Diabetic Retinopathy Update

Evolving Strategies in the Management of Diabetic Retinopathy

Ahmed M. Abu El-Asrar

INTRODUCTION

Diabetic retinopathy (DR), the most common long-term complication of diabetes mellitus, remains one of the leading causes of blindness worldwide. Tight glycemic and blood pressure control has been shown to significantly decrease the risk of development as well as the progression of retinopathy and represents the cornerstone of medical management of DR. The two most threatening complications of DR are diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR). Focal/grid photocoagulation and panretinal photocoagulation are standard treatments for both DME and PDR, respectively. Focal/grid photocoagulation is a better treatment than intravitreal triamcinolone acetonide in eyes with DME. Currently, most experts consider combination focal/grid laser therapy and pharmacotherapy with intravitreal antivascular endothelial growth factor agents in patients with center-involving DME. Combination therapy reduces the frequency of injections needed to control edema. Vitrectomy with removal of the posterior hyaloid seems to be effective in eyes with persistent diffuse DME, particularly in eyes with associated vitreomacular traction. Emerging therapies include fenofibrate, ruboxistaurin, renin-angiotensin system blockers, peroxisome proliferator-activated receptor gamma agonists, pharmacologic vitreolysis, and islet cell transplantation.

Key words: Diabetic Retinopathy, Review, Treatment

The diabetes control and complications trial

The diabetes control and complications trial (DCCT) randomized 1441 patients with type 1 diabetes to receive intensive glycemic or conventional therapy. Over 6.5 years of follow-up, intensive treatment [median HbA1c (glycosylated hemoglobin A1c), 7.2%] reduced the incidence of DR by 76% and progression of DR by 54%, as compared with conventional treatment. Long-term observational DCCT data showed that despite gradual equalization of HbA1c values after study termination, the rate of DR progression in the former intensively treated group remained significantly lower than in the former conventional group (“metabolic memory”), emphasizing the importance of instituting tight glycemic control early in the course of diabetes. Tight glycemic control has two clinical important adverse effects. First, there is risk of early worsening of DR. In the DCCT, this occurred in 13.1% of the intensive versus 7.6% of the conventional treatment group. However, this effect was
reversed by the 18th month, and no case of early worsening resulted in serious visual loss. In the DCCT, the long-term benefits of intensive insulin treatment greatly outweighed the risks of early worsening of DR. Therefore, ophthalmoscopic monitoring before initiation of intensive treatment and at 3-month intervals for 6-12 months thereafter seems to be appropriate when intensive treatment is initiated in patients with long-standing poor glycemic control, particularly if retinopathy is at or past moderate nonproliferative stage. In patients whose retinopathy is already approaching the high-risk stage, it may be prudent to delay the initiation of intensive treatment until photocoagulation can be completed, particularly if the HbA1c level is high. Second, tight glycemic control was associated with more frequent severe hypoglycemic episodes compared with the conventional group.

The United Kingdom Prospective Diabetes Study
The United Kingdom Prospective Diabetes Study (UKPDS) randomized 3867 patients with newly diagnosed type 2 diabetes to receive intensive or conventional therapy. After 12 years of follow-up, the progression of DR was reduced by 21% and the need for laser photocoagulation by 29% in the intensive versus the conventional treatment group. The UKPDS also investigated the influence of tight blood pressure control. A total of 1148 hypertensive patients with type 2 diabetes were randomized to less tight (<180/105 mmHg) and tight blood pressure control (<150/85 mmHg). With a median follow-up of 8.4 years, patients assigned to the tight control group had a 34% reduction in progression of retinopathy and a 47% reduced risk of deterioration in visual acuity of three lines compared with the less tight control group.

The Diabetic Retinopathy Study
The diabetic retinopathy study (DRS) investigated whether scatter (panretinal) photocoagulation, compared with indefinite deferral, could reduce the risk of vision loss from PDR. After 2 years, photocoagulation was shown to significantly reduce severe visual loss (best-corrected visual acuity of 5/200 or worse) from PDR. The benefit persisted through the entire duration of follow-up and was greatest among patients whose eyes had high-risk characteristics. Recently, the Diabetic Retinopathy Clinical Research Network compared the effects of single-sitting versus 4-sitting panretinal photocoagulation on macular edema in subjects with severe nonproliferative or early PDR with relatively good visual acuity and no or mild center-involved macular edema. The results suggest that clinically meaningful differences are unlikely in optical coherence tomography thickness or visual acuity following application in one sitting compared with four sittings.

The Early Treatment Diabetic Retinopathy Study
The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that focal/grid laser photocoagulation reduced the risk of moderate vision loss (i.e., a doubling of the visual angle) from clinically significant macular edema by 50% or more. ETDRS analyses also indicated that for patients with type 2 diabetes, it is especially important to consider scatter photocoagulation at the time of the development of severe nonproliferative or early proliferative retinopathy.

A recent randomized controlled trial compared modified ETDRS direct/grid photocoagulation technique and mild macular grid (MMG) laser technique in which microaneurysms are not treated directly and small mild burns are placed throughout the macula for DME. Twelve months after treatment, the MMG technique was less effective at reducing optical coherence tomography-measured retinal thickening than the current modified ETDRS laser photocoagulation approach. It was concluded that modified ETDRS focal photocoagulation should continue to be a standard approach for treating DME. Recently, the Diabetic Retinopathy Clinical Research Network concluded that focal/grid photocoagulation remains the standard management for DME.

The Diabetic Retinopathy Vitrectomy Study
The Diabetic Retinopathy Vitrectomy Study (DRVS) randomized 616 eyes with recent vitreous hemorrhage reducing visual acuity to 5/200 or less for at least 1 month to undergo early vitrectomy within 6 months or deferral of vitrectomy for one year. After 2 years of follow-up, 25% of the early vitrectomy group had visual acuity of 10/20 or better compared with 15% of the deferral group. In patients with type 1 diabetes, who were on average younger and had more severe PDR, there was a clear-cut advantage for early vitrectomy, as reflected in the percentage of eyes recovering visual acuity of 10/20 or better (36% versus 12% in the deferral group). No such advantage was found in type 2 diabetes group (16% in the early group versus 18% in the deferral group).

The DRVS and the ETDRS showed that laser photocoagulation for DR is effective at slowing the progression of retinopathy and reducing visual loss, but the treatment usually does not restore lost vision. Because these treatments are aimed at preventing vision loss and retinopathy can be asymptomatic, it is important to identify and treat patients early in the disease. To achieve this goal, patients with diabetes should be routinely evaluated to detect treatable disease. Guidelines for the frequency of diabetic eye examinations have been largely based on the severity of retinopathy.

EMERGING THERAPIES

Due to the limitations of the current treatments, new therapeutic approaches are being developed.

Sub-threshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular edema
Sub-threshold diode micropulse laser photocoagulation minimizes chorioretinal damage and demonstrates a beneficial
effect on visual acuity and macular edema resolution. The development of the diode laser with micropulsed emission has allowed subthreshold therapy without a visible burn endpoint. This greatly reduces the risk of structural and functional retinal damage, while retaining the therapeutic efficacy of conventional laser treatment.18-17

**Intravitreal triamcinolone acetonide**

Intravitreal triamcinolone acetonide (IVTA) is reported to generate favorable results in the treatment of diffuse DME. However, the major limitation of IVTA is the recurrence of DME, which develops after a relatively short duration of action necessitating repeated applications of IVTA that carry risk and are inconvenient for patients.18,19 This early disappearance of the effect of IVTA might be consistent with the results reported by Beer et al.,20 who calculated that measurable concentrations of triamcinolone could be expected to last no longer than 3 months in nonvitrectomized eyes.

In a prospective randomized controlled trial, eyes with persistent DME after focal/grid photocoagulation received either 4 mg of IVTA or sham injection (saline injection into the sub-conjunctival space). After 2 years, 19 of 34 (56%) eyes treated with repeated IVTA had a visual acuity improvement of five letters or more compared with 9 of 35 (26%) placebo treated eyes. An increase of intraocular pressure of ≥ 5 mmHg was observed in 23 of 34 (68%) treated versus 3 of 10 (30%) untreated eyes. Glaucoma medication was required in 15 of 34 (44%) treated versus 1 of 30 (3%) untreated eyes. Cataract surgery was performed in 15 of 28 (54%) treated versus 0 of 21 (0%) untreated eyes. Two eyes in the IVTA group required trabeculectomy. There was one case of infectious endophthalmitis in the treatment group.21

Recent systematic reviews and meta-analysis of randomized controlled trials for IVTA for laser-refractory DME concluded that IVTA is effective in improving visual acuity in patients with refractory DME in the short-term, but the benefits do not seem to persist in the long-term. A peak benefit of approximately three lines of visual acuity was achieved 1 month postinjection.18,19

The Diabetic Retinopathy Clinical Research Network22 reported 2-year results of a multicenter randomized clinical trial comparing preservative-free IVTA and focal/grid laser for DME. In this study, 840 eyes were randomized to focal/grid photocoagulation, 1 mg IVTA, or 4 mg IVTA. Retreatment was given for persistent or new edema at 4-month intervals. After 4 months, mean visual acuity was better in the 4-mg IVTA group than in either the laser group or the 1-mg IVTA group. The mean visual acuity 2 years after starting the treatment was better in the laser group compared with the steroid-injected groups. Optical coherence tomography results generally paralleled the visual acuity results. Cataract surgery performed before the 2-year visit was most frequent in the 4-mg IVTA group (51%) versus the 1-mg IVTA group (23%) and the laser group (13%). Increased intraocular pressure from baseline by 10 mmHg or more at any visit was most frequent in the 4-mg IVTA group (33%) versus the 1-mg IVTA group (16%) and the laser group (4%). More recently, the Diabetic Retinopathy Clinical Research Network23 reported that the 3-year visual outcome results were consistent with the previously published 2-year results. The cumulative probability of cataract surgery by 3 years was 31%, 46%, and 83% in the laser and 1- and 4-mg IVTA groups, respectively. Intraocular pressure increased by more than 10 mmHg at any visit in 4%, 18%, and 33% of the eyes, respectively. This randomized study indicated clearly that focal/grid photocoagulation is a better treatment than IVTA in eyes with DME involving the center of the macula with visual acuity between 20/40 and 20/320. The fact that the 4-mg IVTA group had a greater positive treatment response on visual acuity and retinal thickening after 4 months of treatment, whereas the photocoagulation group had a greater positive response later, raises the possibility that combining focal/grid photocoagulation with IVTA may produce greater benefit for DME than either focal/grid photocoagulation or IVTA alone.22

More recently, the Diabetic Retinopathy Clinical Research Network reported that IVTA (4 mg) appeared to reduce the risk of progression of DR. However, the study concluded that use of IVTA to reduce the likelihood of progression of retinopathy is not warranted at this time because of the increased risk of glaucoma and cataract associated with IVTA and because PDR already can be treated successfully and safely with panretinal photocoagulation.24

Several small randomized clinical trials demonstrated that the combination of laser photocoagulation (panretinal and macular) with IVTA was associated with improved best-corrected visual acuity and decreased central macular thickness and total macular volume when compared with laser photocoagulation alone for the treatment of PDR and macular edema.25,26 In contrast, a recent study demonstrated no beneficial effect of combined IVTA plus panretinal photocoagulation and macular photocoagulation in eyes with coexisting high-risk PDR and clinically significant macular edema as compared with panretinal photocoagulation and macular photocoagulation as standard treatment in those patients.27

Recently, two studies compared the morphological and visual acuity outcomes associated with a single intravitreal injection of triamcinolone acetonide versus bevacizumab for the treatment of DME. These studies concluded that one single intravitreal injection of triamcinolone showed better results in reducing DME and in the improvement of visual acuity than that of bevacizumab in the short-term management of DME. The reduction effect of bevacizumab on DME was weaker and shorter than that by triamcinolone. However, intravitreal bevacizumab (IVB) had the advantage of intraocular pressure stability compared with the triamcinolone injection.28,29
Dexamethasone intravitreal implant

Recent studies demonstrated that the biodegradable dexamethasone 0.7 mg sustained-release intravitreal implant (Ozurdex®, Allergan, Inc., Irvine, CA, USA) is a promising new treatment option for patients with persistent DME. 30-32

Fluocinolone acetonide intravitreal implant

Fluocinolone acetonide intravitreal implant (Retisert, Bausch and Lomb, Rochester, NY) has been investigated as a treatment for DME. Despite bringing significant improvements in visual acuity and reduced macular edema, fluocinolone devices are associated with cataract formation, increased intraocular pressure, and surgery to lower intraocular pressure.33,34

Antivascular endothelial growth factor treatment

Currently, there are four Antivascular endothelial growth factor (anti-VEGF) agents that have been used in the management of DR, including pegaptanib (Macugen; Pfizer, Inc., NY, USA), ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA), bevacizumab (Avastin; Genentech, Inc.), and VEGF Trap-Eye (Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA). Pegaptanib

Pegaptanib is a pegylated RNA aptamer directed against the VEGF-A 165 isoform. A phase II clinical trial of intravitreal pegaptanib in patients with DME with 36 weeks of follow-up demonstrated better visual acuity outcomes, reduced central retinal thickness, and reduced need for additional photocoagulation therapy.31 A retrospective analysis of the same study on patients with retinal neovascularization at baseline showed regression of neovascularization after intravitreal pegaptanib administration.36 Recently, Querques et al.37 demonstrated in a retrospective study that repeated intravitreal pegaptanib produced significant improvement in best-corrected visual acuity and reduction in mean central macular thickness in patients with DME. In addition, González et al.38 showed that intravitreal pegaptanib produced short-term marked and rapid regression of diabetic retinal neovascularization. These data suggest that VEGF blockade may be a safe and efficacious adjuvant treatment to panretinal photocoagulation in PDR.

Ranibizumab

Ranibizumab is a recombinant humanized monoclonal antibody fragment with specificity for all isoforms of human VEGF-A. Pilot studies of intravitreal ranibizumab demonstrated reduced foveal thickness and maintained or improved visual acuity in patients with DME.39 Recently, Nguyen et al.40 demonstrated that during a span of 6 months, repeated intravitreal injections of ranibizumab produced a significantly better visual outcome than focal/grid laser treatment in patients with DME. The Diabetic Retinopathy Clinical Research Network41 evaluated intravitreal 0.5 mg ranibizumab or 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for treatment of DME. The 1-year mean change (± standard deviation) in the visual acuity letter score from baseline was significantly greater in the ranibizumab + prompt laser group and ranibizumab + deferred laser group but not in the triamcinolone + prompt laser group compared with the sham + prompt laser group. In the subset of pseudophakic eyes at baseline, visual acuity improvement in the triamcinolone + prompt laser group appeared comparable to that in the ranibizumab groups. Two-year visual acuity outcomes were similar to one-year outcomes. Elevated intraocular pressure and cataract surgery were more frequent in the triamcinolone + prompt laser group and 0.8% had injection-related endophthalmitis in the ranibizumab group.42 Nguyen et al.,43 in a randomized study, showed that intravitreal injection of ranibizumab provided benefit for DME for at least 2 years, and when combined with focal or grid laser treatments, the amount of residual edema was reduced, as were the frequency of injections needed to control edema. The 2- and 3-year results demonstrated the efficacy and safety of repeated intravitreal ranibizumab injections.42,44-46 It was also shown that more extensive focal/grid laser therapy may reduce the need for more frequent ranibizumab injections to control edema.46

Vascular endothelial growth factor Trap-Eye

VEGF Trap is a 115 kDa recombinant fusion protein consisting of the VEGF binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human IgG1. Recent studies showed that intravitreal injection of VEGF Trap-Eye was well tolerated and was effective in patients with DME.49,50

Bevacizumab

Bevacizumab is a full length recombinant humanized antibody active against all isoforms of VEGF-A. It is Food and Drug Administration (FDA)-approved as an adjunctive systemic treatment for metastatic colorectal cancer. Several studies reported the use of the off-label IVB to treat DME, complications of PDR, and iris neovascularization.

To date, all studies regarding IVB (1.25 mg) for DME therapy have demonstrated transient beneficial effects with a requirement for repeated injections.52-55 Increased visual acuity with decrease in macular edema with a single injection of IVB lasts for 4-6 weeks with deterioration of visual acuity and recurrence of macular edema 8-12 weeks later necessitating another injection.28,53 Fang et al.54 reported that the improvement in visual acuity and decrease in macular edema were maintained for 8 weeks in the non-pretreated eyes, and for 2-4 weeks in the pretreated eyes. In addition, Yanalyi et al.56 reported that IVB in DME has no effect on visual acuity and macular edema in previously vitrectomized eyes. Similarly, Lam et al.57 demonstrated that IVB was more effective in eyes without previous DME treatment, which included focal or grid laser photocoagulation. Two recent studies demonstrated that IVB at doses of 1.25 and 2.5 mg seems to have similar treatment
efficacy in patients with DME. Bonini-Filho et al. showed that IVB for DME with severe capillary loss was associated with beneficial effects on vision, central macular thickness, and total macular volume. Soheilian et al. reported that IVB in patients with DME yielded a better visual outcome 24 weeks later compared with macular photocoagulation. The 2-year follow-up demonstrated the beneficial effect of IVB with or without grid laser photocoagulation for diffuse DME.

Several studies demonstrated that IVB injection resulted in marked regression of retinal and iris neovascularization, and rapid resolution of vitreous hemorrhage in patients with PDR. In addition, IVB injection was demonstrated to be an effective adjunctive treatment to PRP in the treatment of high-risk PDR and neovascular glaucoma. IVB injection before PRP was found to be beneficial in preventing PRP-induced visual dysfunction and foveal thickening and was associated with a greater reduction in the area of active leaking vessels than PRP alone in patients with high-risk PDR. In addition, Huang et al. demonstrated that IVB injection with PRP was effective in inducing rapid regression of vitreous hemorrhage and may reduce the need for vitrectomy in eyes with PDR complicated with vitreous hemorrhage.

The use of preoperative IVB injection few days before planned pars plana vitrectomy for the treatment of complications of PDR was also found to be efficacious and safe as an adjuvant treatment to facilitate surgery, prevent rebleeding, and accelerate postoperative vitreous clear-up. However, trabecular retinal detachment may occur or progress shortly following administration of IVB in these patients. Two recent studies demonstrated that IVB injection pretreatment for diabetic vitreectomy did not influence rates of postoperative vitreous hemorrhage or final visual acuity. Several studies determined the clinical effectiveness of IVB combined with cataract surgery for the management of the postoperative increase of retinal thickness in patients with DME. The short-term results suggest that IVB has the potential not only to prevent the increase in retinal thickness, but also reduce the retinal thickness of eyes with DME after cataract surgery.

Intravitreal bevacizumab versus ranibizumab
Most studies do not provide information about long-term results (i.e., more than 2-3 years of follow-up) on the comparative efficacy of anti-VEGF pharmacotherapies. Further evidence is required to support the long-term safety of these pharmacotherapies and their comparative efficacy. The available data suggest no difference in effectiveness between bavacizumab and ranibizumab.

Vitrectomy for persistent diffuse diabetic macular edema
Vitrectomy with removal of the premacular posterior hyaloid for persistent diffuse macular edema has gained rapid widespread acceptance. The large number of series evaluating the efficacy of vitrectomy (with or without internal limiting membrane peeling) has yielded conflicting results. In a prospective randomized trial, Stolba et al. showed that vitrectomy with internal limiting membrane peeling was superior to observation in eyes with persistent diffuse DME that previously failed to respond to conventional laser treatment and positively influenced distance and reading visual acuity as well as the morphology of the edema. However, they suggested the need for larger follow-up and larger series to confirm these findings. Other studies suggested that vitrectomy with and without internal limiting membrane peeling may provide anatomic and visual benefit in eyes with diffuse nontractional unresponsive DME refractory to laser photocoagulation. Best corrected visual acuity continued to improve until 1 year postoperatively and is maintained long-term. The preoperative best corrected visual acuity was the best prognostic factor for final best corrected visual acuity. In contrast, other studies showed that the benefits of vitrectomy for DME in terms of visual acuity and macular thickness were limited to patients who exhibited signs of macular traction, either clinically and/or on optical coherence tomography. Macular detachment on optical coherence tomography was suggested to be an adverse predictive indicator.

The Diabetic Retinopathy Clinical Research Network evaluated vitrectomy for DME associated with vitreomacular traction. At 6 months, median OCT central subfield thickness decreased by 160 microns, with 43% having central subfield thickness < 250 microns and 68% having at least a 50% reduction in thickening. Visual acuity improved by ≥ 10 letters in 38% and deteriorated by ≥ 10 letters in 22%. The factors associated with favorable outcomes after vitrectomy for DME were also evaluated. Greater visual acuity improvement occurred in eyes with worse baseline acuity and in eyes in which an epiretinal membrane was removed. Greater reduction in central subfield thickness occurred with worse baseline visual acuity, greater preoperative retinal thickness, removal of internal limited membrane, and optical coherence tomography evidence of vitreoretinal abnormalities.

The necessity of internal limiting membrane peeling is still unclear. Several studies reported that there was no difference in the absorption rate of macular edema or the functional outcome after vitrectomy with or without internal limiting membrane peeling.

Pharmacologic vitreolysis in the management of diabetic retinopathy
Our enhanced understanding of the role of the vitreous body in DR has led investigators to use pharmacologic vitreolysis in the management of DR. A phase III clinical trial has shown that 55 IU of highly purified ovine hyaluronidase (vitrase) helps to clear vitreous hemorrhage 1 month after intravitreal application. No serious safety issues were reported. In particular, the incidence of retinal detachment was not statistically different between treated eyes and control groups.
Quiram et al. demonstrated that intravitreal injection of microplasmin with induction of the combination of posterior vitreous detachment (PVD) and vitreous liquefaction increased intravitreal oxygen tension. In contrast, hyaluronidase-induced vitreous liquefaction without PVD induction failed to increase intravitreal oxygen tension. Moreover, when microplasmin treated animals were exposed to 100% oxygen, there was an accelerated increase in oxygen levels in the midvitreous cavity compared with control or hyaluronidase treated eyes. These findings suggest that the beneficial effects of surgical vitrectomy in increasing oxygen tension in the vitreous cavity may be reproduced with enzymatic induction of PVD and vitreous liquefaction without the time, risks, and expense of surgery.

It is more difficult to separate vitreous cortex from internal limiting membrane in diabetic eyes than in nondiabetic eyes. This is likely due to the effects of diabetes on the macromolecules of vitreous and the structural consequences. In an experimental rat model of diabetes, the combination of hyaluronidase causing vitreous liquefaction and plasmin acting as a PVD inducer was more effective than plasmolin alone in inducing complete PVD. Plasmin-assisted vitrectomy allowed a more complete and less traumatic posterior vitreous cortex removal with a smooth retinal surface. The internal limiting membrane removed during the plasmin-assisted vitrectomy from eyes with DME demonstrated cleaner and flatter surfaces, whereas the internal limiting membrane removed without the use of autologous plasmin enzyme had remnants of the vitreous cortex more frequently. Autologous plasmin enzyme was also beneficial in the surgical management of PDR. The proliferative membranes became softened and were easily peeled without retinal tears. Recently, Díaz-Llopis et al. demonstrated that intravitreal injection of autologous plasmin enzyme without the performance of vitrectomy induced complete PVD and effectively reduced macular thickening due to refractory diffuse DME and improved visual acuity. Therefore, atraumatic pharmacologic separation of the posterior vitreous cortex with clean cleavage between the internal limiting membrane and the posterior hyaloids without performing a vitrectomy can reduce the risk of intraoperative iatrogenic damage such as retinal tears, and damage to the nerve fibers, and postoperative sequelae.

**Fibrates**

Fibrates are widely prescribed lipid-lowering drug in the treatment of dyslipidemia. Their main clinical effects, mediated by peroxisome proliferative activated receptor alpha activation, are a moderate reduction in total cholesterol and low-density lipoprotein cholesterol levels, a marked reduction in triglycerides and an increase in high-density lipoprotein cholesterol. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study demonstrated that long-term lipid-lowering therapy with fenofibrate reduced the progression of DR and the need for laser treatment in patients with type 2 diabetes, although the mechanism of this effect does not seem to be related to plasma concentration of lipids. Recently, ACCORD Study Group demonstrated that fenofibrate for intensive dyslipidemia therapy reduced the rate of progression of DR in persons with type 2 diabetes.

**Renin-angiotensin system blockers**

Several studies suggested that Renin-angiotensin system (RAS) blockers might reduce the burden of DR. The findings of the Eurodiab Controlled trial of Lisinopril in Insulin-dependent Diabetes (EUCLID) suggested that blockade of the renin-angiotensin system with the angiotensin-converting enzyme inhibitor lisinopril could reduce both incidence and progression of retinopathy in type 1 diabetes. Recently, the Diabetic Retinopathy Candesartan Trials (DIRECT) demonstrated that the angiotensin-receptor antagonist candesartan reduced the incidence of retinopathy in patients with type 1 diabetes, and might induce improvement of retinopathy in type 2 diabetic patients with mild-to-moderate retinopathy.

**Peroxisome proliferator-activated receptor gamma agonists**

The Peroxisome proliferator-activated receptor gamma (PPARγ) agonist rosiglitazone inhibited both the retinal leukostasis and retinal leakage observed in the experimental diabetic rats. In addition, the decreased expression of the endogenous PPARγ in mice leads to the aggravation of retinal leukostasis and retinal leakage in diabetic mice. Rosiglitazone maleate (Avandia; GlaxoSmithKline, NC, USA) is an orally administered medication used to improve glycemic control in patients with diabetes mellitus. This medication activates the PPARγ and leads to insulin sensitization in adipose and other tissues, with potential antiangiogenic activity. Recently, Shen et al. demonstrated that rosiglitazone may delay the onset of PDR in patients with severe nonproliferative DR at baseline. Several studies showed that the use of glitazone class of drugs was associated with DME. However, another retrospective study concluded that rosiglitazone is not linked to DME.

**Ruboxistaurin**

Hyperglycemia activates protein kinase C (PKC) by inducing de novo synthesis of diacylglycerol, a physiologic activator of PKC. Substantial data suggest that the β isoform may play an important role in the development of diabetic microvascular complications. Increased PKC β isoform activity induces retinal
vascular permeability and neovascularization in animal models. Roboxistaurin (RBX) (LY333531; Lilly Research Laboratories, Indianapolis, IN, USA) is a PKC β-selective inhibitor with adequate bioavailability to permit oral administration once daily. In the Protein Kinase C β inhibitor-Diabetic Retinopathy Study 2 (PKC-DRS2), oral administration of RBX (32 mg per day) reduced sustained moderate visual loss, need for laser treatment for macular edema, and macular edema progression, while increasing occurrence of visual improvement in patients with nonproliferative retinopathy. In the Protein Kinase C β inhibitor Diabetic Macular Edema Study (PKC-DMES), RBX treatment also showed a beneficial effect on DME progression relative to placebo. More recently, Davis et al. demonstrated that RBX treatment appears to ameliorate DME-associated visual decline.

**Islet cell transplantation**

Recent studies demonstrated that improved islet transplant outcomes could be observed with enhanced islet isolation, glucocorticoid-free immunosuppression, and provision of an adequate islet mass of more than 10,000 islet equivalents per kilogram of body weight. These improvements have resulted in benefits to type 1 diabetic subjects, including long-term c-peptide secretion, improved glycemic control, and reduced hypoglycemic episodes. Recently, it was demonstrated that islet transplantation yields improved HbA1c and less progression of retinopathy compared with intensive medical therapy during 3 years of follow-up.

**ACKNOWLEDGMENTS**

The authors thank Ms. Connie B. Unisa-Marfil for secretarial work. Supported by Medical Research Chair funded by Dr. Nasser Al-Rasheed (AMA).

**REFERENCES**


Factors associated with visual acuity

Intravitreal plasmin without associated


Sheetz MJ, Aiello LP, Shahri N, Davis MD, Kles KA, Danis RP; Mbdv Study Group. Effect of ruboxistaurin (RBX) on visual acuity decline over a 6-year period with cessation and reinstitution of therapy: Results of an open-label extension of the Protein Kinase C β Inhibitor-Diabetic Retinopathy Study and the Protein Kinase C β Inhibitor-Diabetic Retinopathy Study 2. Retina 2011;31:2084-94.

Sheetz MJ, Aiello LP, Shahri N, Davis MD, Kles KA, Danis RP; Mbdv Study Group. Effect of ruboxistaurin (RBX) on visual acuity decline over a 6-year period with cessation and reinstitution of therapy: Results of an open-label extension of the Protein Kinase C β Inhibitor-Diabetic Retinopathy Study and the Protein Kinase C β Inhibitor-Diabetic Retinopathy Study 2. Retina 2011;31:2084-94.

Sheez J, Aiello LP, Shahri N, Davis MD, Kles KA, Danis RP; Mbdv Study Group. Effect of ruboxistaurin (RBX) on visual acuity decline over a 6-year period with cessation and reinstitution of therapy: Results of an open-label extension of the Protein Kinase C β Inhibitor-Diabetic Retinopathy Study and the Protein Kinase C β Inhibitor-Diabetic Retinopathy Study 2. Retina 2011;31:2084-94.