ABSTRACT

Diabetic retinopathy is not only the major cause of blindness in people with diabetes, but also in working-age adults in the Western world. There are 2 types of diabetic retinopathy: macular edema and degeneration, caused by leaky vessels in the retina; and non-proliferative leading to proliferative retinopathy, caused by the formation of new vessels in ischemic retinal vessels.

Risk factors for diabetic retinopathy include poor glycemic control, hypertension, proteinuria, and hypercholesterolemia. Therapy is, therefore, directed at controlling these risk factors and includes regular eye examinations to detect changes in the retinal vasculature.

However, there are other factors that influence the development of diabetic retinopathy, including the enzyme protein kinase C (PKC), growth hormones, insulin-like growth factor-1, angiotensins, and vascular endothelial growth factor (VEGF), which has been identified as a major factor. As increased PKC activation is involved in increased production of VEGF and its deleterious effects on endothelial cells, randomized controlled trials of a PKC-β inhibitor have been performed with encouraging results.

Other therapies directed at the causative mechanisms of diabetic retinopathy are currently being investigated in clinical trials. These therapies include VEGF aptamers, growth hormone antagonists, and growth hormone receptor antagonists. In addition, steroids and lipid-lowering agents (statins and fibrates) are being reevaluated for their effects on diabetic retinopathy.

These new therapies, plus more aggressive screening and control of risk factors, should lead to a better outcome for patients with diabetic retinopathy.

in better management and outcome of diabetic retinopathy in the future.

**ETIOLOGY OF DIABETIC RETINOPATHY**

Diabetic retinopathy results either from capillary leakage or from new vessel formation (neovascularization, angiogenesis) caused by capillary closure and retinal ischemia. As shown in Figure 1 (left panel), the capillaries leak lipid products and fluid in the area around the fovea and thicken the retina, which may lead to macular edema. Also shown in Figure 1 (left panel) is angiogenesis, a result of retinal ischemia; preretinal hemorrhages are visible. The hemorrhage can enter the vitreous and cause sudden loss of vision. This may result in poor retinal visualization by the ophthalmologist, thus delaying laser treatment.

How does diabetes cause these sight-threatening changes in the retinal vessels? As illustrated in Figure 2, there are several mechanisms and metabolic and physiologic abnormalities, acting alone or in concert with each other, that lead to capillary cell death, leakage, and occlusion. These conditions lead to the release of growth factors, resulting in new vessel formation and increased vascular permeability.

Studies show that VEGF is increased in the ocular fluids of patients with diabetic retinopathy. VEGF has deleterious effects on endothelial cells, including increased vascular permeability, and is believed to be involved in the development of macular edema and angiogenesis. Experimental studies have shown that injecting VEGF into the eyes produces leakage and edema into the retinal layer as well as angiogenesis; pretreatment with a PKC-β inhibitor may reverse these deleterious effects. VEGF antibodies and antagonists also have the potential to reverse these effects. Thus, based on these data from animal experiments, VEGF is a promising therapeutic target.

Whereas VEGF is involved in vascular leakage and angiogenesis, growth hormones and the insulin-like growth factor-1 (IGF-1) are involved, as mediators, predominantly in angiogenesis. At present, inhibitors of these growth factors are under investigation in clinical trials in patients with diabetic retinopathy.

Fibroblast growth factor (FGF) acts synergistically with growth hormones and IGF-1, but there is no FGF antagonist available at this time for clinical study in patients with diabetic retinopathy.

**THERAPEUTIC TARGETS**

In addition to therapies targeting VEGF and growth factors, which will be addressed in greater detail later in this article, other therapies have been developed to interfere with several other mechanisms and abnormalities involved in diabetic retinopathy (Figure 2).

---

**Figure 1. Retinal Vessel Leakage and Angiogenesis**

Left panel: Leakage of fat and fluid in the area of the fovea. Right panel: Angiogenesis resulting from retinal ischemia. Note the 2 strands of preretinal hemorrhage.

**Figure 2. Metabolic Features, Vascular Features, and Mechanisms Involved in Diabetic Retinopathy**

The mechanisms and metabolic and physiologic abnormalities involved in diabetic retinopathy are depicted, as are the therapies that target these mechanisms and abnormalities.

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; ARI = aldose reductase inhibitors; DAG = diacylglycerol; FGF = fibroblast growth factor; IGF-1 = insulin-like growth factor-1; LAR = long-acting regimen; LDL = low-density lipoprotein; PKC = protein kinase C; VEGF = vascular endothelial growth factor.
Some therapies, such as the aldose reductase inhibitors that were developed to block the polyol pathway, have shown no clinical benefit in the retinal microvascular complications of diabetes mellitus. Other therapies, such as statins, which lower low-density lipoprotein (LDL) cholesterol levels, and angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ARBs) to control blood pressure levels, have shown great efficacy in reducing cardiovascular risk factors. The international, large-scale, ongoing Diabetic Retinopathy Candesartan Trial (DIRECT) is assessing the therapeutic potential of ARBs in primary and secondary prevention in patients with diabetic retinopathy. Current randomized controlled studies evaluating the impact of lipid lowering with statins and fibrates on retinopathy are nearing completion, and publication of their results is eagerly awaited.

Aspirin has been used to reduce platelet aggregation, but there are no solid data that it has a beneficial effect on diabetic retinopathy. Nevertheless, the American Diabetes Association and diabetes societies throughout Europe have recommended aspirin for all patients with diabetes mellitus, as this therapy reduces macrovascular disease endpoints.

Although diabetic retinopathy is not classified as an inflammatory disease, the use of intravitreal or systemic steroids is showing potential therapeutic efficacy in recent studies. Randomized controlled trials assessing the intravitreal use of steroids are now underway.

PKC-β INHIBITION AND DIABETIC RETINOPATHY

Inhibition of the enzyme PKC represents an exciting therapeutic approach to managing diabetic retinopathy because PKC is involved in the activation of the VEGF gene and its involvement in the development of diabetic retinopathy. Inhibition of the β isoform of PKC inhibits VEGF in animal experiments. PKC inhibition is especially exciting in ophthalmology because VEGF also is involved in other ocular diseases, including retinal vein occlusion, glaucoma, and age-related macular degeneration.

The first clinical studies of PKC inhibition, specifically with ruboxistaurin, an orally active inhibitor of the β₁ and β₂ isoforms of PKC, demonstrated it could be used safely by patients. Phase II studies yielded such positive results with regard to diabetic microvascular complications that subsequent phase II/phase III trials were designed to evaluate ruboxistaurin in diabetic patients with neuropathy, peripheral vascular disease, diabetic macular edema, preproliferative retinopathy, and nephropathy.

The first trial to evaluate ruboxistaurin in humans with diabetic retinopathy was a month-long phase IB study, which reported that the PKC-β inhibitor not only increased retinal blood flow and decreased mean circulation time, but preliminary evidence suggested that it was safe for patients and well-tolerated. Two pivotal phase II/III trials, the Diabetic Retinopathy Study (DRS) and the Diabetic Macular Edema (DME) study, have now been completed, and further randomized controlled studies in patients with diabetic macular edema are underway in the United States and Europe.

The DRS evaluated the effects of ruboxistaurin 8 mg, 16 mg, and 32 mg versus a placebo on the progression of preproliferative (ischemic) retinopathy in 252 patients, while the DME study evaluated the effects of the same doses of ruboxistaurin versus a placebo on the progression of diabetic macular edema in 686 patients. Because both trials evaluated 3 different dosages of ruboxistaurin before determining which was the most effective dosage, the power of the trials to observe an effect was reduced. The overall rate of disease progression was much lower than predicted in the groups taking a placebo; there was a high drop-out rate of 30%, which was attributed to the reluctance of many patients to undergo periodic 7-field stereophotography. Neither of these studies demonstrated any significant changes in primary endpoints. As a result, subsequent trials have reduced the amount of retinal photography used for evaluation and have focused on the 32-mg dosage.

However, some interesting data from the DME study convinced investigators that continued study of ruboxistaurin in diabetic retinopathy was warranted. As shown in Figure 3, a dosage of ruboxistaurin 32 mg significantly reduced the progression of macular edema in patients with glycosylated hemoglobin (HbA₁c) levels between 7.9% and 10%, as compared with a placebo. No significant effect was seen in patients with very good (<7.9%) or very poor (>10%) glycemic control. A plausible explanation for this result is that ruboxistaurin is ineffective if no excess glucose or excessive hyperglycemia is present, but it is effective when HbA₁c levels are between 8% and 10%, which in fact represents a significant proportion of patients with suboptimally controlled diabetes.
Findings from the DRS, which evaluated ruboxistaurin in patients with pre-proliferative diabetic retinopathy, also showed favorable effects. As shown in Figure 4, a dosage of ruboxistaurin 32 mg significantly reduced the cumulative prevalence of moderate vision loss (defined as a decrease of 15 letters or more), as compared with a placebo. Further analysis of sustained vision loss yielded similar results, with the lower cumulative prevalence of vision loss also related to less progression of macular edema.

These trials clearly show that further investigation of macular edema is warranted. Patients with diabetes with macular edema currently are being recruited in the United States and Europe for a large 3-year study.

Data from the month-long phase IB trial demonstrated that ruboxistaurin was safe for patients and well tolerated. Despite interactions between ruboxistaurin and various elimination enzymes that could increase levels of certain drugs relevant in diabetes (eg, antiviral and antifungal agents, amitriptyline, flecainide, metoprolol), the only adverse effect reported in the phase IB study and the longer-term DRS and DME trials was mild, self-limiting diarrhea.

**Vascular Endothelial Growth Factor Aptamers**

Another therapeutic approach that targets VEGF is the use of VEGF aptamers—antibody-like oligonucleotides that adhere to VEGF particles and block their action at the cellular level. Aptamers are available in microsphere preparations that can be injected into the vitreous, after application of a topical anesthetic, on an outpatient basis.

Initial data from trials involving patients with exudative age-related macular degeneration are promising, with these aptamers stabilizing vision in many patients and even improving the vision in some patients.

**Steroids**

Perhaps the most surprising therapy coming into clinical practice for diabetic retinopathy is the use of steroids. Ophthalmologists have long used triamcinolone (and, more recently, fluocinolone) for the treatment of uveitis. Small amounts of both of these agents can be injected into the vitreous, where they remain active for 1 to 3 months. Case reports suggest there may be beneficial effects of intravitreal steroid injection in diabetic retinopathy, and animal experiments have suggested that one mode of action is the alteration of VEGF gene transcription and stabilization of VEGF messenger RNA.

Preliminary results of 2 trials, each evaluating 0.5 mg intravitreal steroid implants in 100 patients with laser-
resistant diffuse macular edema and deteriorating vision, were reported at the 2003 meeting of the American Academy of Ophthalmology. Findings in both trials were favorable with regard to visual acuity, macular edema, and retinal thickness.

There are 2 drawbacks to using intravitreal steroid implants: increased intraocular pressure (glaucoma), which rose by more than 30-mm Hg in some of the patients in both studies, and endophthalmitis may occur, with poor visual outcome.

Nevertheless, large randomized controlled trials evaluating this approach are underway in the United States and in the United Kingdom.

**Growth Hormone and Growth Hormone Receptor Antagonists**

Growth hormones and IGF-1 are important mediators of angiogenesis in the retina. In vitro and in vivo studies have confirmed that somatostatin and the more recently discovered corticostatin are potent inhibitors of growth hormones and IGF-1. Animal studies have shown that the retina seems to be active in the production of somatostatin and corticostatin, although there is no hard data to explain this occurrence. However, somatostatin does appear to have an effect on fluid transport from the retinal pigment epithelium to the choroid, a process that is relevant in the development of macular edema.

Treatment with the first somatostatin analogue (octreotide) was onerous, requiring 3 injections a day. Results of initial pilot studies with octreotide were not promising as there was little consistency of effect. However, 2 more recent small controlled trials using the long-acting analogue sandostatin preparation have suggested potential clinical benefit in delaying the progression to proliferative diabetic retinopathy.

As a result of this finding, 2 large ongoing randomized controlled studies are evaluating the effects of the sandostatin analogue (sandostatin LAR) on pre-proliferative diabetic retinopathy, using the primary endpoint of slowing 3-step progression to retinopathy on the Early Treatment Diabetic Retinopathy Study scale. The first trial is evaluating the effects of 20 mg and 30 mg dosages of sandostatin monthly versus a placebo in 585 patients in Europe; the second trial is comparing the 30-mg monthly dose versus a placebo in 311 patients in the United States, Canada, and South America.

Pegvisomant, the mutated human growth hormone molecule that binds to the IGF-1 receptor, is a growth hormone receptor antagonist. Animal models have suggested that pegvisomant may have a favorable impact on diabetic microvascular complications, particularly retinopathy. In an open-label, phase IIA study evaluating this agent (20 mg/day for 3 months) in 13 patients with type 1 preproliferative retinopathy and in 12 patients with type 2, there was not an obvious beneficial effect, although 16 patients remained stable and 9 patients showed deterioration in retinopathy.

Larger trials are therefore needed to assess possible therapeutic potential and to help in identifying whether growth hormones or IGF-1, or both, are involved in retinal angiogenesis.

**Lipid-Lowering Therapy**

Lipid-lowering therapy is a logical therapeutic target in the management of diabetic retinopathy, as an increasing LDL cholesterol level is a proven risk factor for diabetic retinopathy. The potential mechanism may be the increased oxidation of LDL in diabetic patients, which has been shown to be toxic to retinal endothelial cells in in vitro experiments.

Early trials with fibrates demonstrated that these agents did reduce retinal exudation. However, the studies included only patients with advanced exudative maculopathy and poor vision. These trials demonstrated definite reduction in retinal exudation, but there was no change in vision; therefore, this therapeutic approach was abandoned. In hindsight, a more logical population for this evaluation would have been patients with fewer exudates and better vision (ie, early macular disease), as the macula laser trials later showed that no change in vision would have been expected in diabetic patients with advanced maculopathy and poor vision. Such a population was subsequently evaluated in 3 small pilot studies using statins, with all patients demonstrating reduced exudation and reduced progression to exudation.

Although the findings from these small studies should not be used to draw generalized conclusions about lipid-lowering therapy in diabetic retinopathy, the results of 3 large trials studying the potential of this therapeutic approach have been reported very recently or are expected shortly: the ASPEN study, a predominantly secondary prevention trial with atorvastatin that includes 900 graded fundus photographs; the CARDS trial, a recently completed primary prevention trial with
atorvastatin; and the FIELD study, with fenofibrate, which is still recruiting patients in Australia.

CONCLUSIONS

New treatments for diabetic retinopathy that go beyond reduction of glycemia, blood pressure, and cholesterol levels are clearly needed. Laser photoocoagulation, the mainstay of treatment of proliferative retinopathy and maculopathy for 3 decades, is currently considered to be only 60% to 70% effective. Moreover, once-promising agents such as aldose reductase inhibitors have not provided clinical benefits or have been too toxic for long-term use by patients.

The next few years may well demonstrate exciting new therapies for diabetic microvascular complications, including retinopathy. In addition to the reduction of established risk factors and better retinopathy screening programs utilizing digital imaging, there are encouraging results from studies of therapies that block VEGF, the PKC-β enzyme pathway, and growth hormones and IGF-1. The results of trials assessing intravitreal steroid injection therapy, angiotensin receptor blockers (the DIRECT study), statins, and fibrates are all eagerly awaited—with the expectation that at least 1 or more of these therapies will be of tremendous benefit to patients with diabetic retinopathy.

REFERENCES