Diabetic Retinopathy

ETIOLOGY AND PATHOPHYSIOLOGY

Introduction

Diabetic retinopathy—described by ICD-10 code H36.0+—is the leading cause of new blindness among adults aged 20–74 (Fong DS, 2003). This condition is characterized by abnormal blood vessel growth in the retina, the light-sensitive tissue at the back of the eye that communicates light signals to the brain. Diabetic retinopathy can be classified by severity into a first stage of nonproliferative retinopathy and a later, progressive stage of proliferative retinopathy. Uncontrolled proliferative retinopathy can progress to the point where complications can eventually lead to severe visual acuity loss and/or blindness.

Anatomy

Figure 1 illustrates the anatomy of the eye. Hyperglycemia-mediated damage to the eye occurs primarily in the retina, the nerve-dense, light-sensitive tissue that lines the interior of the eye. The macula is the avascular center portion of the retina responsible for central vision. At the center of the macula is the fovea, a further specialized retinal section that is responsible for fine, sharp vision.

Retinal tissue (also detailed in Figure 1) consists of three primary cell types: neurons, glial cells, and blood vessels. Inputs from four types of retinal neurons (photoreceptors and amacrine, bipolar, and horizontal cells) are transmitted to the cells of the ganglia, which then convey electrical output to the nerve fiber layer and optic nerve. Retinal neurons are highly redundant; approximately half of neural cells can be damaged or destroyed before significant functional impairment or visual acuity loss will occur.
Müller cells and astrocytes are the two key glial cell types found in the retina, and they function as the metabolic modulators for neural and vascular components of the retina (Abbott NJ, 1992). Both cell types regulate ion concentrations, neurotransmitters, and nutrients for neural cells. Astrocytes also play an important role in the development and differentiation of vascular endothelial cells, particularly during fetal development (Zhang Y, 1997).

Capillaries, arterioles, and venules constitute the important components of the retinal vascular network. Arterioles are the main “valves” through which blood flows into the retina. Smooth muscle present in arterioles allows them to regulate the resistance they pose to blood flow. Venules are largely passive vessels that drain blood out of the retina. Although passive, venules do possess a large number of receptors for vasoactive agents.

All retinal blood vessels contain two types of cells: endothelial cells and pericytes. Pericytes act like modified smooth muscle cells to control capillary tone in the retina. The endothelial cells in the retina are like other vascular cells in the body except that they have tight junctions that prevent leakage. These tight junctions are the functional component of the blood-retina barrier that allows the retina to self-regulate metabolism and homeostasis and to protect retinal neurons from circulating cytotoxic agents. A number of proteins, including occludin and claudins, are responsible for maintaining the tight junctions and limiting fluid flow between endothelial cells (Gardner TW, 2002).
Pathophysiology

In many cases, the early stages of diabetic retinopathy do not manifest any obvious symptoms (e.g., visual acuity loss). Therefore, the pathophysiology of the disease is described primarily by clinical signs of retinal abnormalities. Figure 2 illustrates the common clinical signs of diabetic retinopathy. Vascular changes are the hallmark of diabetic retinopathy, but recent research also points to cellular-level deficits in neural function that may be an equally important component of the disease.

**Microvascular Abnormalities.** With the onset of diabetic retinopathy, two important changes occur in capillary cells. The tight junctions between endothelial cells loosen and the capillaries become permeable, allowing the infiltration of glial cells, leukocytes, and other materials. This influx of cellular material—which adheres to vessel walls—eventually causes capillary occlusion. Second, pericytes die and leave behind “pericyte ghosts.” Without the smooth-muscle activity of the pericytes, the capillaries dilate beyond normal levels, allowing the formation of microaneurysms and other early intraretinal microvascular abnormalities (IRMAs). Capillary microaneurysms appear as small red dots distributed sporadically throughout the retina. As this condition worsens, arteriovenous shunts occur, and bleeding into the nerve fiber layer causes flame-shaped, blot-shaped, or linear lesions.
Neovascularization (growth of new blood vessels) reflects the eye’s attempt to restore retinal blood flow to areas rendered hypoxic by ischemia and significant vascular occlusion. New blood vessels grow perpendicularly from the surface plane of the retina into the vitreous space. These new vessels are typically hyperpermeable (allowing the influx of materials) and more prone to hemorrhage than the normal retinal microvasculature. Consistent with wound healing in other tissues, the vessels are eventually subjected to a process of remodeling that includes fibrosis and replacement with collagen (Gardner TW, 2000). The fibrovascular tissue can hemorrhage and/or scar, causing preretinal hemorrhage, vitreous hemorrhage, and/or retinal detachment (described later in the section “Complications”).

Retinal Neurodegeneration. Research suggests that defects in retinal glial cell and neuron function precede the development of microvascular abnormalities in diabetic retinopathy and may be an important step in disease pathogenesis.

Indicators of glial cells’ metabolic dysfunction include decreased production of glial fibrillary acidic protein (GFAP; a marker of astrocyte function), decreased conversion of glutamate to glutamine by Müller cells, and increased production of cytokines that are known to increase vascular permeability (Gardner TW, 2002). Subtle defects in vision also suggest that retinal neurons incur damage from hyperglycemia. Using electroretinogram (ERG) measurements of retinal neuron electrical activity, researchers demonstrated that the amplitude of oscillatory potentials was reduced in type 1 diabetics within the first five years after disease onset but before the development of clinical signs of retinopathy (Frost-Larsen K, 1980).

Disease Severity. Diabetic retinopathy is graded in two severity stages: nonproliferative and proliferative. The gold standard for measurement of severity is the criteria developed more than a decade ago in the Early Treatment Diabetic Retinopathy Study (ETDRS). This staging system relies on clinical signs that are evident with fundus photography using seven standard stereoscopic fields, and the combined number and position of microvascular abnormalities dictates the severity level (ETDRS Research Group, 1991). Although widely used in clinical trials, the ETDRS staging system is fairly complex and not commonly used for severity grading in practice. In an attempt to simplify the ETDRS criteria, the International Council on Ophthalmology recently proposed new severity scales for diabetic retinopathy (Ciulla TA, 2003; International Council on Ophthalmology, 2002). The International Diabetic Retinopathy Severity Scale is essentially a simplification of the ETDRS classifications but is intended for use with dilated ophthalmoscopy investigation. Table 1 summarizes the international scale.

Nonproliferative retinopathy (previously called background retinopathy) is the slowly progressing, less severe stage of the disease that is characterized by non-neovascular changes in the retina. The severity of nonproliferative retinopathy is determined by the location and quantity of retinal microvascular abnormalities, including microaneurysms, intraretinal hemorrhages, venous beading, and other vascular lesions. Proliferative retinopathy is characterized by neovascularization
TABLE 1. Proposed International Clinical Diabetic Retinopathy Disease Severity Scale

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>Dilated Ophthalmoscopy Findings</th>
<th>Comparable ETDRS Stage(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No apparent retinopathy</td>
<td>No retinal abnormalities</td>
<td>No retinopathy: Level 10</td>
</tr>
<tr>
<td>Nonproliferative diabetic retinopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Microaneurysms present, no other clinical signs</td>
<td>Very mild nonproliferative diabetic retinopathy: Level 20</td>
</tr>
<tr>
<td>Moderate</td>
<td>Microaneurysms and other signs (intraretinal hemorrhages, venous beading, and/or IRMA) present, but less than severe nonproliferative diabetic retinopathy</td>
<td>Moderate nonproliferative diabetic retinopathy: Levels 35–47</td>
</tr>
<tr>
<td>Severe</td>
<td>No signs of proliferative diabetic retinopathy, with any of the following: &gt;20 intraretinal hemorrhages in each of four quadrants, definite venous beading in ≥2 quadrants, prominent IRMA in ≥1 quadrant</td>
<td>Severe and very severe non-proliferative diabetic retinopathy: Level 53</td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy</td>
<td>Neovascularization and/or vitreous or preretinal hemorrhage</td>
<td>All stages (high-risk, very severe, and/or advanced proliferative diabetic retinopathy): Levels 61 and higher</td>
</tr>
</tbody>
</table>

ETDRS = Early Treatment Diabetic Retinopathy Study.
IRMA = Intraretinal microvascular anomalies.

on the retina, disc, and/or iris and is a quickly progressing, vision-threatening stage of disease.

Research has demonstrated that in the preclinical stage of diabetic retinopathy, changes in retinal function (as measured by ERG) can cause perceptive resolution deficits, including impaired contrast sensitivity (particularly blue-yellow contrast) and impaired night vision (Bangstad HJ, 1994; Barber AJ, 2003; Della Sala S, 1985; Sokol S, 1985). However, because it precludes the development of classic vascular abnormalities, preclinical diabetic retinopathy is not a widely accepted disease severity stage.

Complications. Macular edema and retinal traction detachment are significant complications of diabetic retinopathy that can, if left untreated, lead to blindness. Macular edema is a thickening/swelling of the center portion of the retina caused by deterioration of the blood-retina barrier that allows leakage from retinal capillaries into normally nonperfused tissues. Clinically significant macular edema (CSME) is defined as thickening of the macula or the area within 500 µm of the macula, hard exudates within 500 µm of the macula, and/or any thickening of the retina one disk area or more in diameter that is within one disk diameter of the center of the retina (ETDRS Research Group, 1985).
Retinal detachment generally describes the separation of the retina from the underlying retinal pigment epithelium (RPE). There are three main types of retinal detachment: rhegmatogenous, where a tear in the retina causes detachment; exudative, where fluid accumulation in the subretina causes detachment; and tractional, where scar tissue on the retinal surface contracts and pulls the retina off the RPE. The tractional type is most often associated with diabetic retinopathy. The fibro-vascular tissue produced in the proliferative stage of disease eventually scars, causing retinal contraction and traction detachment. If the area of detachment includes the macula, significant vision impairment can arise.

**Etiology**

**The Growth Factor Hypothesis.** In 1948, I.C. Michaelson published what has been termed the “growth factor hypothesis” (Aiello LP, 2000; Michaelson IC, 1948). His hypothesis was that retinal ischemia (like that found in diabetic retinopathy) promotes production of angiogenic growth factors that would be responsible for proliferative neovascularization. Researchers have since focused on a number of likely candidates, including basic fibroblast growth factor (bFGF), growth hormone (GH), and hepatocyte growth factor (HGF). However, a large body of in vitro and in vivo evidence has narrowed the focus of this search to one highly probable etiological factor: vascular endothelial growth factor (VEGF).

VEGF is a potent angiogenic agent whose production is upregulated by hypoxia in RPE cells and retinal pericytes (Adamis AP, 1993; Plouet J, 1993). A study of ocular fluid taken from the eyes of patients with diabetic retinopathy and other neovascularizing eye disorders confirmed VEGF’s association with neovascular retinal disorders (Aiello LP, 1994). In the ocular fluid of diabetics, VEGF was detectable in 83% of samples from patients with active proliferative diabetic retinopathy, 22% of samples from patients with quiescent proliferative diabetic retinopathy, and only 8% of samples from patients with nonproliferative diabetic retinopathy.

Not only does VEGF promote retinal neovascularization, but it is also a highly effective inducer of vascular permeability. Research with bovine retinal endothelial cell cultures demonstrated that the administration of VEGF causes a 46–54% reduction in occludin concentrations (Antonetti DA, 1998). Occludin is the “glue” between retinal endothelial cells that helps maintain the blood-retina barrier, so this research suggests that VEGF-mediated loss of occludin may be a key process underlying the retinal vascular “leakiness” and hemorrhage that occur in diabetic retinopathy.

**The Role of Hyperglycemia.** The metabolic abnormalities of diabetes contribute to the destruction of blood vessels in the eye, just as these abnormalities affect blood vessels in many other organs. The etiological link between hyperglycemia and diabetic retinopathy has not been conclusively established, but several metabolic mechanisms have been proposed to explain how chronic hyperglycemia leads to retinal damage (Figure 3):
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FIGURE 3. Pathways of hyperglycemia-induced damage.

- The activation of the enzyme protein kinase C.
- The accumulation of advanced glycation end-products (AGEs).
- The overactivation of the polyol pathway.

Protein Kinase C. The protein kinase C isoforms are a family of 12 related serine/threonine enzymes found in nearly every tissue and cell type in the body (Aiello LP, 2000; Koya D, 1998). These enzymes have many responsibilities, including cell proliferation, differentiation, and apoptosis. One member of this family, protein-kinase-C beta (PKCβ), has been the target of diabetes research since researchers linked it to hyperglycemia-induced processes. The predominant hypothesis holds that AGEs and oxidants produced in nonenzymatic glycation and the polyol pathway, respectively, are converted to diacylglycerol (DAG). In turn, DAG synthesis promotes the activation of PKCβ (Xia P, 1994). Diabetic
animal models have shown high levels of the enzyme in the retina, heart tissues, and renal glomeruli.

PKCβ activation in the retina is believed to promote the overgrowth of blood vessels characterizing diabetic retinopathy, primarily through its relationship to VEGF activity. The β isozyme primarily causes cell proliferation, and both animal and human models have shown that blockade of PKCβ stops hypertrophy of the retinal vasculature. PKCβ promotes the expression of VEGF and is a critical mediator of the proliferative and permeability effects of VEGF (Aiello LP, 1997; Xia P, 1996). Furthermore, PKCβ can mediate signal transduction initiated by hormones such as vasopression and angiotensin II, possibly leading to renin-angiotensin-aldosterone system (RAAS) dysfunction. The RAAS is a critical factor in the regulation of the vasculature in the retina and in other body tissues.

Advanced Glycation End Products. Advanced glycation end products (AGEs) are formed through a process called nonenzymatic glycosylation. AGEs make up a heterogeneous group of proteins, nucleic acids, and lipids that have been exposed and irreversibly bound to reducing sugars. They are believed to form when blood and tissue glucose levels increase, thereby chemically modifying various extracellular and intracellular macromolecules. One such AGE is glycosylated hemoglobin A₁c (HbA₁c), the overproduction of which is a key clinical marker of diabetes-related hyperglycemia.

AGEs can alter the structural and functional properties of proteins. Much of this damage is believed to originate intracellularly, particularly in vasculature endothelial cells. It is believed that AGEs damage endothelial cells by intensifying oxidative stress and possibly by upregulating gene transcription, both of which may contribute to vascular disease. The AGE-mediated overproduction of superoxide anion (O₂⁻) creates oxidative stress, which can promote abnormal regulation of apoptosis (cell death). Hyperglycemia also affects the primary enzyme that detoxifies O₂⁻, superoxide dismutase 1 (SOD1), which is deactivated by glycosylation, leaving no counterbalance to the damage caused by AGEs. AGEs accumulate in the retinal capillaries, leading to capillary basement membrane thickening, decreased elasticity, and increased leakiness.

The Polyol Pathway. A large body of research has studied the role of the enzyme aldose reductase in diabetic complications. Excessive activity of aldose reductase, which reduces glucose to sorbitol via the polyol pathway, causes sorbitol to overaccumulate in cells, producing osmotic stress and creating structural and functional abnormalities in sensitive tissues such as the eye. Because aldose reductase has a low affinity for glucose, the polyol pathway has only minimal importance in people with normal glucose levels. In people with hyperglycemia, however, the excessive availability of glucose pushes this reaction in favor of aldose reductase activity. The polyol pathway can account for as much as 30% of glucose metabolism in diabetics with hyperglycemia.

Excessive aldose reductase activity may be responsible for overactivation of the GLUT-1 transport mechanism, allowing excessive amounts of glucose to enter
endothelial cells. Myoinositol competes with glucose for transport into cells. If aldose reductase enables glucose uptake to increase significantly, myoinositol will be unable to enter the cell. Abnormal sorbitol and myoinositol levels have also been implicated in increased vascular permeability in the blood/retinal barrier, as well as glomerular hyperfiltration (a kidney abnormality that is an early symptom of diabetes) and nerve cell dysfunction.

**Risk Factors**

**Duration of Diabetes.** The strongest predictor for both development and progression of diabetic retinopathy is the duration of diabetes. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) found that the prevalence of diabetic retinopathy (any stage) was 8% at 3 years after type 1 diabetes diagnosis, increasing to fully 80% at 15 years (Klein R, 1984[a]). The prevalence of PDR was 0% at 3 years and 25% at 15 years.

**Glycemic Control.** Observational data from the WESDR showed a significant correlation between HbA1c at baseline at the development or progression of diabetic retinopathy among type 1 diabetics, type 2 diabetics who used insulin, and type 2 diabetics who did not use insulin. Depending upon type of diabetes and HbA1c level, the relative risk of developing diabetic retinopathy was 1.1–2.7 compared with the quartile of patients with the lowest average HbA1c. The risk of any disease progression was 1.1–4.3, and the risk of progression to proliferative diabetic retinopathy was 1.2–13.8 (Klein R, 1988; Klein R, 1994; Klein R, 2000).

The 1993 publication of the landmark Diabetes Control and Complications Trial (DCCT) conclusively demonstrated that interventional strict glycemic control prevents the development and slows the progression of microvascular complications (including diabetic retinopathy) in type 1 diabetics. The United Kingdom Prospective Diabetes Study (UKPDS) and the Steno Type 2 Randomized Trial found similar results in type 2 diabetics. Table 2 highlights key points from these trials.

**Hypertension.** Hypertension is assumed to be a risk factor for diabetic retinopathy, although it has not been proved to play a role in the progression from the nonproliferative stage to the proliferative one. Researchers believe hyperglycemia causes an increase in retinal blood pressure that causes capillary damage. The role of systemic hypertension in diabetic retinopathy is less clear; studies investigating a possible link have produced conflicting results.

Observational studies have examined the role of hypertension in development and/or progression of diabetic retinopathy. The UKPDS compared retinal photographs from 1,919 newly diagnosed type 2 diabetics at diagnosis and six years later. The study found that systolic blood pressure at baseline was significantly associated with the incidence of diabetic retinopathy, and patients in the highest blood pressure tertile were 2.8 times more likely to develop diabetic retinopathy than patients in the lowest tertile (Stratton IM, 2001). However, baseline blood pressure was not significantly associated with progression of existing retinopathy.
TABLE 2. Hyperglycemia and Diabetic Retinopathy: Select Results from Clinical Trials

<table>
<thead>
<tr>
<th>Trial Details of Study</th>
<th>Selected Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Control and Complications Trial (DCCT)</td>
<td>In patients with no initial retinopathy, IIT reduced the risk of sustained disease by 76%. In patients with mild initial retinopathy, IIT reduced the risk of sustained retinopathy by 54%, the risk of developing severe proliferative retinopathy by 47%, and the need for laser treatment by 56% (The DCCT Group, 1993).</td>
</tr>
<tr>
<td>The U.K. Prospective Diabetes Study (UKPDS)</td>
<td>A modest decrease in HbA1c (11%) reduced the risks for progression to retinopathy by 21%. This reduction in HbA1c lowered the risk of microvascular complications by as much as 25%. The median complication-free interval was 1.3 years longer for the intensive treatment group (UKPDS Group, 1998[a]).</td>
</tr>
<tr>
<td>The Steno Type 2 Randomized Trial</td>
<td>Progression of retinopathy — either a worsening of existing retinopathy or development of new retinopathy — occurred in 19 intensively treated and 33 conventionally treated patients (Gaede P, 1999).</td>
</tr>
</tbody>
</table>

Full source citations appear in “References.”

The WESDR also found that the risk of proliferative retinopathy after 14 years of follow-up was positively correlated with diastolic blood pressure at baseline among type 1 diabetics. However, neither systolic nor diastolic blood pressure was associated with incidence or progression of diabetic retinopathy among type 2 diabetics (Klein R, 1998, Klein R, 2002).

The first interventional trial to catch the attention of physicians and other experts was the EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes (EUCLID). For two years, 530 type 1 diabetics in European centers were randomized to either placebo or lisinopril (10 or 20 mg, depending on severity of hypertension). At baseline, 65% of the placebo group and 59% of the lisinopril group had some evidence of retinopathy. The control of blood
pressure with lisinopril resulted in a 50% reduction in the number of patients whose retinopathy progressed one or more stages compared with the placebo group, after controlling for glycemic control (Chaturvedi N, 1997). It should be noted, however, that the results of this trial are a matter of some debate. The lisinopril-treated group had a significantly lower average HbA1c at baseline, and some researchers have postulated that its positive effect was due to lowering of undetected baseline hypertension (Fong DS, 2003).

In a UKPDS interventional study, 1,148 hypertensive type 2 diabetics were randomized to tight blood pressure control (goal of 150/85 mm Hg or lower) with an ACE inhibitor or a beta blocker or to less tight control (goal of 180/105 mm Hg or lower). Tight blood pressure control was associated with a 35% lower risk of progression of diabetic retinopathy (two or more steps on the modified ETDRS scale) during the median 7.5-year follow-up, and a 47% lower risk of visual acuity loss (three or more lines on the ETDRS chart). There was no significant difference in these effects between the two antihypertensive agents (UKPDS Group, 1998[b]). A similar study—the Appropriate Blood Pressure Control in Diabetes (ABCD) trial—randomized 470 hypertensive type 2 diabetics to intensive (goal of 75 mm Hg diastolic pressure) or moderate (goal of 80–89 mm Hg diastolic pressure) blood pressure control. At the end of the five-year follow-up, the data showed no significant difference between the groups in the progression of diabetic retinopathy (Estacio RO, 2000).

Taken together, the available data (both observational and interventional) do not paint an entirely conclusive picture of the association between hypertension and diabetic retinopathy. However, most physicians and researchers believe that the link is highly plausible and that well-designed studies in the future will provide evidence of a clear causal relationship.

**Diabetic Nephropathy.** Epidemiological data have shown that the incidence and progression of diabetic retinopathy is highly correlated with diabetic nephropathy, as measured by micro- and/or macroalbuminuria (Cruickshanks KJ, 1993; Klein R, 1993; West KM, 1980). In fact, some researchers believe microalbuminuria alone is a predictor of increased diabetic retinopathy risk. It is unlikely that diabetic nephropathy itself influences the development of retinopathy, but researchers believe hyperglycemia inflicts similar damage to kidneys and the retina. One hypothesis proposes that increased VEGF in both retinal and renal tissues is to blame, given that diabetics with retinopathy display increased VEGF levels in the eye, and elevated VEGF levels are often found in the urine of diabetics with proteinuria.

**CURRENT THERAPIES**

The only proven pharmacological therapy for diabetic retinopathy is the prophylactic achievement of near-normal glucose control. As described in “Etiology and Pathophysiology,” studies have found that rigorous glycemic control can prevent the development of nonproliferative retinopathy and delay progression to proliferative disease (DCCT Group, 1993; Gaede P, 1999; UKPDS Group, 1998[a]).
Most physicians and other experts have consequently tightened glycemic control in retinopathy patients, particularly since the publication of the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) results.

Besides antidiabetic agents, only antihypertensive drugs have been shown to have a positive effect on the development and progression of diabetic retinopathy. Nevertheless, physicians do not routinely prescribe antihypertensives specifically for the treatment of diabetic retinopathy. Many diabetics already take one or more antihypertensive agents, either for cardiovascular disease or renal dysfunction, at the time of retinopathy diagnosis. Most physicians are unwilling to prescribe antihypertensives to diabetics who are normotensive and have no discernible renal dysfunction. When antihypertensives are used in these patients, they are, almost without exception, angiotensin-converting enzyme (ACE) inhibitors; they are described here and in Table 3.

ACE Inhibitors

Overview. Since the 1997 publication of the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID, described later in the section “Lisinopril”), many physicians and researchers contend that strong evidence proves the beneficial effect of ACE inhibitors on the progression of diabetic retinopathy. This section highlights the agents in the class for which there are significant findings from high-quality clinical trials. Other ACE inhibitors that are also prescribed for diabetic retinopathy (and diabetics in general) include ramipril (Aventis’ Altace/Triatec, AstraZeneca’s Vesdil/Unipril), enalapril (Boehringer Ingelheim’s Pres, Merck’s Vasotec, generics), fosinopril (Bristol-Myers Squibb’s Monopril/Fosinorm, Merck’s Fozitec), and quinapril (Pfizer’s Accupril/Accupro, Sanofi-Synthélabo’s Korec).

Mechanism of Action. ACE inhibitors lower blood pressure by inhibiting the vasoconstrictive action of the renin-angiotensin-aldosterone system (RAAS). Additionally, ACE inhibitors are known to have some action in preventing cell

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**DIABETIC RETINOPATHY**

**TABLE 3. Current Therapies Used for Diabetic Retinopathy**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Company/Brand</th>
<th>Daily Dose</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>AstraZeneca’s Zestril/Acerbon,</td>
<td>5–10 mg qd or bid</td>
<td>US, F, G, I, S, UK, J</td>
</tr>
<tr>
<td></td>
<td>Bristol-Myers Squibb’s Carace/Coric,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Merck’s Prinivil,</td>
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<tr>
<td></td>
<td>generics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>Bristol-Myers Squibb’s Lopirin/Capoten,</td>
<td>25–50 mg qd or bid</td>
<td>US, F, G, I, S, UK, J</td>
</tr>
<tr>
<td></td>
<td>Sanofi-Synthélabo’s Alopresin,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>generics</td>
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</tbody>
</table>

ACE = Angiotension-converting enzyme; bid = Twice daily; qd = Once daily.  
US = United States; F = France; G = Germany; I = Italy; S = Spain; UK = United Kingdom; J = Japan.
proliferation, reducing platelet aggregation, and enhancing fibrinolysis (Lonn EM, 1998). Pharmacologically, ACE inhibitors act to prevent the ACE-mediated conversion of angiotensin I into angiotensin II (AII)—a potent vasoconstrictive agent that also promotes cardiovascular tissue growth and water and sodium retention. AII is also known to stimulate contraction of the vascular smooth-muscle cells lining the vascular wall, an action ultimately leading to hypertrophy (an increase in cell size) and hyperplasia (an increase in cell number). This action manifests as a thickening of the arterial wall and a narrowing of the lumen, developments that generate an increase in the peripheral resistance of the vasculature. AII also increases production of excess reactive oxygen species, which in turn increase vasoconstriction and damage the endothelial wall (Sowers JR, 2002).

**Lisinopril.** Lisinopril (Merck’s Prinivil, AstraZeneca’s Zestril, generics) (Figure 4) was approved in the United States in December 1987 for use as an antihypertensive agent. The agent is now available in all seven markets under study.

The EUCLID study enrolled 530 type 1 diabetics who were both normotensive and either normoalbuminuric (85%) or microalbuminuric (15%) from 15 European centers. At baseline, 65% of the placebo group and 59% of the lisinopril group had some evidence of retinopathy. Patients were randomized to either placebo or lisinopril (10 mg or 20 mg). After two years, treatment with lisinopril resulted in a 50% reduction in the number of patients whose retinopathy progressed one or more stages compared with the placebo group, after controlling for glycemic control (Chaturvedi N, 1997). It should be noted, however, that the results of this trial are a matter of some debate. The lisinopril-treated group had a significantly lower average HbA1c at baseline, and some researchers have postulated that the drug’s positive effect was due to lowering of undetected baseline hypertension (Fong DS, 2003).

Lisinopril’s adverse events profile is similar to that of other ACE inhibitors. A common side effect of agents in this class is a dry, nonproductive cough, which can occur in 5–20% of patients. Independently of their action on the RAAS, ACE inhibitors reduce breakdown of the vasodilator bradykinin, accounting for the cough frequently associated with ACE inhibitor prescription. ACE inhibitors are
contraindicated in pregnancy (the FDA has rated this class of drugs as Pregnancy Category C [risk cannot be ruled out] in the first trimester and Category D [published documentation of risk exists] for the second and third trimesters). ACE inhibitors are also contraindicated for patients with serious renal stenosis or widespread vascular lesions in the kidney due to potentially decreased renal perfusion. A further concern is angioedema (swelling and accumulation of fluid in the deep layer of the skin and the connective tissue that underlies mucous membranes); angioedema occurs in approximately 0.1% of patients taking ACE inhibitors.

**Captopril.** Captopril (Bristol-Myers Squibb’s Capoten, generics) (Figure 5) is available in all seven markets under study.

In a UKPDS study, 1,148 hypertensive type 2 diabetics were randomized to tight blood pressure control (goal of blood pressure lower than 150/85 mm Hg) with either captopril or a beta blocker (atenolol; AstraZeneca’s Tenormin, generics) or to less tight control (goal of blood pressure lower than 180/105 mm Hg). Tight blood pressure control was associated with a 35% lower risk of progression of diabetic retinopathy (an increase of two or more steps on the modified Early Treatment Diabetic Retinopathy Study [ETDRS] scale) during the median 7.5-year follow-up, and a 47% lower risk of visual acuity loss (an increase of three or more lines on the ETDRS chart). There was no significant difference in these effects between the two antihypertensive agents (UKPDS Group, 1998[b]).

Like lisinopril, captopril is associated with a dry, unproductive cough. It is also known to cause rashes in 2–7% of treated patients, generally within the first few weeks of treatment. Captopril is contraindicated in patients with renal insufficiency or angioedema.

**Nonpharmacological Approaches**

Although tight control of hyperglycemia and hypertension are effective in slowing the progression of diabetic retinopathy, the modest benefits conferred by pharmacological agents are not sufficient to completely prevent neovascularization. For this reason, nonpharmacological approaches such as laser photocoagulation and surgery are the only effective means to prevent vision loss.

**Laser Photocoagulation.** Photocoagulation destroys large sections of the hypoxic retina, thereby reducing the stimulus for abnormal vascular proliferation. Generally, photocoagulation involves placing a contact lens on a patient’s
eye after dilation and then focusing a laser beam (argon or krypton) on the retina using a slit lamp. Two techniques are commonly used to treat diabetic eye disease: panretinal photocoagulation (also called scatter photocoagulation) and focal photocoagulation.

Panretinal photocoagulation treats a large section of the retina, excluding the macular and foveal areas. Using a blue-green laser, physicians apply moderately intense burns for 0.1 second. Panretinal treatment usually consists of 1,200 to 1,500 of these burns, spaced a half-burn diameter apart from one another. Most patients undergo multiple sessions of 600 to 800 burns each.

Panretinal treatment is indicated for proliferative retinopathy but may also be used in patients with severe preproliferative retinopathy, depending on the physician’s assessment of the need for aggressive treatment. In the Diabetic Retinopathy Study (DRS), in which 1,742 patients were randomly assigned to either argon or xenon laser treatment, panretinal photocoagulation reduced severe vision loss by 60% after three years. The same trial also showed a 90% reduction in blindness at five years after photocoagulation (Diabetic Retinopathy Study Research Group, 1978).

Focal photocoagulation is often used for macular edema, a common complication of diabetic retinopathy, as well as for specific discrete vascular abnormalities elsewhere on the retina of diabetic retinopathy patients. This technique employs the same laser used in panretinal photocoagulation but at a lower energy level (commonly an argon green-only laser). The laser is applied either in a grid pattern or directly to leaking microaneurysms to destroy the blood vessels. In the Early Treatment Diabetic Retinopathy Study (ETDRS), focal/grid photocoagulation reduced by approximately 50% the risk of moderate visual acuity loss (defined as doubling of visual angle) in patients with clinically significant macular edema (ETDRS Research Group, 1985; ETDRS Research Group, 1987).

Photocoagulation therapy is generally safe, but it can produce serious side effects and complications in a minority of patients. For example, some patients lose their peripheral vision—in the DRS, 5% of argon-treated eyes and 25% of xenon-treated eyes experienced a constriction of visual field to less than 45° but greater than 30° (DRS Research Group, 1981[b]). Patients may also develop night vision problems. Potentially more serious is the risk that the laser might burn the wrong part of the retina, causing further deterioration and/or loss of vision. Among argon-treated eyes in the DRS, 11% had a treatment-related persistent decrease in visual acuity of one line, while 3% had a persistent decrease of two or more lines. Xenon-treated eyes had a higher rate of treatment-related side effects—19% had a persistent decrease in visual acuity of one line, and another 11% had a persistent decrease of two or more lines (DRS Research Group, 1981[b]).

**Vitrectomy.** Vitrectomy is indicated for media opacities (primarily vitreous hemorrhage), retinal traction detachment, and, rarely, traction-induced macular edema. A more substantial surgical undertaking than photocoagulation, vitrectomy usually requires hospitalization and general anesthesia. The goal of
Diabetic Retinopathy

Vitrectomy is removal of the posterior vitreous surface, which provides the “scaffolding” upon which neovascular tissue grows in diabetic retinopathy. The procedure involves making three incisions into the pars plana of the eye, the region behind the iris and in front of the retina. Three instruments are inserted into the incisions: a small light pipe to provide illumination; an infusion port to maintain proper fluid balance during the procedure; and the vitrector, or cutting device. Once the instruments are positioned inside the eye, subhyaloid blood is extracted and the posterior two-thirds of the vitreous gel and posterior vitreous surface are excised. Fibrovascular tissue causing retinal traction detachment may also be excised by this method. Photocoagulation may be applied thereafter in a panretinal pattern.

The Diabetic Retinopathy Vitrectomy Study (DRVS) conducted two randomized trials to assess the efficacy of early vitrectomy in type 1 and 2 diabetics and conducted an observational study of a third group of diabetics. One interventional arm of the trial enrolled 616 diabetic patients with severe vision loss from a recent vitreous hemorrhage (5/200 or less for one month or longer). Patients were randomized to either early vitrectomy or deferral of vitrectomy for one year (conventional therapy). The results showed that 25% of the early vitrectomy group recovered good vision (10/20 or better) at two years, compared with 15% of those who received the conventional therapy (DRVS Research Group, 1985). The second interventional arm randomized 381 patients with proliferative retinopathy who still had useful vision (10/200 or better) in at least one eye to either early vitrectomy or conventional therapy. In this arm, the early vitrectomy group had a 36% recovery rate at two years, versus 12% of the conventional group (DRVS Research Group, 1988).

Although the findings of the DRVS and other studies show that vitrectomy can produce positive results, the procedure’s complicated nature has relegated its use only to cases of severe diabetic retinopathy when photocoagulation has failed or proved technically impossible. The operation puts patients at much higher risk for complications than photocoagulation does; the complications include the buildup of silicon fluid in the eye, recurrent vitreous hemorrhage, retinal detachment, and anterior hyaloidal fibrovascular proliferation (vessel proliferation at the front of the eye, behind the lens capsule).

Emerging Therapies

Of all the agents in development for the treatment of the diabetic microvascular complications, the agents outlined in this section are potentially the most exciting. No current pharmacotherapy, with the possible exception of antihypertensives, can halt the progression of retinopathy. While effective, the current retinopathy treatments (photocoagulation or surgery) are appropriate only for patients who have progressed to the more severe, proliferative stage of disease, leaving few options other than tightened glycemic control for the treatment of patients with nonproliferative disease. Most pharmacotherapies in development target the aberrant angiogenesis that characterizes proliferative diabetic retinopathy, while some
are also being tested for related diabetic macular edema. The most interesting therapies in development for diabetic retinopathy are outlined in Table 4.

**Protein Kinase Cβ Inhibitors**

**Overview.** Protein kinase C (PKC) inhibitors are potential treatments for diabetic retinopathy. Eli Lilly’s PKCβ inhibitor, ruboxistaurin, was the first potential oral drug therapy for the indication to reach late-stage development. However, recent clinical trial data have cast some doubt on the potential of this class of drugs.

**Mechanism of Action.** The protein kinase C family consists of several structurally related enzyme isoforms that are present throughout the body. Experimental evidence has shown that the beta isoform (PKCβ) is a key mediator of diabetes-induced retinal abnormalities. When activated by diacylglycerol—cellular levels of which are increased by a chronic hyperglycemic state—PKCβ promotes the synthesis of vascular endothelial growth factor (VEGF), a potent promoter of angiogenesis known to play a role in inducing proliferative diabetic retinopathy (Frank RN, 2002). Agents that inhibit the activation and/or activity of PKCβ could therefore block the effects of VEGF, including promotion of vascular angiogenesis and hyperpermeability.

**Ruboxistaurin.** Eli Lilly’s PKCβ inhibitor ruboxistaurin (LY-333531), an orally available agent, has been discontinued. For purely historical purposes, it is of interest to note that it was highly selective for the β isozyme from the PKC family, and did reach Phase III development in the United States and Europe. In early 2004, Takeda and Eli Lilly agreed to codevelop and comarket ruboxistaurin in Japan, where it was in Phase II. Ruboxistaurin was also in Phase III development for the treatment of diabetic peripheral neuropathy.

The first data published from Phase III trials of ruboxistaurin in diabetic retinopathy were not as promising as physicians and researchers had expected. The Protein Kinase C Diabetic Retinopathy Study (PKC-DRS) was a Phase II/III, multicenter, double-blind, placebo-controlled, randomized trial. Two hundred fifty-two patients with either type 1 (19%) or type 2 (81%) diabetes were randomized to one of three ruboxistaurin doses (8, 16, or 32 mg daily) or placebo for a minimum of 36 months. At baseline, patients had either moderate to severe nonproliferative diabetic retinopathy: as judged by the severity of disease in the worst affected eye, 45% had retinopathy of Early Treatment Diabetic Retinopathy Study (ETDRS) severity level 47, and 55% were at level 53. The primary outcomes measured were progression of retinopathy by three or more steps on the ETDRS scale or application of photocoagulation. At 42 months, ruboxistaurin did not have any significant effect on those primary end points: event-rate estimates were 57%, 72%, and 52% in the 8, 16, and 32 mg groups, respectively, compared with 55% in the placebo group. However, the highest-dose ruboxistaurin group did show a trend toward a positive effect on some outcome measure. The rates of moderate visual loss (loss of 15 or more letters on the Snellen chart) were
TABLE 4. Emerging Therapies in Development for Diabetic Retinopathy

<table>
<thead>
<tr>
<th>Compound</th>
<th>Development Phase</th>
<th>Marketing Company</th>
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<tr>
<td><strong>Protein kinase C(\beta) inhibitors</strong></td>
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<tr>
<td>Ruboxistaurin</td>
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<tr>
<td>United States</td>
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<td>Eli Lilly</td>
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<td><strong>Ocular corticosteroid implants</strong></td>
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<td>Fluocinolone acetonide (Retisert)</td>
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<td>United States</td>
<td>III</td>
<td>Bausch &amp; Lomb/Control Delivery Systems</td>
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<td>Dexamethasone (Posurdex)</td>
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<td>United States</td>
<td>III(^a)</td>
<td>Allergan/Oculex Pharmaceuticals</td>
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<td><strong>Somatostatin analogues</strong></td>
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<td>Octreotide (Sandostatin LAR)</td>
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<td>Europe</td>
<td>III(^b)</td>
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<td>BIM-23190</td>
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<td><strong>Angiotensin II receptor antagonists</strong></td>
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<td>Candesartan (Atacand)</td>
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<td><strong>VEGF antagonists</strong></td>
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<td>Pegaptanib (Macugen)(^c)</td>
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<tr>
<td>United States</td>
<td>II</td>
<td>Eyetech Pharmaceuticals/Pfizer</td>
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<td><strong>Hyaluronidase modulators</strong></td>
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<td>Hyaluronidase (Vitrase)(^d)</td>
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<td>Japan</td>
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\(^a\) Phase III trials are being conducted in diabetic macular edema patients.
\(^b\) Phase III trials are being conducted in Switzerland.
\(^c\) Phase II trials are being conducted in diabetic macular edema patients. Pfizer and Eyetech have publicly discussed the potential for additional diabetic retinopathy trials, but to date no such formal development program has been announced.
\(^d\) Vitrase is preregistered in the United States for the treatment of vitreous hemorrhage and as a dispersion agent for other ophthalmic drugs. It is in Phase III development in Europe and preclinical development in Japan for vitreous hemorrhage, and Phase II trials for diabetic retinopathy have been conducted in Mexico. PC = Preclinical (including discovery).
PR = Preregistered.
lower in the 32 mg group than in the placebo group at 12 months (12% versus 20%), 24 months (8% versus 29%), and 36 months (19% versus 28%), with an average risk reduction of 35% (Milton R, 2003).

The second Phase III trial of ruboxistaurin—the Protein Kinase C Diabetic Macular Edema Study (PKC-DMES)—measured the drug’s effect on diabetic macular edema (DME) and found similar results. Ruboxistaurin had no significant effect on either the progression of DME or the application of photocoagulation, but data revealed a trend, with a 32 mg daily dose, toward a positive effect on the development of DME that involves or imminently threatens the center of the macula (Eli Lilly, press release, August 25, 2003).

One possible explanation for the largely disappointing results from these two Phase III trials (which used partially overlapping patient populations) was the lower-than-expected event rates in the placebo groups (Davis MD, 2003). The trials were designed based upon event-rate data from the ETDRS, where the rates of both diabetic retinopathy and DME events were notably higher than those found in the PKC-DRS or PKC-DMES. Thus, the PKC-DRS and PKC-DMES were perhaps not powered sufficiently to show a treatment effect, if any existed. Eli Lilly stated already in December 2002 that these results would delay the EU and U.S. regulatory filings for ruboxistaurin for diabetic retinopathy, but that additional Phase III studies were to be conducted that would, the company had hoped, address the methodological issues of the PKC-DRS.

These hopes did not come to fruition.

**Ocular Corticosteroid Implants**

**Overview.** Corticosteroids have been utilized in eyedrop formulations for a number of ophthalmic indications. However, these products are unable to penetrate the vitreous and retinal areas and therefore have little effect on retinal vasculature and inflammation. Corticosteroid implants currently in development for diabetic macular edema and retinopathy may allow site-specific delivery of these compounds, which have potent anti-inflammatory and antiangiogenic qualities.

**Mechanism of Action.** Corticosteroids act as anti-inflammatory, immunosuppressive, and antiangiogenic agents through multiple effects: inhibiting synthesis of proinflammatory mediators (prostaglandins, leukotrienes, and cytokines); disrupting cellular activation, migration, and proliferation; and blocking edema formation. Although systemic corticosteroids are effective against many inflammatory and immune-mediated disorders, their prolonged use is associated with a high risk of side effects. Insomnia, night sweats, mood changes, and altered glucose metabolism may occur shortly after beginning corticosteroid use, while long-term use of systemic corticosteroids is associated with adrenal atrophy, osteoporosis, hypertension, cataracts, acne, abnormal fat deposition, and excessive hair growth. Local corticosteroid delivery in the form of ocular drops, injections, or sustained-release implants has been postulated as a therapeutic option that would target inflammation and neovascular processes in numerous
retinal disorders—including diabetic retinopathy—in the hopes of minimizing the risk of systemic side effects.

**Fluocinolone Acetonide.** Fluocinolone Intraocular implant has been discontinued.

Originally, Bausch & Lomb and Control Delivery Systems were developing a sustained-release intravitreal fluocinolone implant (Retisert) using Control Delivery Systems’ Envision TD delivery technology. The agent did reach Phase III development in the United States for diabetic macular edema and diabetic retinopathy, as well as Phase III trials for uveitis and Phase II trials for age-related macular degeneration (AMD).

Twelve-month data from the first Phase III trial demonstrating the fluocinolone implants’ efficacy were presented at the 2003 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO). Eighty patients with diabetic macular edema were randomized to fluocinolone implant (0.5 mg or 2 mg) or standard of care (observation or laser photocoagulation). The 2 mg implant was discontinued early in the trial when investigators determined it conferred no additional treatment benefit compared with the 0.5 mg implant. After 12 months, the fluocinolone implant had a significant effect on retinal thickness (macular edema)—49% of patients receiving the 0.5 mg implant had complete response, compared with 25% of the control group (Bausch & Lomb, press release, May 7, 2003).

This trial was not powered to demonstrate significant effects on diabetic retinopathy or overall visual acuity, but those data were presented and suggested a trend toward an effect. Fewer fluocinolone-treated patients demonstrated a worsening of diabetic retinopathy (5%) than did patients in the control group (30%). Although the results for visual acuity changes were not statistically significant, patients receiving the fluocinolone implant did demonstrate a trend toward a treatment effect. More fluocinolone-treated patients had stable (70%) or improved (19.5%; 15 or more letters) visual acuity than did control patients (50% and 7.1%, respectively).

Although the 12-month data from the Phase III trial looked promising—particularly for the treatment of diabetic macular edema—fluocinolone treatment was also associated with a number of side effects. Nearly 20% of fluocinolone-treated patients had a serious increase in intraocular pressure (≥30 mm Hg), whereas no control-group patients did. Cataract progression at six months was evident in 55% of patients in the fluocinolone-treated group, compared with no patients in the control group. After discussions concerning the adverse event rates from this trial, the FDA had requested additional 12-month safety data from additional fluocinolone-implanted diabetic eyes.

Eventually, these effects resulted in the discontinuation of the fluocinolone intraocular implant.

**Dexamethasone.** Oculex has developed a biodegradable, sustained-release dexamethasone implant (Posurdex) for the treatment of macular edema. In October 2003, Allergan purchased Oculex and began to design and plan Phase III

Preliminary data from a Phase II, randomized, dose-ranging trial of intravitreal dexamethasone were presented at the 2003 annual meeting of ARVO. The study enrolled patients with persistent macular edema associated with diabetes \((n = 171)\), uveitis or Irvine-Gass syndrome \((n = 40)\), or central or branch retinal vein occlusion \((n = 103)\), all with visual acuity of 20/40 or worse. Patients were randomized to intravitreal dexamethasone \((350 \mu g \text{ or } 700 \mu g)\) or standard of care/observation \((\text{Haller JA, 2003; Kuppermann BD, 2003; Williams GA, 2003}).\) Efficacy data were reported for a combined study population of 306 patients three months after treatment initiation. Patients who received the 700 \(\mu g\) demonstrated significant improvements in visual acuity (two or more lines) compared with the control group. Both the 350 \(\mu g\) and 700 \(\mu g\) intravitreal dexamethasone groups showed significant decreases in retinal thickness and fluorescein leakage compared with control \((\text{Oculex, press release, May 8, 2003}).\)

Like the fluocinolone implant, intravitreal dexamethasone was associated with an increased risk of glaucoma—4% of treated patients had developed elevated intraocular pressure in the three-month assessment. Although this rate is lower than reported in the previously described trial of the fluocinolone implant, it is premature to assume that intravitreal dexamethasone will have a more favorable adverse event profile. Preliminary data regarding the fluocinolone implant also demonstrated a low occurrence of serious side effects, and not until longer-term data were available did the serious adverse event rate become substantial (approximately 40–50%).

According to Allergan, the intended Phase III development program for intravitreal dexamethasone will include approximately 700 patients (diabetic and nondiabetic), with treatment periods of at least six months and follow-up periods of a year or more.

**Somatostatin Analogues**

**Overview.** The normal process of retinal vascular growth and apoptosis involves both proangiogenic and antiangiogenic elements. In an attempt to capitalize on the body’s naturally antiangiogenic compounds, researchers are developing analogues of somatostatin, a naturally occurring hormone with strong inhibitory effects on the endocrine system and possibly on the retinal vasculature specifically.

**Mechanism of Action.** Somatostatin is an endogenous hormone that is secreted in a number of body tissues, including the hypothalamus, intestines, and pancreas. It has a potent and multifaceted inhibitory effect on the endocrine system—endogenous somatostatin release inhibits the secretion of growth factors such as insulin, thyroid-stimulating hormone (TSH), human growth hormone (GH), and insulin-like growth factor 1 (IGF-1). Case studies and other experimental evidence have demonstrated that GH and IGF-1, in particular, are angiogenic factors that contribute to retinal neovascularization in diabetics. Some diabetics
who have undergone hypophysectomy (removal of the pituitary gland) experienced reversals of proliferative retinopathy that correlated with the degree of GH deficiency postsurgery (Patterson JH, 1974; Poulsen JE, 1953; Sharp PS, 1987). Serum and vitreal concentrations of IGF-1 correlate positively with the presence of proliferative retinopathy in diabetics (Burgos R, 2000; Merimee TJ, 1983). Thus, by mimicking the inhibitory effects of endogenous somatostatin and blocking the secretion of GH, IGF-1, and other growth factors, somatostatin analogues may be effective against neovascularization in the diabetic retina.

**Octreotide.** Novartis’s octreotide (Figure 6) is a somatostatin analogue marketed as Sandostatin and as Sandostatin LAR, a long-acting release formulation, worldwide for the treatment of acromegaly and diarrhea. The long-acting formulation is in Phase III trials in Switzerland for diabetic retinopathy.

A 15-month pilot study of 23 patients with type 1 or type 2 diabetes and severe nonproliferative diabetic retinopathy was conducted in the United States. Octreotide-treated patients received four daily subcutaneous injections of short-acting octreotide at the maximum tolerable dose for each individual (total daily doses ranged from 200 µg to 5,000 µg). The number of patients requiring panretinal photocoagulation (PRP) during the study period was significantly reduced in the octreotide-treated group: 1 of 22 eyes required PRP compared with 9 of 24 eyes in the control group. In addition, the incidence of progression to require PRP (ETDRS score 71 or 75) was 42% in the control group compared with 9% in the octreotide group, although those results were not statistically significant (Grant MB, 2000).

In a small U.K. trial, 18 patients (type 1 or type 2 diabetics) with persistent proliferative retinopathy after laser photocoagulation were randomized to either octreotide treatment (n = 9) or a control group (no placebo; n = 9). Octreotide-treated patients received three times daily subcutaneous 100 µg injections of short-acting octreotide. After three years of treatment, octreotide reduced the risk of vitreous hemorrhage and vitreoretinal surgery significantly compared with control. Average visual acuity remained stable in the octreotide-treated patients but decreased in the control group (Boehm BO, 2001).

The currently marketed short-acting product is an intramuscular injection that requires physician administration, and trials using this formulation of octreotide in retinopathy have used thrice-daily injections. The ongoing Phase III diabetic retinopathy trial is utilizing the sustained-release octreotide LAR, and the dosing protocol in the study will use monthly injections. However, octreotide LAR is an intramuscular injection that requires in-office administration by a physician, so it may not offer a large convenience benefit over daily but self-administered injections of the short-acting octreotide product.
BIM-23190. Ipsen’s BIM-23190 is a somatostatin analogue that is highly selective for the human somatostatin analogue receptor subtype 2 (Morgan JP, 1996). In July 2003, Teijin signed an exclusive codevelopment and co-marketing agreement with Ipsen for BIM-23190 in Japan for the treatment of diabetic retinopathy.

No human trial data are yet published that would allow for direct comparison of BIM-23190’s efficacy and safety with those of octreotide, but it appears that BIM-23190 will also be administered parenterally.

Angiotension II Receptor Antagonists

Overview. Since the 1997 publication of the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID, described in the “Current Therapies” section), antihypertensives (specifically, ACE inhibitors) have been posited to have a strong effect on the progression of diabetic retinopathy. However, EUCLID was not designed with incidence or progression of diabetic retinopathy as primary outcomes, leaving some uncertainty about antihypertensives’ effects on the disease (Sjolie AK, 2002). Another question remains as well: Will agents that produce the same antihypertensive effect as ACE inhibitors via different mechanisms be comparable or superior to those agents in the treatment of diabetic retinopathy? To that end, angiotensin II receptor antagonists (AIIRAs) are under investigation as potential therapies for this indication.

Mechanism of Action. Angiotensin II (AII) is a potent vasoconstrictive agent that also promotes cardiovascular tissue growth and water and sodium retention. AII is also known to stimulate contraction of the vascular smooth-muscle cells lining the vascular wall, an action ultimately leading to hypertrophy (an increase in cell size) and hyperplasia (an increase in cell number). This action manifests as a thickening of the arterial wall and a narrowing of the lumen, developments that generate an increase in the peripheral resistance of the vasculature. AII also increases production of excess reactive oxygen species, which in turn increase vasoconstriction and damage the endothelial wall (Sowers J, 2002). AIIRAs, like ACE inhibitors, act on the renin-angiotensin-aldosterone system (RAAS) to block the activity of AII; however, AIIRAs selectively antagonize the angiotensin II receptor subtype 1 (AT1), whereas ACE inhibitors function by blocking AII generation. Data from animal models have shown that AII can stimulate retinal neovascularization in vitro (Otani A, 1998) and that AIIRA treatment can inhibit retinal VEGF expression and angiogenesis in vivo (Moravski CJ, 2000; Nagisa Y, 2001).

Candesartan. Candesartan (AstraZeneca’s Atacand/Ratacand/Amias, Takeda’s Kenzen/Blopress) (Figure 7) is marketed in all regions under study for the treatment of hypertension and is currently in Phase III trials for diabetic retinopathy. A large-scale Phase III diabetic retinopathy trial of candesartan was initiated in early 2003. The Diabetic Retinopathy Candesartan Trial (DIRECT) is a multicenter, placebo-controlled, double-blind, randomized clinical trial consisting of
three study arms. The three arms of the DIRECT study are a primary prevention trial in type 1 diabetics with no retinopathy, a secondary prevention trial in type 1 diabetics with nonproliferative retinopathy, and a secondary prevention trial in type 2 diabetics with nonproliferative retinopathy. Study investigators plan to enroll approximately 4,500 participants from 20 countries who will be randomized to either candesartan (up to 32 mg/day) or placebo for at least three years. The primary endpoints to be measured in DIRECT are incidence of retinopathy in those with no retinopathy at baseline (a two-step increase in ETDRS severity grade) and progression of existing retinopathy (a three-step or greater increase in ETDRS severity grade) (Chaturvedi N, 2002). According to AstraZeneca and Takeda, full results of the DIRECT study are expected by 2006.

VEGF Antagonists

**Overview.** Although many agents in development inhibit the production of vascular endothelial growth factor (VEGF), research has also focused on agents that can antagonize circulating ocular VEGF. The majority of VEGF antagonists are in active development for retinal neovascularization disorders such as AMD. However, by virtue of the common VEGF-mediated pathways that result in diabetic retinopathy and/or diabetic macular edema, these indications may be logical additional targets for those same anti-VEGF agents.

**Mechanism of Action.** Unlike antiangiogenesis agents, which inhibit the production of VEGF through enzymatic or other processes, VEGF antagonists are a heterogeneous group of drugs in development that bind to free VEGF and render it unable to activate receptors in the retinal vasculature (or theoretically in any body tissue). Agents that can be classified into this group include receptor fusion proteins, anti-VEGF aptamers, and monoclonal antibodies. Though different in composition and structure, all VEGF antagonists share the ability to mimic endogenous VEGF receptors and thus “capture” the molecule and render it inactive.

**Pegaptanib.** Pfizer and Eyetech are jointly developing pegaptanib (EYE-001; Macugen), an intravitreal injection in Phase III trials for the treatment of
AMD and Phase II trials for diabetic macular edema. Pegaptanib is an anti-VEGF aptamer, a synthetic oligonucleotide with high affinity and selectivity for VEGF165. Eyetech originally licensed pegaptanib from Gilead in 2000, and in December 2002, Pfizer and Eyetech entered a codevelopment and comarketing agreement for the molecule. Under this agreement, Pfizer will fund most of the remaining development, and the companies will copromote pegaptanib in the United States. Pfizer has exclusive marketing rights outside the United States.

Pegaptanib has not been tested in diabetic retinopathy patients, but Phase IIa data in AMD patients were presented in May 2002 at the TIDES meeting, a joint event that included the Sixth International Oligonucleotide Technology Conference and the Fifth International Peptide Technology Conference. Patients received three monthly intravitreal injections (0.1 mL) of pegaptanib either alone or in conjunction with photodynamic therapy (PDT). At three months, 86% of pegaptanib-treated patients demonstrated stabilization of AMD progression, compared with 51% of patients receiving PDT alone. Three-line improvements in visual acuity were evident in 26% of pegaptanib-treated patients, compared with 2% of PDT-treated patients. The combined effect of pegaptanib and PDT was even more beneficial: 60% of patients receiving combination therapy achieved a three-line or better improvement in visual acuity (Scypinski S, 2002).

These Phase II AMD data suggest that after just three months, pegaptanib can inhibit the progression of retinal neovascularization. These results are promising for the use of this anti-VEGF aptamer to halt or possibly reverse retinal neovascularization associated with other conditions, including diabetic retinopathy. The general transferability of pegaptanib’s AMD trial results to diabetic retinopathy remains to be proven, however, because of key differences in the pathology and pathogenesis of each disease. The pathology of AMD neovascularization is distinct (the former occurs in the choroid, a normally avascular portion of the eye posterior to the retina), and the natural history of AMD progression follows a more rapid, progressively degenerative course than does the metabolic-dependent progression of diabetic retinopathy.

Hyaluronidase Modulators

Overview. Vitreous hemorrhage (leakage of the vitreous humor into the retina) is a complication of retinopathy that is difficult to treat and can occlude the imaging of the retina for screening or laser photocoagulation. The current treatment method, surgical vitrectomy, is generally effective but highly invasive. Hyaluronidase modulators, which are preparations of a naturally occurring enzyme, offer promise as treatment for vitreous hemorrhage secondary to proliferative diabetic retinopathy and may also be effective for preventing progression of nonproliferative disease.

Mechanism of Action. Hyaluronidase is a naturally occurring enzyme that digests proteoglycans. This group of molecules, which are largely present in connective tissues, includes hyaluronan, hyaluronic acid, and chondroitin sulfate. When introduced into a medium containing proteoglycans, hyaluronidase digests
the molecules and decreases the viscosity of the medium. Research has shown that intraocular injections of hyaluronidase can induce posterior vitreous detachment (PVD; a loosening or separation of the vitreous humor from the retina), which allows for the clearing of vitreous hemorrhage. Researchers postulate that liquefaction or detachment of the vitreous humor will remove the “scaffolding” upon which retinal neovascular tissue forms and therefore may prevent or delay progression to proliferative retinopathy.

Hyaluronidase. Ista Pharmaceuticals is developing an intravitreal injection of highly purified ovine hyaluronidase (Vitrase) for the treatment of vitreous hemorrhage and diabetic retinopathy and as a spreading agent to facilitate the dispersion and absorption of other ophthalmic agents. Ista partnered with Allergan in March 2000 to comarket hyaluronidase in the United States and all international markets except Mexico and Japan. In late 2001, Ista gave exclusive development and marketing rights for hyaluronidase in Japan to Otsuka.

Hyaluronidase is currently in preregistration in the United States and Japan and in Phase III development in Europe for the treatment of vitreous hemorrhage. The FDA gave hyaluronidase fast-track designation in 1998 for this indication. Ista submitted hyaluronidase for FDA approval in December 2002 for the treatment of vitreous hemorrhage but received an approvable letter in April 2003 citing insufficient statistical evidence to support its approval. In August 2003, Ista filed a second NDA for hyaluronidase for approval as a dispersion enhancer for other ophthalmic agents. The FDA has accepted this second NDA. In addition to these development programs, Phase II trials for diabetic retinopathy have been conducted in Mexico.

Initial results from a randomized, placebo-controlled, Phase IIa trial of hyaluronidase showed it was effective at inducing PVD. The study enrolled approximately 60 diabetics with nonproliferative retinopathy from Mexico City. Patients were randomized to receive one of four treatments: an injection of hyaluronidase, a placebo (saline) injection, a single treatment with sulfur-hexafluoride gas (SF6; a surgical adjunct for retinal detachment treatment), or a single, combination treatment with SF6 and a hyaluronidase injection. Interim results showed that 16 weeks following treatment, 60% of patients who received hyaluronidase injections demonstrated complete PVD, as measured via ultrasound. Complete PVD rates were 53% in the SF6-treated group, 50% in the SF6/hyaluronidase combination group, and 6% in the placebo group (Ista, press release, October 19, 2000).

The full one-year data measured the effect of hyaluronidase on ETDRS diabetic retinopathy levels and found that the agent prevented worsening of diabetic retinopathy. At 12 months, 67% of hyaluronidase-treated patients had stable ETDRS scores, compared with 40%, 43%, and 38% of the SF6-treated group, the SF6/hyaluronidase combination group, and the placebo group, respectively. Fewer hyaluronidase-treated patients (13%) had a worsening of ETDRS severity, compared with 20% of the SF6-treated group, 21% of the SF6/hyaluronidase combination group, and 38% of the placebo group (Ista, press release, January 8, 2002).
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