Pharmacologic therapies for diabetic retinopathy and diabetic macular edema

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Abstract: Diabetic retinopathy (DR) and diabetic macular edema (DME) are leading causes of blindness in the working-aged population of most developed countries. The increasing number of persons with diabetes worldwide suggests that DR/DME will continue to be major contributors to vision loss and associated functional impairment for years to come. Early detection of retinopathy in persons with diabetes is critical in preventing visual loss, but current methods of screening fail to identify a sizable number of high-risk patients. The control of diabetes-associated metabolic abnormalities (ie, hyperglycemia, hyperlipidemia, and hypertension) is also important in preserving visual function, as these conditions have been identified as risk factors for both the development and progression of DR/DME. The non-pharmacologic interventions for DR/DME, laser photocoagulation and vitrectomy, only target advanced stages of disease. Several biochemical mechanisms, including increased vascular endothelial growth factor production, protein kinase C β activation, oxidative stress, and accumulation of intracellular sorbitol and advanced glycosylation end products, may contribute to the vascular disruptions that characterize DR/DME. The inhibition of these pathways holds the promise of the intervention for diabetic retinopathy with higher success rate and also at earlier, non-sight-threatening stages.

Recent pathophysiologic insights

Diabetic retinopathy/diabetic macular edema (DR/DME) are common microvascular complications in patients with diabetes, and may have a sudden, and debilitating impact on visual acuity (VA), eventually leading to blindness. DR is characterized by the growth of abnormal retinal blood vessels secondary to ischemia. These blood vessels grow in an attempt to supply oxygenated blood to the hypoxic retina. At any time during the progression of DR, patients with diabetes mellitus can also develop DME, which involves retinal thickening in the macular area. DME occurs following breakdown of the blood–retinal barrier due to leakage of dilated, hyperpermeable capillaries and microaneurysms. The current management strategy for DR/DME requires early detection and optimal metabolic control to slow the progression of disease. Adherence to these recommendations is hampered by the fact that the condition is generally asymptomatic at early stages. The non-pharmacological treatments for DR/DME, laser photocoagulation and vitrectomy, only target advanced stages of DR/DME. Several pharmacologic therapies, mainly intravitreal triamcinolone and more recently anti vascular growth factor agents are currently used as an adjunctive therapy for DR/DME. Other pharmacologic therapies are developed to treat DR/DME. This review will focus on the current understanding of the pathophysiology of DR/DME and its present and potential future pharmacologic treatments.

DR/DME pathophysiology

Many studies have demonstrated that chronic hyperglycemia, as well as hypertension, and probably hyperlipidemia, contribute to the pathogenesis of DR (Klein et al 1988, 1991; The Diabetes Control and Complications Trial Research Group 1993; Chew et al 1996; Chaturvedi et al 1998; UK Prospective Diabetes Study Group 1998a, 1998b, 1998c).

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The exact mechanisms by which elevated glucose initiates the vascular disruption in retinopathy remain poorly defined. Different biochemical mechanisms have been suggested as explanations for the development and progression of diabetic retinopathy and have led to exploration of possible treatments (Table 1).

The vascular disruptions of DR/DME are characterized by abnormal vascular flow, disruptions in permeability, and/or nonperfusion of capillaries. A hallmark of early DR is the change in the structure and cellular composition of the microvasculature (Kubawara and Cogan 1962; Sims 1986; Antonelli-Orlidge et al 1989). Endothelial cells are responsible for maintaining the blood-retinal barrier, and damage to them results in increased vascular permeability. In early stages of DME, breakdown of the inner blood-retinal barrier occurs, resulting in accumulation of extracellular fluid in the macula (Ferris and Patz 1984; Antcliff and Marshall 1999). Abnormal vessel permeability results in leakage of water, blood cells, proteins, and lipoproteins into the surrounding retinal tissue, and subsequent dysfunction of the macula resulting in decreased vision.

Pericytes are essential cellular components in the regulation of retinal capillary perfusion, and damage to these cells in diabetes mellitus leads to altered retinal hemodynamics, including abnormal autoregulation of retinal blood flow (Ciulla et al 2002). Loss of retinal pericytes represents another early feature of DR (Speiser et al 1968; Ansari et al 1998; Paget et al 1998), and correlates with microaneurysm formation (Cogan et al 1961; Kubawara and Cogan 1962; Speiser et al 1968).

Table 1 DR/DME proposed mechanism and currently/near future available corresponding therapy

Mechanism	Mechanism-related therapy
Elevated VEGF	Anti VEGF • Ranibizumab (Lucentis) • Bevacizumab (Avastin) • Pegaptanib (Macugen)
Relative/absolute insufficiency of PEDF	PEDF gene – early stages of research
Inflammation	Intravitreal Steroids • Triamcinolone (Kenalog) effective but with side effects • Dexamethasone (Posurdex) – in Phase III trial • Fluocinolone acetonide implant (Retisert) – at present, proven for uveitis only
Activation of PKC	PKC β Inhibitor • Ruboxistaurin (Arxxant) – proven in Phase III trial, under FDA review
Genetics	None at present

Abbreviations: VEGF, vascular endothelial growth factor; PEDF, pigment epithelium-derived factor; PKC, protein kinase C.

There is evidence that retinal leukostasis may also play an important role in the pathogenesis of DR. Leukocytes possess large cell volume, high cytoplasmic rigidity, a natural tendency to adhere to the vascular endothelium, and a capacity to generate toxic superoxide radicals and proteolytic enzymes (Miyamoto and Ogura 1999). In diabetes, there is increased retinal leukostasis that affects retinal endothelial function, retinal perfusion, angiogenesis, and vascular permeability. In particular, leukocytes in diabetes are less deformable, a higher proportion are activated and they may be involved in capillary non-perfusion, endothelial cell damage, and vascular leakage in the retinal microcirculation (Miyamoto and Ogura 1999). Streptozotocin-induced diabetic rats showed that diabetic vascular leakage and nonperfusion are temporally and spatially associated with retinal leukostasis (Miyamoto et al 1999). Serial acridine orange leukocyte fluorography and fluorescein angiography (FA) show trapped leukocytes directly associated with areas of downstream nonperfusion in the diabetic retinal microcirculation (Miyamoto and Ogura 1999). While leukostasis probably plays a key role in the pathogenesis of DR, platelets and red blood cells are also involved in this process.

As a result of occluded capillaries, retinal ischemia stimulates a pathologic neovascularization mediated by angiogenic factors, such as vascular endothelial growth factor (VEGF), which results in proliferative DR (PDR) (Aiello et al 1994, 2001; Miller et al 1997). This neovascularization is the predominant feature of PDR. VEGF also plays an important role in the development of DME (Nguyen et al 2006). Another common feature of DR is the thickening of the capillary basement membrane and increased deposition of extracellular matrix components. This may contribute to the development of abnormal retinal hemodynamics (Williamson and Kilo 1984), including abnormal autoregulation of retinal blood flow. Understanding the diabetes-induced mechanisms that contribute to pericyte loss, endothelial cell proliferation, neovascularization, and alterations in basement membrane structure is therefore central to the design of pharmacologic therapeutic strategies to treat and prevent early diabetes-related microvascular changes.

DR/DME management and treatment

Control of systemic metabolic abnormalities

Control of the metabolic abnormalities of diabetes has a major effect on the development of diabetic microvascular complications (Aiello and Cahill 2001). The DCCT and the United

Kingdom Prospective Diabetes Study (UKPDS) showed that optimal metabolic control could reduce the incidence and progression of DR (The Diabetes Control and Complications Trial Research Group 1993; UK Prospective Diabetes Study Group 1998a). The benefits of intensive glycemic control persisted over an extended follow up (Diabetes Control and Complications Trial 2000). Thus, optimal metabolic control should be an important treatment goal and should be implemented early and maintained for as long as it is safely possible (Diabetes Control and Complications Trial 2000). Rigid control of hypertension is also effective in reducing disease progression (Chaturvedi et al 1998; UK Prospective Diabetes Study Group 1998b, 1998c). Hyperlipidemia has been linked to the presence of retinal hard exudates in patients with DR (Klein et al 1991; Chew et al 1996). The Early Treatment Diabetic Retinopathy Study (ETDRS) (Chew et al 1996) had indirectly found that elevated cholesterol resulted in doubling the risk of retinal hard exudates at baseline, increasing the risks of developing hard exudates during follow-up and moderate vision loss at 5 years by 50%, each. Also, some evidence suggests that lipid-lowering therapy may reduce hard exudates and microaneurysms (Gordon et al 1991). The Action to Control Cardiovascular Risk in Diabetes (ACCORD), a randomized, multicenter trial involving 10,000 patients with type 2 diabetes mellitus patients is currently being conducted in the US (NIH News Release 2003). Around 4000 patients within the ACCORD trial participate in an ophthalmic sub-study, which should directly assess the role of cholesterol control and other metabolic parameters in preventing and slowing the progression of DR/DME. ACCORD trial results are expected in 2010.

The following are the recommended values for hemoglobin $A1_c$ ($HbA1_c$ < 6.5%–7%), blood pressure (<130/<85 mm Hg), and low-density lipoprotein (LDL) cholesterol Assoc. of Clinical Endocrinologists 2000; Hutchinson et al 2000). However, many patients fail to achieve or maintain these levels of metabolic control. In patients who do achieve a significant reduction in $HbA1_c$, there is an associated increased risk of severe hypoglycemia (The Diabetes Control and Complications Trial Research Group 1993; UK Prospective Diabetes Study Group 1998a; Chase et al 2001). Primary care physicians need to recognize correctable risk factors (ie, hyperglycemia, hypertension, and/or hyperlipidemia) so that appropriate monitoring and referral for eye care can be implemented.

DR/DME non-pharmacologic therapies

Laser photocoagulation therapy has proven effective in reducing DR progression, and vitrectomy can in many cases prevent severe vision loss in patients with advanced stages of DR. Unfortunately, both treatments carry a risk of additional vision loss, and neither is effective at restoring the vision to normal. Laser photocoagulation is used to treat both DR and DME. The goal of macular laser photocoagulation for DME is to limit vascular leakage through a series of focal laser burns at leaking microaneurysms or grid laser burns in regions of diffuse breakdown of the blood-retinal barrier and macular areas with capillary non-perfusion. The rationale of focal/grid laser treatment is to reduce the leakage from the microaneurysms and hence reducing the macular edema, reduce the macular area in the inner retina which is ischemic and hypoxic, and perhaps to allow oxygen from the choriocapillaris to diffuse to the hypoxic inner retina near it. The rationale of panretinal photocoagulation for PDR is to ablate ischemic areas of the peripheral retina and thereby reduce the induction of angiogenic growth factors. Results of the Diabetic Retinopathy Study (DRS) demonstrated that panretinal photocoagulation effectively reduces the risk of vision loss in a majority (60%) of patients with PDR (Ferris 1993). The Early Treatment Diabetic Retinopathy Study (ETDRS) compared outcomes in eyes assigned to either deferral of macular laser photocoagulation or immediate treatment for clinically-significant DME, [defined as; retinal edema within 500 μm of the center of the fovea; hard exudates within 500 μm of the fovea, if associated with adjacent retinal thickening (which may be outside the 500 μm limit); retinal edema that is one disc area (1500 μm) or larger, any part of which is within one disc diameter or the center of the fovea] (Early Treatment Diabetic Retinopathy Study Research Group 1985). ETDRS results showed that macular laser photocoagulation reduced the risk of vision loss by 50% for patients with clinically-significant DME. Macular focal and grid laser photocoagulation is indicated for clinically-significant DME, and panretinal photocoagulation is indicated for high-risk PDR (Mogensen et al 1979; Early Treatment Diabetic Retinopathy Study Research Group 1985; Raskin and Arauz-Pacheco 1992; Ferris 1993). In more severe cases of DR, specifically those with tractional retinal detachment or severe non-clearing vitreous hemorrhage, vitrectomy is indicated to prevent blindness and/or severe visual loss (Mason et al 2006). Vitrectomy is clearly beneficial for the treatment of advanced, active PDR (Diabetic Retinopathy Vitrectomy Study Research Group 1988). Early vitrectomy increased the percentage of eyes with a VA of ≥ 10/20 or better to 44%, compared with 28% in a conventionally managed group (Diabetic Retinopathy Vitrectomy Study (DRVS) Research Group

1988). The use of early vitrectomy is also warranted for eyes with very severe PDR, but not for patients with less severe DR (DRVS Research Group 1988; DRVS Research Group 1990). However, recent advances in surgical techniques and technology since the DRVS have led to enhancement of the risk/benefit ratio for pars plana vitrectomy and widening indications for this procedure (Mason et al 2006). Vitrectomy may be of benefit in the management of DME. An ongoing study by the Diabetic Retinopathy Clinical Research Network, is currently evaluating the role of focal/grid laser compared with vitrectomy for DME (Mason et al 2006). A recently published paper compared the effects of PPV and dye-enhanced ILM peel with grid laser in diffuse DME (Kumar et al 2006). Kumar et al study involved 24 eyes of 24 patients with metabolically stable diabetes and with diffuse DME, and found that at the end of 6 months follow-up, the foveal thickness and macular volume have decreased more significantly in the PPV/ILM group compared to the laser group ($p = 0.001$), without any significant benefit to the visual acuity ($p = 0.525$). In this study (Kumar et al 2006), no correlation was found between the improvement in visual acuity and the reduction of foveal thickness.

Given the risk of blindness without treatment, laser photocoagulation and/or vitrectomy will continue to have a major role in the management of DR/DME. Both laser photocoagulation and vitrectomy improve quality of life for patients with DR and are cost-effective (Javitt et al 1989; Sharma et al 2000; Sharma et al 2001). However, these interventions are indicated only when DR has progressed to a measurably advanced stage in which some visual acuity may already be lost. Side effects, such as loss of peripheral, night, or color vision, are noted by some photocoagulation-treated patients (Early Treatment Diabetic Retinopathy Study Research Group 1991b). Vitrectomy can accelerate cataract formation and includes risks of retinal detachment and endophthalmitis, which are fortunately rare (Lewis et al 1992). In some patients treated with photocoagulation, DR continues to progress and ongoing treatment is necessary. DME can also reoccur. These limitations, together with the growing numbers of diabetics worldwide, have led the pharmaceutical industry to invest in the study of pharmacologic therapies for DR/DME.

Current and potential near future DR/DME pharmacologic therapies

Due to the limitations of non-pharmacologic DR/DME treatments, the use of current available pharmacological therapies is increasing, while other pharmacologic agents, targeting the underlying biochemical DR/DME mechanisms that cause DR/DME are being developed.

Role of steroids for diabetic macular edema

Corticosteroids are known to reduce vascular permeability, reduce blood-retinal barrier breakdown, downregulate VEGF production, and inhibit certain matrix metalloproteinases. (Bhavsar 2006) There are several steroids that are being investigated for the treatment of diabetic retinopathy and its complications.

Triamcinolone acetonide (Kenalog®)

Intravitreal injections of triamcinolone acetonide (IVTA) are mostely given at a dose of 4 mg/0.1 ml but may be given at a higher dose of 20–25 mg/0.2 ml, as given by Jonas et al Over the last several years are gaining popularity by ophthalmologists around the world, as an adjunctive therapy to DME. The major complications of IVTA include elevated intraocular pressure in approximately 30%–50% of patients, cataract, and less commonly severe inflammatory response, and endophthalmitis (Bhavsar 2006). Since no pharmaceutical company support the study of commercially available triamcinolone acetonide, nearly all the publications in this topic are on relatively small and uncontrolled studies. An exception is Gillis et al recently published prospective, double-masked, placebo-controlled, randomized clinical trial on the 2-year safety and efficacy outcomes of intravitreal triamcinolone injections (4 mg/0.1 ml) for DME (Gillies et al 2006). Sixty-nine eyes of 43 patients with impaired vision that persisted or recurred after laser treatment entered into the study. Thirty four eyes randomized to receive active treatment and 35 placebo. Two-year data were available for 60 of 69 (87%) eyes of 35 of 41 (85%) patients. Eyes randomized to placebo received a subconjunctival injection of saline. Improvement of > or = 5 letters' best-corrected visual acuity was found in 19 of 34 (56%) eyes treated with intravitreal triamcinolone compared with 9 of 35 (26%) eyes treated with the placebo ($p = 0.006$). The mean improvement in VA was 5.7 letters more in the triamcinolone-treated eyes than in those treated with the placebo. An increase of intraocular pressure (IOP) of > or = 5 mmHg was observed in 23 of 34 (68%) treated versus 3 of 30 (10%) untreated eyes ($p < 0.0001$). Glaucoma medication was required in 15 of 34 (44%) treated versus 1 of 30 (3%) untreated eyes ($p = 0.0002$). Cataract surgery was performed in 15 of 28 (54%) treated versus 0 of 21 (0%) untreated eyes ($p < 0.0001$). Two eyes in the intravitreal triamcinolone-treated group required trabeculectomy.

Also, there was one case of infectious endophthalmitis in the treatment group.

Due to concerns regarding the possible toxic effects of the preservatives (mainly from the benzyl alcohol) within the commercially available triamcinolone acetonide (Kenalog®), Allergan has developed a preservative free triamcinolone acetonide, which is used now by the Diabetic Retinopathy Clinical Research Network for DME and also by the National Eye Institute in cases of retinal vein occlusion (SCORE trial). However, a recent human study, in which 4 mg of Kenalog was given intravitreally to DME, refractory to grid laser, did not find electroretinographic evidence of a retinotoxic effect of commercially avaliable Kenalog (Lang et al 2007).

Dexamethasone: Posurdex

The dexamethasone implant, Posurdex (Allergan Pharmaceuticals, Irvine, CA), is a biodegradable copolymer of poly [lactic-glycolic] acid and is designed for intravitreal delivery of dexamethasone for approximately 6 months (pers. comm., unpublished). A Phase II multicenter, controlled trial in patients with persistent macular edema due to a variety of causes including diabetic retinopathy, retinal vein occlusions, pseudophakic CME, and uveitis randomized 306 patients 1:1:1 to Posurdex 350 μg, Posurdex 750 μg, or observation (Diabetic Retinopathy 2006). Within this study, there were 172 patients with DME. In this subset of patients, there was a statistically significant benefit of reduction of fluorescein angiographic leakage at day 90 and reduction of retinal thickness with both the 350 μg, and 700 μg, implants. With respect to safety at day 180 in the DME subset, 4.1% (350 μg) and 6.1% (700 μg) of eyes had an intraocular pressure of 25 mmHg compared with 0.0% of eyes in the observation group. The presence or absence of cataract was similar among all groups.

Phase III clinical trials for DME (as well as for retinal vein occlusion) are currently being conducted, in which Posurdex is being injected intravitreally using a single use applicator.

Fluocinolone acetonide implant (Retisert)

The fluocinolone acetonide implant Retisert (Control Delivery Systems and Bausch and Lomb, Rochester, NY) is still being investigated for decreasing diabetic macular edema. This implant, approximately 2X2X6 mm in size, is designed to provide sustained release of fluocinolone for 1,000 days. The implant is inserted in the operating room through a pars plana incision and is sutured to the sclera, similar to the insertion of the ganciclovir implant. In a Phase III multicenter, masked, controlled, safety and efficacy study, 80 patients were randomized to either the 0.5 mg implant or the 2 mg implant versus standard of care (SOC), macular grid laser or observation (Pearson et al 2004). At 24 months, the 0.5 mg implant of fluocinolone showed resolution of macular edema in 53.7% of eyes versus 28.6% of the SOC eyes; 2 grade reduction in retinal thickness at the center of the macula in 46.2% of eyes versus 14.8% of SOC eyes; and a trend toward stabilizing or improving diabetic retinopathy scores in 87.2% of eyes versus 62.9% in SOC eyes. The major serious adverse events included elevation of intraocular pressure in 31.7% of the 0.5 mg group versus none of the standard of care group, with 19.5% of patients in the 0.5 mg group requiring trabeculectomy surgery and serious cataract progression and cataract extraction in 74.2% of eyes with the 0.5 mg group compared with 13.3% of eyes in the standard of care group (Bhavsar 2006).

Role of angiogenic factors and use of anti-angiogenic agents

The VEGFs (vascular endothelial growth factors) are a family of peptides produced from a single gene by alternative splicing (Frank 2004). VEGF isoforms are specifically mitogenic for vascular endothelial cells and also increase permeability at blood–tissue barriers. VEGF is essential for the formation of the fetal vascular system and its expression decreases substantially after birth. Some cells, however, constitutively secrete picomolar amounts; cells in the neural retina secrete 15–20 pg per milligram of protein, and cells in the combined choroid and retinal pigment epithelium secrete 50 pg per milligram of protein. Constitutive VEGF secretion from the retinal pigment epithelium is asymmetric, occurring primarily from the basal surface of these cells. VEGF expression is enhanced by hypoxia, which is a major stimulus for retinal neovascularization. Reduced retinal blood flow and accompanying hypoxia may be present even before the early signs of retinopathy, such as loss of capillary pericytes and endothelial cells, are identified, and these changes are likely to be accompanied by an increase in the synthesis and secretion of VEGF. Increased VEGF protein has been demonstrated in nonvascular cells in the eyes of persons with diabetes even in the absence of retinopathy supporting the hypothesis that diabetic retinopathy begins as a disease of retinal neurons and glia and only later involves the retinal vasculature. (Frank 2004).

Clinical studies have shown that VEGF levels increase in patients as they progress from nonproliferative DR to active PDR (Aiello et al 1994; Miller et al 1997). Successful

panretinal photocoagulation has been found to reduce intraocular VEGF levels by 75% (p = 0.008) in patients treated for ocular neovascularization (Aiello et al 1994). This has led to the use of anti VEGFs in DR/DME. There are at present three major anti VEGFs which are being used for DR/DME. Two anti VEGFs are in advanced clinical trials: pegaptanib sodium, Macugen (Eyetech, New York, NY), and ranibizumab, Lucentis (Genentech, San Francisco, CA). The third, bevacizumab (Avastin), is widely used since 2006 as an off-labeled indication for different retinal diseases, mainly, wet age-related macular degeneration, but more recently for other retinal diseases, including DR/DME.

Pegaptanib is an aptamer that binds to the $VEGF_{165}$ isoform of the VEGF-A gene. The Phase II DME trial of pegaptanib randomized 169 patients to one of three doses of intravitreal pegaptanib, 0.3 mg, 1 mg, or 3 mg versus standard of care with injections every 6 weeks for 12 weeks, with continued injections at the discretion of the investigators for up to 30 weeks. Thermal laser was permitted after 12 weeks (Macugen Diabetic Retinopathy Study Group 2005). The eyes that were treated with the 0.3 mg dose had a statistically significant gain in BCVA of 0 to 3 lines compared with the usual care eyes (73% versus 51%). Initial safety data show that pegaptanib appears to be well tolerated. The same study found Pegaptanib to cause either a temporary regression of neovascularization on fundus photographs or regression or absence of fluorescein leakage from neovascularization (Macugen Diabetic Retinopathy Study Group).

Ranibizumab is an affinity matured antibody fragment that binds to all of the isoforms of VEGF produced by the VEGF-A gene. Ranibizumab is currently being investigated in the treatment of diabetic macular edema in Phase II clinical studies. Recently, an open-label study to investigate the effect of intravitreal injections of 0.5 mg of ranibizumab in 10 patients with DME was published by Nguyen et al (2006). Ranibizumab was intravitreally injected at study entry and at one, two, four, and six months after entry. Mean values at baseline were 503 μm for foveal thickness and 28.1 letters (20/80) read on an ETDRS visual acuity chart. At seven months (one month after the fifth injection), the mean foveal thickness was 257 μm (a reduction of 246 μm; p = 0.005) and the mean visual acuity was 40.4 letters (20/40), which was an improvement of 12.3 letters (p = 0.005). Also, the injections were well-tolerated with no ocular or systemic adverse events.

Another ranibizumab/DME study, by Chun et al has recently been published (Chun et al 2006). This was a single-center, open-label, dose-escalating pilot study, with a total of 10 eyes of 10 patients. Three intravitreal injections of ranibizumab (0.3 mg or 0.5 mg, 5 patients each) administered on day 0, month 1, and month 2, and observation until month 24. At month 3, 4 of 10 patients gained > or = 15 letters, 5 of 10 gained > or = 10 letters, and 8 of 10 gained > or = 1 letters. At month 3, the mean decrease in retinal thickness of the center point of the central subfield was 45.3 +/– 196.3 μm for the low-dose group and 197.8 +/– 85.9 μm for the high-dose group. Also, intravitreal ranibizumab was well tolerated and no systemic adverse events were reported.

The efficacy of intraviteal injections of 1.25 mg bevacizumab (Avastin; Genentech) for the treatment of diabetic macular edema was recently tested in prospective, consecutive, noncomparative case series included 51 diabetic patients. (Haritoglou et al 2006). All patients completed 6 weeks of follow-up and 23 (45%) completed 12 weeks of follow-up. Sixteen patients (70%) had received at least two intravitreal injections. All patients had undergone previous treatments, such as focal laser therapy (35%), full-scatter panretinal laser therapy (37%), vitrectomy (12%), and intravitreal injection of triamcinolone (33%). The mean diameter of the foveal avascular zone was 503 μm, with 49% with values of >500 μm. At baseline, mean visual acuity was 0.86 +/– 0.38 logMAR of Snellen letters. Mean central retinal thickness by OCT was 501 +/– 163 μm. Mean visual acuity increased to 0.75 +/– 0.37 logMAR of Snellen letters at 6 weeks after injection (p = 0.001), with some regression to 0.84 +/– 0.41 logMAR of Snellen letters after 12 weeks. Mean retinal thickness +/– SD decreased to 425 +/– 180 μm at 2 weeks (p = 0.002), 416 +/– 180 μm at 6 weeks (p = 0.001), and 377 +/– 117 μm at 12 weeks (p = 0.001). Changes of retinal thickness and visual acuity correlated weakly (r = –0.480 and p = 0.03 at 6 weeks; r = –0.462 and p = 0.07 at 12 weeks).

The effect of a single intravitreal 1.5 mg bevacizumab (Avastin) for persistent new vessels (NV) associated with proliferative diabetic retinopathy was recently tested in a prospective, nonrandomized open-label study of diabetic patients with actively leaking NV refractory to laser treatment and best-corrected ETDRS visual acuity worse than 20/40 (Jorge et al 2006) . Fifteen consecutive patients were included and all completed the 12-week follow-up study period. The mean area of active leaking NV decreased significantly from 27.79 +/– 6.29 mm^2 at baseline to 5.43 +/– 2.18 mm^2 and 5.50 +/– 1.24 mm^2 ($p < 0.05$) at 1 and 12 weeks postinjection, respectively. At week 6 no leakage was observed. The mean visual acuity improved significantly from 0.90 (20/160) +/– 0.11 at baseline to 0.76 (20/125(+2)) +/– 0.12, 0.77 (20/125(+2)) +/– 0.11, and

0.77 (20/125(+2)) +/– 0.12 at weeks 1, 6, and 12, respectively ($p < 0.05$). No major adverse events were observed.

Role of PKC β pathway and use of PKC β inhibitors

Experimental studies have shown that protein kinase C (PKC) activity and levels of diacylglycerol (DAG), an activator of PKC, are increased following exposure of vascular tissues to elevated glucose (Inoguchi et al 1992; Xia et al 1994). Diabetes-induced DAG may derive from hydrolysis of phosphatidylinositides, metabolism of phosphatidylcholine or de novo synthesis of phosphatidic acid (Koya and King 1998). PKC activity is also increased following exposure of vascular endothelial cells to oxidative stress (Taher et al 1993; Nishikawa et al 2000a). PKC, β and δ have been identified as the predominant isoforms activated in vascular tissues in response to hyperglycemia (Inoguchi et al 1992; Koya and King 1998). PKC β has been shown to have an important role in regulating endothelial cell permeability (Nagpala et al 1996) and is an important signaling component for VEGF (Xia et al 1996). Transgenic animals overexpressing PKC β in vascular tissues developed retinal hemodynamic abnormalities similar to those observed in human DR (Takahara et al 1999).

The role of PKC in many cellular processes suggests that inhibition of all PKC isoforms would cause unacceptable toxicity (Jirousek et al 1996; Arevalo et al 2007). Ruboxistaurin, a specific inhibitor of PKC β1 and β2, (Jirousek et al 1996) has been shown to prevent and reverse microvascular complications in animal models of diabetes (Ishii et al 1996), to block neovascularization associated with retinal ischemia (Danis et al 1998), and to inhibit the effect of VEGF on retinal permeability and endothelial cell growth (Aiello et al 1997).

The results of a Phase III, 36 months, randomized, double-masked, placebo-controlled, parallel, multicenter trial evaluating the effect of oral ruboxistaurin on vision loss in patients with diabetes was recently published (PKC-DRS2 Group 2006). Six hundred eighty-five patients randomized at 70 clinical sites and had ophthalmologic examination at screening and at each 3-month visit. Eligible patients had a best-corrected visual acuity (VA) score of > or = 45 letters, and no prior panretinal photocoagulation in at least one eye. The main outcome was the effect of oral ruboxistaurin (32 mg/day) on reduction of sustained moderate visual loss (> or = 15-letter decrease in ETDRS VA score maintained > or = 6 months) in patients with moderately severe to very severe nonproliferative diabetic retinopathy. It was shown that sustained moderate visual loss occurred in 9.1% of placebo-treated patients versus 5.5% of ruboxistaurin-treated patients (40% risk reduction, $p = 0.034$). When clinically significant macular edema was >100 μm from the center of the macula at baseline, ruboxistaurin treatment was associated with less frequent progression of edema to within 100 microm (68% vs 50%, $p = 0.003$). Also, initial laser treatment for macular edema was 26% less frequent in eyes of ruboxistaurin-treated patients ($p = 0.008$).

Conclusions

Diabetic eye disease severely impacts quality of life for patients with diabetes by decreasing visual acuity and increasing the risk of blindness. DR condition results in loss of capillary integrity, microaneurysm formation, and ischemia, which in turn drive the progression of PDR. Accumulation of fluid in the retina secondary to capillary leakage and/or microaneurysms results in DME, which contributes to loss of vision in DR. There is substantial evidence that control over metabolic factors can effectively prevent the development and progression of DR/DME. However, many patients fail to achieve or maintain optimal levels of metabolic control. For such patients early detection and timely treatment of DR remains the standard of care. Although they are effective, sight-saving interventions, laser photocoagulation therapy and vitrectomy are invasive, associated with destructive side effects, and only treat the late stages of disease. In cases where laser insufficient controls PDR/DME, we can now add pharmacologic therapies directly into the vitreous. Also, a number of pharmacological agents that could slow the progression of DR/DME in earlier stages are now being tested. The first to be proven is the PKC inhibitor. These therapies have derived from improved understanding of the complex and often overlapping pathways involved in diabetes-induced microvascular damage. It is likely that in the future we would use a combination of pharmacological agents and at earlier stages of DR/DME. It is critical that healthcare providers interact with one another in managing patients to ensure that high-risk individuals are screened and treated early enough to benefit from the progress in the DR/DME treatment modalities and hence to better preserve vision.

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