

## Experimental Treatments for Diabetic Macular Edema

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### Abstract

Diabetic macular edema (DME) is the most common reason for the loss of reading vision in diabetes patients. Systemic control of blood sugar, blood pressure, and lipids is an important aspect of the management of DME. In these patients, macular laser photocoagulation has been shown to reduce the incidence of moderate visual loss by 50 %. Significant visual improvement occurs in a small minority. Other treatment modalities, such as intravitreal steroids and anti-vascular endothelial growth factor (VEGF) drugs, have become increasingly popular. Case series and small clinical studies are suggestive of a beneficial effect, while large-scale clinical trials are ongoing. Currently, it appears that macular laser photocoagulation remains the gold standard for the treatment of DME. Intravitreal steroids and anti-VEGF agents are useful adjuncts that may improve visual outcomes. Current treatments and ongoing clinical trials are discussed.

### Keywords

Anti-vascular endothelial growth factor drugs, diabetic retinopathy, diabetic retinopathy clinical trials, experimental diabetic treatments, macular edema, steroids

**Disclosure:** Homayoun Tabandeh, MD, MS, FRCOphth, has a financial interest in Regeneron Pharmaceuticals. David Boyer, MD, is a clinical professor at Keck School of Medicine, USC, and a consultant/speaker/scientific advisor to Allergan, Genentech, Novartis, Pfizer, Alcon, and iCo.

**Received:** April 21, 2011 **Accepted:** May 23, 2011 **Citation:** *US Ophthalmic Review*, 2011;4(2):125–130 DOI: 10.17925/USOR.2011.04.02.125

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Diabetic retinopathy remains the most frequent cause of newly diagnosed blindness in the working-age population. This is despite improvements in therapies for blood glucose and blood pressure control, and the many different treatment modalities that are currently available including laser, vitreous surgery, and intravitreal injections.

Diabetic macular edema (DME) is the most common reason for loss of reading vision in diabetes patients. After 15 years of known diabetes, DME is present in 20 % of patients with type 1 diabetes mellitus (DM) and in 14 % of patients with type two DM who do not take insulin. DME is present in 30 % of patients who have had diabetes for longer than 20 years. In eyes with mild non-proliferative diabetic retinopathy, the prevalence of DME is 3 %, rising to 38 % in eyes with moderate to severe non-proliferative retinopathy, and to 71 % in eyes with proliferative retinopathy.<sup>1-5</sup>

Age at onset and the duration of diabetes are the major predictors for development and progression of retinopathy. Blood glucose and blood pressure control are among the most important elements of management. The Diabetes control and complications trial (DCCT) demonstrated that tighter glycemic control reduced vision loss in type one diabetics.<sup>6</sup> The UK prospective diabetes study (UKPDS) found that every point decrease in hemoglobin A1C produced a 35 % reduction in microvascular complications.<sup>7</sup> This study also concluded that tight blood pressure control reduced microvascular complications.

DME is primarily the result of a microvasculopathy caused by abnormal glucose metabolism. Pericyte loss and thickening of the basement membranes are associated with a breakdown in the inner blood–retina barrier. The process is influenced by a number of chemicals, including mediators of inflammation and vascular endothelial growth factor (VEGF). In some patients with DME, ischemia of the peripheral retina may promote production of VEGF, which in turn results in increased vascular permeability and macular edema. This is supported by wide-field fluorescein angiographic findings indicating peripheral retinal capillary non-perfusion in some patients with DME.

Laser treatment remains the mainstay treatment for each form of diabetic retinopathy. The Diabetic retinopathy study (DRS) showed that pan-retinal laser photocoagulation (PRP) significantly reduced the risk of severe visual loss (5/200 or worse) in patients with high-risk characteristics.<sup>8</sup> The Early treatment diabetic retinopathy study (ETDRS) demonstrated that macular photocoagulation of eyes with clinically significant macular edema (CSME) reduced the risk of moderate visual loss (doubling of visual angle) from 30 to 15 % at three years.<sup>9</sup> In addition, about 20 % of patients undergoing laser treatment had some improvement in vision.

Though glucose and blood pressure control and laser treatments are helpful, the number of patients who gain vision is small. New potential treatments are being evaluated for their effectiveness in controlling abnormal vascular permeability, reducing macular edema, and improving

vision. Many of these new treatment modalities target the inflammatory and VEGF pathways, in order to decrease vascular permeability and therefore macular edema.

### Corticosteroids Intravitreal Triamcinolone Acetonide

Intravitreal triamcinolone acetonide (IVTA) has been used for treatment of DME. IVTA has also been used as an adjunct for patients undergoing panretinal photocoagulation (PRP) to reduce post-laser macular edema, prior to macular laser photocoagulation to reduce edema, and intraoperatively to better visualize the posterior cortical vitreous, and to decrease post-operative vascular permeability. Limited retrospective and prospective studies have shown improvements or stabilization of visual acuity in the short term, especially in patients with cystoid macular edema.<sup>10-15</sup> In a prospective randomized trial the best corrected visual acuity (BCVA) improved by  $\geq 5$  letters after two years in 56 % of treated eyes, compared with 26 % of eyes in the placebo group.<sup>15</sup> An increase in intraocular pressure (IOP) of  $\geq 5$  mmHg was observed in 68 % of treated eyes. Glaucoma medication was required in 44 %, and surgery was required in 5 % of the treated eyes. Cataract surgery was performed in 54 % of treated eyes within the two-year follow-up period. There was one case of infectious endophthalmitis in the treatment group.

In another study, 88 eyes with DME were randomized to 4 mg IVTA or laser photocoagulation.<sup>16</sup> Patients were assessed and treated every four months. Optical coherence tomography (OCT) showed a reduction in central subfield thickness (CST) of 82.0  $\mu\text{m}$  with IVTA and 62.3  $\mu\text{m}$  with laser at 12 months. The ETDRS scores remained the same in both groups. In the IVTA group, 22 of 43 eyes required ocular antihypertensives, and one eye developed sterile endophthalmitis. This study did not show a benefit from intravitreal triamcinolone over conventional laser therapy for patients with chronic DME.

Higher-dose IVTA may be associated with improved outcomes as well as increased side effects. In a study of 63 eyes of 63 patients with DME, the eyes were randomized to 4, 6, and 8 mg IVTA. Although all groups demonstrated improvement in BCVA and macular thickness, the mean BCVA improvement at six months was significantly higher in the 8 mg group. Elevated IOP occurred in 39 % of the 4 mg and 55 % of the 8 mg group.<sup>17</sup>

The combination of IVTA and macular laser photocoagulation was studied in 86 eyes with diffuse DME who were randomized to IVTA alone or IVTA followed by macular laser photocoagulation three weeks later. The logarithm of the minimum angle of resolution (logMAR) visual acuity was significantly better in the combination group at three and six months.<sup>18</sup>

The Diabetic Retinopathy Clinical Research Network (DRCRnet) is a collaborative network dedicated to facilitating multicenter clinical research of diabetic retinal diseases. The network was formed in September 2002 and currently includes over 150 participating sites with over 500 physicians. The network is funded by the National Eye Institute (NEI). DRCRnet recently reported on the results of protocol B comparing focal laser photocoagulation to 1 mg or 4 mg IVTA for treatment of DME. Eight hundred forty eyes with DME were randomized to macular laser photocoagulation, 1 mg IVTA, or 4 mg IVTA. Retreatment was given for

persistent or new edema at four-month intervals. At four months, mean visual acuity was better in the 4 mg triamcinolone group than in either the laser group or the 1 mg triamcinolone group. By one year, there were no significant differences among groups in mean visual acuity. At the 16-month visit and extending through the primary outcome visit at two years, mean BCVA was better in the laser group than in the other two groups. OCT results of central subfield thickness generally paralleled the visual acuity results. The study concluded that over a two-year period, focal/grid photocoagulation is more effective and has fewer side effects than 1 or 4 mg doses of IVTA and should be the benchmark against which other treatments are compared in clinical trials of DME.<sup>19</sup>

### Sustained-release Fluocinolone Acetonide

Sustained-release fluocinolone acetonide (FA) (Retisert™, Bausch and Lomb) is an implantable non-biodegradable intraocular device that delivers 0.59 mg FA for up to three years at a rate of 0.5  $\mu\text{g}$  per day.<sup>20</sup> The implant is constructed of a 1.5 mm core of drug and a silicone/polyvinyl acetonide laminated coating affixed to a strut. Sustained-release FA implant is currently Food and Drug Administration (FDA)-approved for chronic non-infectious posterior uveitis. Its use in DME was evaluated in a Phase II clinical trial that randomized 197 patients to receive either the 0.59 mg implant or standard of care (repeat laser or observation).<sup>21</sup> At three years, the implant eyes had less macular edema than controls. Fifty-eight per cent of the implant eyes showed no evidence of edema, compared with 30 % of those receiving standard of care. Visual acuity improved by  $\geq 3$  lines in 28 % of the implant group and in 15 % of the standard-of-care group. The most common adverse events were cataract surgery in 95 % of the phakic eyes and an IOP rise in 35 %. Twenty-eight per cent of the implanted eyes required a glaucoma filtering procedure and 5 % had the implant removed to control IOP.

### Medidur

Medidur™ (Alimera and pSivida) is an injectable non-biodegradable device that delivers FA into the vitreous cavity. Unlike Retisert, which is placed in the operating room, Medidur is administered in the office setting, providing a low daily dose of FA for 24–36 months. It is inserted using a 25-gauge needle, which allows for a self-sealing wound.

Alimera Sciences, Inc., recently reported on its interim month-three safety and efficacy results from the first human pharmacokinetic study of Medidur FA, which it intends to market under the trade name Iluvien if approved by the FDA. The 36-month, open-label Phase II study, running concurrently with the Phase III FA in DME (FAME) study, was designed primarily to assess systemic exposure of the corticosteroid FA after administration of Iluvien in patients with DME. Of the 37 subjects enrolled in the trial, 20 were on the low dose (approximately 0.23  $\mu\text{g}/\text{day}$ ) and 17 were on the high dose (approximately 0.45  $\mu\text{g}/\text{day}$ ). Preliminary results indicated that 20 % of the low-dose patients and 18 % of the high-dose patients showed an improvement in BCVA of  $\geq 15$  letters. Mean macular thickness decreased in both groups. No adverse events related to IOP were observed in the low-dose patients; 12 % of the high-dose patients experienced IOP elevation greater than 30 mmHg. The posterior location of the implant may reduce the incidence of glaucoma. Cataract formation was reported in a patient in the high-dose group. Additional interim results will be published at months six, 12, 18, 24, 30, and 36.

The Fluocinolone acetonide macular edema (FAME) study consists of two masked, randomized, multicenter trials that are fully enrolled, with 956 patients in the US, Canada, Europe, and India who will be followed up for 36 months. The trials began in September 2005.

### Posurdex

Posurdex® (Allergan) is an intravitreal extended-release, biodegradable dexamethasone implant. A Phase II multicenter trial showed significant improvement of vision in patients with DME. A total of 306 patients were randomized 1:1:1 to Posurdex 350 µg, Posurdex 700 µg, or observation. The patients' macular edema was secondary to diabetic retinopathy, retinal vein occlusion, Irvine-Gass syndrome, and uveitis. At six-month follow-up 36 % of the 700 µg group and 27 % of the 350 µg group had at least a two-line improvement in BCVA, compared with 19 % of the observation patients. Nineteen per cent of the 700 µg group had an improvement of ≥3 lines compared with 8 % of the observation group. The average change in CST was -142 µm for the 700 µg dose and -61 µm for the 350 µg dose. There was an increase of 11 µm in the observation group. Seventeen per cent of the 700 µg group experienced an increase in IOP of 10 mmHg or more at some point during the study, compared with 12 % for the 350 µg patients and 3 % for the observation group. The original study was performed with an implantable biodegradable system placed in the operating room. An office-based, 22-gauge injector system is currently being used in Phase III trials. Allergan 012 is a multicenter, randomized, double-blind clinical trial that is evaluating the safety and efficacy of the intravitreal implant of dexamethasone (700 µg every six months) in combination with macular laser photocoagulation, compared with macular laser photocoagulation alone, in patients with DME. Outcome measures include BCVA at month 12, CST, vascular leakage (FA), and time to retreatment. This study started in May 2007 and is currently recruiting participants. The trial has not proceeded to Phase 2.

### I-vation

I-vation™ (SurModics) implant contains triamcinolone acetonide. In a multicenter Phase I study 31 patients were randomized to receive the 925 µg implant in either the slow-release or fast-release version. The interim data on 24 patients at 18 months showed no surgical complications, and no uncontrollable IOP above 22 mmHg.<sup>22</sup> One patient developed endophthalmitis. No systemic side effects were noted. BCVA improved from a baseline of 46 letters (ETDRS) to 64 letters and CST decreased from a baseline of 395 to 158 µm at 18 months. This implant may be easily explanted if IOP becomes elevated.

### Nova63035

Nova63035 (Novagali) is an injectable emulsion that contains a tissue-activated corticosteroid prodrug. The prodrug is converted into the drug by the enzymes that are present in the retina and choroid. A Phase I non-randomized, open-label, dose-escalation clinical study to assess the safety and tolerability of Nova63035 in patients with DME is currently recruiting participants.

## Anti-vascular Endothelial Growth Factor Drugs

### Ranibizumab

Ranibizumab (Genentech/Roche) is a humanized antigen-binding fragment against all isoforms of VEGF. Currently, it is the only FDA-approved

anti-VEGF drug that has been shown to improve vision in patients with choroidal neovascularization. A single-center dose-escalating pilot study of ranibizumab in patients with central DME showed improved vision in the majority of patients, particularly at higher doses. Improvement of macular edema was observed, with a reduction of 45.3 µm in the low dose and 197.8 µm in the high dose group.<sup>23</sup>

In a Phase I study, Ranibizumab for edema of the macula in diabetes (READ-1), Nguyen et al. reported an improvement in both visual acuity and OCT in patients (n=10) who received 0.5 mg ranibizumab at baseline and months 1, 2, 4, and 6. At month seven, the mean improvement in BCVA was 14 ETDRS letters. The CST improved by 246 µm.<sup>24</sup>

The READ-2 study is a Phase II randomized, multicenter clinical trial, which started in December 2006. It is designed to evaluate the long-term safety and effectiveness of injections of ranibizumab in patients with DME. In addition, the trial evaluates the efficacy of ranibizumab versus conventional treatment with laser photocoagulation therapy, or a combination of ranibizumab and laser photocoagulation. One hundred and twenty-six patients have been randomized to receive one of three interventions: ranibizumab, laser photocoagulation, or a combination of the two treatments. The study recently ended at six months, and patients will be monitored for a further two years. The interim results, reported at the 2008 annual meeting of the Association for Research in Vision and Ophthalmology, indicated patients treated with ranibizumab experienced greater improvements in BCVA compared with patients receiving either of the other interventions. On average, the BCVA of ranibizumab-treated patients improved to 20/63 at month six, compared with an unchanged BCVA of about 20/80 in both the laser and the combination treatment groups. In addition, patients treated with ranibizumab had a 56 % reduction in excess retinal thickness, whereas only an 11 % reduction was seen in those receiving laser treatments.

DRCRnet protocol I is an ongoing Phase III randomized, multicenter clinical trial studying intravitreal ranibizumab or IVTA in combination with laser photocoagulation for treatment of center-involving DME (CST >250 µm). Outcome measures include BCVA at 12 months, change in CST and retinal volume measured on OCT, and number of injections in the first year.

The Study of ranibizumab injection in subjects with CSME with center involvement secondary to diabetes mellitus (RIDE) and Ranibizumab injection in subjects with CSME (RISE) studies are Phase III double-masked, multicenter, randomized, sham injection-controlled trials of the efficacy and safety of 0.5 mg intravitreal ranibizumab injection every four weeks for 24 months in patients with center-involving DME. The studies started in May 2007 and are currently recruiting participants. RIDE and RISE are sponsored by Genentech. Outcome measures include proportion of subjects who gain at least 15 letters in BCVA, mean change in BCVA and central foveal thickness, proportion of subjects with resolution of leakage, mean number of macular laser treatments, and change in contrast sensitivity.

The Safety and efficacy of ranibizumab in DME (RESOLVE) study is a randomized, double-masked, multicenter, Phase II study assessing the safety and efficacy of two concentrations of intravitreal ranibizumab

injections compared with non-treatment control for the treatment of DME with center involvement. This study is ongoing, but is not recruiting participants.

The Combined approach to treatment using ranibizumab and efalizumab for DME (CAPTURE) study is a Phase I randomized, open-label, dose-comparison, safety/efficacy study evaluating combination treatment using ranibizumab and efalizumab (Raptiva®, Genentech) for DME. Efalizumab inhibits the binding of leukocyte function-associated antigen-1 (LFA-1) to intercellular adhesion molecule-1 (ICAM-1), thereby inhibiting the adhesion of leukocytes to other cell types. Patients are randomized to 0.5 mg intravitreal ranibizumab alone every four weeks, 1 mg/kg subcutaneous efalizumab alone weekly, or combination. It should be noted, however, that at the time of writing the study had been terminated and the results have not been published.

### Bevacizumab (Avastin)

Bevacizumab (Avastin®, Genentech) is a full-length humanized antibody against all isoforms of VEGF. Small series have shown short-term improvement in DME, regression of proliferative retinopathy, clearing of vitreous hemorrhage and regression of rubeosis.<sup>25-30</sup> The DRCRnet study group recently reported on a Phase II randomized clinical trial of intravitreal bevacizumab in DME.<sup>31</sup> The group provided data on the short-term effect of intravitreal bevacizumab in DME. One hundred and twenty-one eyes of 121 subjects with DME and BCVA ranging from 20/32 to 20/320 were randomized to one of five groups

- focal photocoagulation at baseline;
- intravitreal injection of 1.25 mg bevacizumab at baseline and six weeks;
- intravitreal injection of 2.5 mg bevacizumab at baseline and six weeks;
- intravitreal injection of 1.25 mg bevacizumab at baseline and sham injection at six weeks; or
- intravitreal injection of 1.25 mg bevacizumab at baseline and six weeks with photocoagulation at three weeks.

At baseline, median CST was 411 µm and median BCVA was 20/50. Compared with group A, groups B and C had a greater reduction in CST at three weeks and about one line better median BCVA over 12 weeks. There were no major differences between groups B and C in CST reduction or BCVA improvement. A CST reduction was present at three weeks in 43 % of bevacizumab-treated eyes and 28 % of eyes treated with laser alone, and at six weeks in 37 and 50 % of eyes, respectively. Combining focal photocoagulation with bevacizumab resulted in no apparent short-term benefit or adverse outcomes. DRCRnet results demonstrated that intravitreal bevacizumab can reduce DME in some eyes, but the study was not designed to determine whether treatment is beneficial.

### Pegaptanib

VEGF levels have been found to be elevated in the vitreous and the anterior chamber samples in patients with diabetic retinopathy.<sup>32</sup> Pegaptanib (Macugen®, OSI/Eyetech, Pfizer) is an aptamer active that inhibits VEGF 165. It was the first anti-VEGF treatment that the FDA approved for neovascular age-related macular degeneration. In a prospective multicenter, randomized Phase II trial of patients with DME, pegaptanib at 0.3, 1, and 3 mg, versus sham injection, was administered at six-week intervals via intravitreal injection.<sup>33,34</sup> Focal laser therapy

was allowed prior to enrollment and after week 18. Patients received injections at baseline, week six and week 12 and additional injections as needed until week 30. There were 172 participants with 39 assigned to the 0.3 mg dose. Visual acuity improvement of 10 or more letters was observed in 34 % of study eyes compared with 10 % of controls. CST decreased by 64 µm in the 0.3 mg treated group versus a gain of 4 µm in the standard-of-care group. Regression of proliferative retinopathy, less severe venous beading, reduction of intraretinal microvascular abnormalities, and reduced need for photocoagulation were also observed.

### Vascular Endothelial Growth Factor Trap

The VEGF Trap (Regeneron and Bayer Health Care) is a fully human soluble decoy smaller than an antibody consisting of the Ig-2 domain of VEGF receptor-1 and the Ig-3 domain of VEGF receptor-2 fused to an Fc fragment protein that binds all VEGF isoforms as well as placental growth factor.<sup>35</sup> VEGF Trap is now completing Phase II studies for the treatment of choroidal neovascularization secondary to age-related macular degeneration. In a Phase I study of VEGF Trap in DME the drug was administered as a single 4.0 mg intravitreal injection to five patients with long-standing diabetes and multiple prior treatments for DME. The single injection resulted in a decrease in mean CST and mean macular volume throughout the six-week observation period. The six-month results showed all patients treated with VEGF Trap had a statistically significant improvement in vision over sham treatment

### Bevasiranib

Bevasiranib (OPKO) is a small interfering RNA (siRNA) drug designed to silence the genes that produce VEGF. The RNAi assessment of bevasiranib in DME (RACE) trial was a pilot Phase II study of the safety and efficacy of bevasiranib in patients with DME. The study indicated a trend for improvement in macular thickness between weeks eight and 12.

### Pharmacological Vitrectomy

It is hypothesized that posterior vitreous detachment (PVD) may protect against the development and progression of macular edema and proliferative diabetic retinopathy. Vitrectomy has been suggested as an adjunct to the treatment of DME in selective cases. The rationale for vitrectomy surgery includes relief of anteroposterior and tangential traction, removal of vasoproliferative and vasopermeable factors, and possibly improved oxygenation.

Pharmacological vitrectomy involves the dissolution of the vitreous by chemical means. The results of small uncontrolled studies have been encouraging. A purified form of hyaluronidase, Vitrase™ (ISTA Pharmaceuticals, Irvine, CA), was studied in Phase III trials and showed a significant reduction in vitreous hemorrhage which allowed laser treatment.<sup>36,37</sup> No serious safety issues were reported and the incidence of retinal detachment was not statistically different between treated eyes and control groups. The study did not report on PVD induction. Animal studies of intravitreal hyaluronidase in rabbit eyes did not demonstrate an increase in induction of PVD.<sup>38</sup> Vitrase is currently not FDA approved for treatment of vitreous hemorrhage although it has been used off-label.

Plasmin is a non-specific protease mediating the fibrinolytic process. It also acts on glycoproteins including laminin and fibronectin, present

at the vitreoretinal interface. Experimental studies indicate intravitreal injection of plasmin can induce PVD in some cases.<sup>39-41</sup> Plasmin is not available for clinical application. Autologous plasminogen has been reported to assist vitreoretinal surgery by achieving spontaneous or easy removal of the posterior hyaloid.<sup>42-44</sup> Recombinant microplasmin (ThromboGenics Ltd, Dublin) is a truncated molecule containing the catalytic domain of human plasmin that is currently under clinical investigation. A Phase II randomized trial, Multicenter study to compare multiple doses of intravitreal microplasmin versus sham injection for treatment of patients with DME (MIVI-II) is currently recruiting participants for non-surgical PVD induction for treatment of patients with DME.

A Phase III safety and efficacy study of intravitreal injection of carbamide (VitreoSolve®) (Vitreoretinal Technologies, CA) for non-proliferative diabetic retinopathy started in March 2008 and is currently ongoing. The primary outcome includes development of PVD confirmed by B-scan ultrasound. The study is expected to enroll 400 subjects. The Phase 1 trial demonstrated good safety profile and a biologic signal of activity. A Phase 2 trial is underway.

### iCo-007

Multiple growth factors are implicated in the etiology of DME and diabetic retinopathy. iCo-007 (ISIS Pharmaceuticals) is a second-generation antisense drug that binds to the mRNA molecule, decreasing the production of C-raf kinase through which multiple growth factors, including VEGF, signal. iCo-007 has the potential to inhibit the growth of new blood vessels and decrease vascular permeability. Antisense therapeutics may have increased target-binding affinity and improved resistance to degradation, possibly resulting in less frequent dosing.

### Sirolimus

Sirolimus (Rapamycin, MacuSight) is an FDA-approved anti-rejection drug used systemically following renal transplants. It has antifibrotic, antiangiogenic, antipermeability, and antiproliferative properties. Subconjunctival and intravitreal injections of sirolimus have been evaluated in a Phase I study. The preliminary results showed a positive response in BCVA and CST with both routes of administration. A Phase II trial using the subconjunctival route is starting enrollment.

### Infliximab

Infliximab (Remicade®, Johnson and Johnson) is a genetically engineered antibody against tumor necrosis factor-alpha (TNF- $\alpha$ ). A Phase I non-randomized, open-label study of intravitreal infliximab (0.5 mg/0.05 ml) in patients with refractory DME is currently recruiting participants.

### Ruboxistaurin (Arxxant)

Hyperglycemia increases serum and cellular levels of diacylglycerol, which is a physiologic activator of protein kinase C (PKC). Activated PKC levels are associated with both increased levels of VEGF and increased vascular permeability.<sup>45,46</sup> Ruboxistaurin (RBX) is a selective inhibitor of PKC. A Phase III study indicated that 32 mg/day RBX taken orally was effective in delaying the occurrence of moderate visual loss. Moderate visual loss occurred in 9.1 % of placebo-treated patients versus 5.5 % of RBX-treated patients. Visual improvement of >15 letters was seen in 4.9 % treated versus 2.4 %

placebo. Laser treatment for macular edema was reduced in the treated group, but a reduction in progression of diabetic retinopathy from moderately severe to very severe was not observed.<sup>47</sup>

The PKC inhibitor DME study (PKC-DMES) group reported the 30-month results of a multicenter, double-masked, randomized clinical trial evaluating the safety and efficacy of orally administered RBX in patients with DME. Six hundred eighty-six patients received placebo or RBX orally (4, 16, or 32 mg/day) for 30 months. The primary study outcome was progression to sight-threatening DME or application of macular photocoagulation for DME. The delay in progression to the primary outcome was not statistically significant. RBX was well-tolerated in this study.<sup>48</sup> The FDA has requested additional trials before approval of RBX.

### Octreotide

Two Phase III studies (Study 802 and 804) using the insulin-like growth factor antagonist octreotide (Sandostatin® LAR) have been completed. The purpose of these studies was to evaluate the 20 and 30 mg doses of Sandostatin LAR given intramuscularly monthly on progression of pre-existing diabetic retinopathy. The secondary endpoints were time to development of macular edema and the loss of visual acuity. Study patients from sites in the US, Canada, and Brazil (Study 804) who received the 30 mg dose did show a delay in progression of retinopathy. No effect was observed for visual acuity or progression to macular edema. The European study (802), however, did not confirm the delay in progression of retinopathy. Neither study showed a positive effect on visual acuity or reducing the progression of edema. The side effects observed were significant and included diarrhea, cholelithiasis, and mild hypoglycemia.

### Topical Medications

Mecamylamine (CoMentis) inhibits endothelial nicotinic acetylcholine (nACh) receptors and decreases angiogenesis and vascular permeability. A Phase II study of the safety and bioactivity of topical ocular mecamylamine administered twice a day for 12 weeks for the treatment of DME has recently been completed. Bromfenac (Xibrom™, ISTA) is a non-steroidal anti-inflammatory drug (NSAID) that is currently undergoing a non-randomized, open-label, uncontrolled Phase I pilot study for treatment of DME.

### Conclusions

Treatment of DME remains a major challenge despite improvements in management of blood glucose and pressure, use of laser photocoagulation, and improved vitreoretinal surgical techniques. Most new therapies are designed to reduce vascular permeability and improve macular edema through treatment of the anti-inflammatory and/or anti-VEGF mechanisms. With the addition of pharmacotherapy, either alone or in combination, improved visual outcomes may be possible. Currently retinal laser photocoagulation remains an integral component of the management of diabetic retinopathy. Further research is warranted in order to establish the role of peripheral retinal laser photocoagulation in the treatment of patients with DME and peripheral capillary non-perfusion. It is important to realize that short-term visual improvements with the new experimental treatments are exciting, but one must use caution as DME may be a long-term chronic problem. ■

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