.5 vs >2.5 DA) and visual acuity (<58 vs ≥58 ETDRS letters) to receive 1 of 3 different pegaptanib doses (0.3, 1, and 3 mg). The mean change in central retinal thickness at the center point of the central subfield (shown here, with 95% CIs in parentheses) was one of the main outcome measures. This figure shows that mean central retinal thickness decreased by 68 µm with 0.3 mg pegaptanib vs an increase of 3.7 µm with sham (\(P = .02\)). Larger proportions of those receiving 0.3 mg had an absolute decrease of both ≥100 µm (42% vs 16%; \(P = .02\)) and ≥75 µm (49% vs 19%; \(P = .008\)). CI = confidence interval; DA = disc areas; ETDRS = Early Treatment Diabetic Retinopathy Study.

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central subfield, at month 3, was 45.3 ± 196.3 µm for the 0.3-mg ranibizumab group and 197.8 ± 85.9 µm for the 0.5-mg ranibizumab group. By 6 months, the mean decreases were 74 ± 115 µm and 223.5 ± 148 µm, respectively.9 In both studies, no systemic adverse effects were noted, and only 5 occurrences of mild-to-moderate ocular inflammation were observed. In spite of the overall benefits seen with ranibizumab treatment in both studies, it is important to recognize that the magnitude of the effect was modest and variable among the study patients. Results from the ongoing phase III clinical trials will be required before we will know the efficacy, safety, and pertinent patient populations that may benefit from these treatments.

**BEVACIZUMAB**

Bevacizumab is a humanized, modified monoclonal anti-VEGF antibody with extremely high affinity for all VEGF isoforms. It is intravitreally injected every 4 to 6 weeks. It is approved in the United States for cancer treatment and is not approved for ocular indications. However, at least partly because of its very low per-dose cost compared to the other 2 anti-VEGF agents, bevacizumab currently enjoys widespread use off-label for the indications of wet AMD and DME. The DRCR Network performed a phase II, randomized clinical trial to evaluate the effect of intravitreal bevacizumab on DME.10 There were 121 subjects with DME and Snellen visual acuity equivalent ranging from 20/32 to 20/320; 109 eyes were eligible for analysis. The main reason for ineligibility was insufficient thickening of the central macula on OCT. The study was designed with 5 treatment groups: a laser-only group, 1.25-mg and 2.5-mg bevacizumab groups (receiving injections at baseline and at 6 weeks), a 1.25-mg bevacizumab group with injections at baseline and sham injection at 6 weeks, and a 1.25-mg bevacizumab group with injection at baseline and 6 weeks and photocoagulation at 3 weeks. The primary outcome measures were central subfield thickness changes on OCT and visual acuity changes, up to 24 weeks. Overall, the study showed a favorable effect of both doses of bevacizumab on DME when compared with focal photocoagulation at specific time points in terms of retinal thickening and visual acuity, although the differences were modest. There did not appear to be a benefit in combining bevacizumab with focal laser photocoagulation. In addition, the 2.5-mg dose of bevacizumab did not have an appreciably larger effect on DME than the 1.25-mg dose with regard to primary outcome measures or duration of effect. At 12 weeks, median visual acuity was better by 1 line in the groups treated with 1.25-mg and 2.5-mg bevacizumab as compared with the group treated with laser alone ($P = .01$ and .003, respectively). Interestingly, the effects on retinal thickening were most apparent by week 3, but with increasing follow-up, the laser benefit became significantly more evident such that the difference in retinal thickening was not statistically significant by week 12. The data suggest that more frequent injection intervals than used in this study (eg, every 4 weeks) may be more appropriate. It is important to note that the study was not designed to definitively evaluate safety and efficacy of bevacizumab in the treatment of DME, but rather to gather enough data to plan a larger, long-term phase III trial. Thus, the short-term results of this study should not be inter-
Anecdotal and small, uncontrolled study data suggest that anti-VEGF therapy may be remarkably effective for the temporary treatment of PDR and neovascular glaucoma.12-14 Extensive NVD, NVE, and rubeosis iridis appear to regress extremely rapidly after anti-VEGF treatment, with some responses seen within 1 day. In addition, these forms of neovascularization appear to be exquisitely sensitive to anti-VEGF compounds with responses documented at doses 10- to 100-fold lower than generally used. However, the effect of these anti-VEGF agents does wear off with subsequent return of neovascularization. Thus, at this time, anti-VEGF therapy for PDR is generally being studied as a temporizing measure before adding panretinal photocoagulation, or as part of preoperative management to make surgery easier and reduce intraoperative bleeding in eyes going to vitrectomy. The apparently robust response in these early studies of PDR to anti-VEGF, as opposed to the more variable and incomplete response of DME, suggest that VEGF-independent pathways may be playing a more prominent role in the pathophysiology of DME.19

**Protein Kinase C-β Inhibition for DME**

Therapies aimed at counteracting intracellular second-messenger activation have included inhibitors of protein kinase C-β (PKC-β). Ruboxistaurin is an orally administered PKC-β inhibitor that has been studied in several multicenter, randomized, double-masked, placebo-controlled, parallel, clinical trials. These clinical studies have consistently shown varying extent of benefit of ruboxistaurin treatment in preventing vision loss over time. The PKC-DRS2 trial evaluated the effect of treatment with 32-mg ruboxistaurin on the reduction of sustained moderate visual loss (≥15-letter decrease in ETDRS visual acuity score maintained ≥6 months) in 685 patients with moderately severe-to-very severe NPDR.9 After 36 months of treatment, patients treated with ruboxistaurin had a risk reduction of 40% in sustained moderate vision loss (P = .034). Patients on ruboxistaurin had twice the chance of a 3-line or greater improvement in vision as compared with patients receiving placebo (P = .027), and approximately two-thirds the chance of vision loss of 3 lines or greater (P = .044). Ruboxistaurin treatment also significantly reduced the progression of DME from center-threatening (CSME located >100 μm from the fovea) to center-involving and reduced the need of first application of focal/grid photocoagulation during the study (P = .008). There have been no differences in DR progression between the ruboxistaurin and placebo-treated groups observed in any of the studies.20 Because these studies did not lead to regulatory approval by the US FDA, these medications are not available at this time to treat DR or macular edema.

**Intravitreal Steroid Approaches**

Triamcinolone acetonide is not approved in the United States for use in DR or DME. It is approved for intramuscular or intra-articular injection rather than intraocular use and is not commercially available in a preservative-free form. Nonetheless, numerous case series, uncontrolled studies, and small, controlled studies have been published regarding its use in treating DME and other ocular pathologies. Treatment with triamcinolone does appear to have a substantial beneficial effect on retinal thickness, but repeat injections are often necessary. Improved visual acuity has been observed in some, but not all, treated eyes. Side effects of triamcinolone treatment include increased intraocular pressure, cataract formation, sterile inflammation, and endophthalmitis.

To better understand the safety and efficacy of intravitreal triamcinolone for DME, the DCRR Network is currently conducting a randomized trial with more than 693 patients enrolled to date comparing intravitreal triamcinolone with laser photocoagulation for DME. The steroid formulation used in this study is specifically designed for intravitreal use. It is preservative- and endotoxin-free, with single-dose packaging. As of this writing, study subjects have been followed for more than 2 years. The primary 2-year outcome results of this study are expected within the next year.

Two additional phase III studies involving treatment with intravitreal triamcinolone are currently ongoing. Both of these are being conducted by the DCRR Network. The first study is a comparison of adjunctive treatment with intravitreal triamcinolone versus ranibizumab for patients with macular edema who are undergoing macular focal photocoagulation compared with focal photocoagulation only. There also is an arm of ranibizumab alone to be compared with the focal photocoagulation-only arm. The second study is a comparison of adjunctive treatment with
intravitreal triamcinolone versus ranibizumab in patients who have central retinal thickening as measured by OCT and who are undergoing panretinal laser photocoagulation for advanced DR.

In 2007, the DRCR Network reported results from a multicenter (32 US sites), phase II, randomized study of peribulbar triamcinolone injection with and without focal photocoagulation for mild DME with relatively good visual acuity (N = 109, 129 eyes). Both anterior and posterior sub-Tenon's injections were performed and evaluated. After 34 weeks of follow-up, the results showed no apparent benefit with this method of triamcinolone delivery, either with or without macular laser photocoagulation. No further evaluation of this technique is planned by the DRCR Network.

**FUTURE DIRECTIONS**

The field of antiangiogenic treatment and research in DR and DME is extraordinarily active at this time. Several different tactics for targeting the VEGF pathway are under development, including anti-VEGF antibodies (eg, bevacizumab and ranibizumab); anti-VEGF aptamers (eg, pegaptanib); blockers of second-messenger cellular activation by VEGF, including PKC inhibitors (eg, ruboxistaurin and PTK787) and squalamine (a naturally occurring sterol); VEGF receptor analogs (VEGF trap); and small interfering RNA compounds to inhibit production of VEGF and its receptor (eg, Cand5 and SIRNA-027). As of 2007, there are at least 10 antiangiogenic drugs approved by the US FDA for at least 1 indication, and all of them are in further studies for other indications. There are also 43 agents in clinical trials that have shown preclinical antiangiogenic activity, although not all in ophthalmology.

In a recent review by Folkman, the categorization of antiangiogenic treatments based on breadth of action is discussed: Type I, blocks 1 main angiogenic protein; Type II, blocks 2 or 3 main angiogenic proteins; and Type III, blocks a broad range of angiogenic regulators. Although Type II and Type III antiangiogenic compounds are still in development, they offer the enticing promise of being able to treat multiple mechanisms of action with 1 compound. This is especially appealing for the treatment of DME, for which Type I anti-VEGF drugs appear to have a modest and often clinically variable effect. It is likely that to obtain a more effective response, single-agent medical therapy for DME will need to be broad-based and directed against a variety of molecular mechanisms, or multiple concurrent therapies may be required.

Although there has been wide interest in the application of anti-VEGF agents in the treatment of diabetic eye disease, clinical research is also moving beyond VEGF. As of January, 2008, 71 DR-related trials were recruiting patients worldwide (32 within the United States) for a wide array of treatments, including those for neuroprotection/inflammation (eg, doxycycline, bromfenac, and rapamycin) and vitreolysis (microplasmin), as well as further studies on anti-VEGF compounds (eg, pegaptanib, ranibizumab, and bevacizumab), steroids (eg, triamcinolone, dexamethasone, fluocinolone, and implants), PKC-β inhibitors (eg, ruboxistaurin), and interventional techniques (eg, laser and pars plana vitrectomy).

**CONCLUSIONS**

There is a wide array of research into the pathophysiology and treatment of DR and DME. Many new compounds are in clinical trials and definitive data on some should be forthcoming within the next few years. However, at this time, laser photocoagulation should still be considered first-line therapy for patients in most situations. New laser techniques and delivery modalities that may offer less discomfort to the patient are being evaluated. Anti-VEGF therapies, PKC-β inhibitors, and intravitreal steroids have shown promising results for treatment of DME. In the future, we are very likely to have additional therapeutic options, both invasive and pharmacologic, available for treatment of DR and DME. Individual compounds that affect multiple different pathways, or combinations of therapies directed against different underlying mechanisms, are also likely to evolve as our efforts to prevent the worldwide burden of visual loss from the ocular complications of diabetes progress.

**REFERENCES**


