Translational Science Review

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Diabetic Macular Edema: Pathophysiology and Novel Therapeutic Targets

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Diabetic macular edema (DME) is the major cause of vision loss in diabetic persons. Alteration of the blood–retinal barrier is the hallmark of this disease, characterized by pericyte loss and endothelial cell–cell junction breakdown. Recent animal and clinical studies strongly indicate that DME is an inflammatory disease. Multiple cytokines and chemokines are involved in the pathogenesis of DME, with multiple cellular involvement affecting the neurovascular unit. With the introduction of anti–vascular endothelial growth factor (VEGF) agents, the treatment of DME has been revolutionized, and the indication for laser therapy has been limited. However, the response to anti-VEGF drugs in DME is not as robust as in proliferative diabetic retinopathy, and many patients with DME do not show complete resolution of fluid despite multiple intravitreal injections. Potential novel therapies targeting molecules other than VEGF and using new drug-delivery systems currently are being developed and evaluated in clinical trials. *Ophthalmology 2015;122:1375-1394 © 2015 by the American Academy of Ophthalmology.*

Diabetes mellitus is the global epidemic of the 21st century. At present, there are 382 million diabetic persons in the world, and this number is projected to reach 592 million by the year 2035.[1] Diabetic retinopathy, a microvascular complication of diabetes, is prevalent in approximately 35% of people with diabetes.[2] Diabetic macular edema (DME) is the major cause of visual loss in diabetic persons, in whom the breakdown of the blood–retinal barrier (BRB) occurs, with leakage of plasma and lipid in the macula. It is important to emphasize that diabetic maculopathy is a broader term that also includes patients with macular ischemia (often with poor prognosis) in addition to macular edema. In this review, we discuss the pathogenesis of DME and the treatment strategies currently available for the treatment of this disease and those in development.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a large population-based study, reported the incidence of macular edema over a period of 25 years as 29% in type 1 diabetic persons.[3] The Diabetes Control and Complications Trial (DCCT), a landmark study, showed that 27% of type 1 diabetic persons developed macular edema within 9 years of diabetes onset.[4] The incidence of macular edema in type 2 diabetic persons reported in another WESDR study was 25.4% in those who required insulin and 13.9% in those who did not require insulin.[5] Of note, proliferative diabetic retinopathy (PDR) occurs in only 50% of type 1 diabetic persons after 15 years of diabetes and in 10% of type 2 diabetic persons after a similar duration.[6]

Clinical Features of Diabetic Macular Edema

Clinical Features and Grading of Severity

Macular edema can occur in any stage of diabetic retinopathy, either nonproliferative or proliferative retinopathy. When the thickening involves the fovea or threatens to involve the fovea, the patient becomes symptomatic with metamorphopsia and vision loss. The examination of DME requires stereoscopic biomicroscopy of the macula or stereoscopic fundus photography. The Early Treatment Diabetic Retinopathy Study (ETDRS) defined "clinically significant macular edema" as (1) thickening of the retina at or within 500 μm of the center of the macula; (2) hard exudates at or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina; or (3) a zone of retinal thickening ≥1 disc area, any part of which lies within 1 disc diameter of the center of the macula.[7] The Global Diabetic Retinopathy Project Group has a simplified international classification for grading of DME. This grading is based on the distance of retinal thickening and/or lipid from the fovea: (1) mild DME:

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eyes with some edema or lipid in the posterior pole but distant from the center of the macula; (2) moderate DME: eyes with edema or lipid approaching the center but not involving it; and (3) severe DME: eyes with edema or lipid involving the center of the macula.[8] Although the clinical examination is still the gold standard for diagnosis of DME, optical coherence tomography (OCT) has now become a fast, convenient diagnostic tool for quantitative measurement and mapping of macular thickening. Serial OCT measurements of central subfield mean thickness are now considered an important means of measuring the outcome of treatment and re-treatment with anti−vascular endothelial growth factor (VEGF) agents because they are highly reproducible and can be correlated with other measurements of the central macula.[9] Mean thickness in other subfields (inner and outer subfield mean thickness) and total macular volume are useful in measuring extrafoveal macular changes. A recent Diabetic Retinopathy Clinical Research (DRCR) Network study showed modest correlation between OCT-measured center point thickness and visual acuity in DME.[10] However, a wide range of visual acuity was seen for a given degree of retinal edema, and the OCT measurements could not be reliably substituted as a surrogate for visual acuity at a given point in time. The definite source of leakage from retinal microvessels could be better assessed by fluorescein angiography (FA). In addition to areas of leakage from microaneurysms, microvascular abnormalities, and telangiectasis, FA can detect areas of capillary nonperfusion and macular ischemia that cannot be diagnosed with the OCT technique. An abnormally enlarged foveal avascular zone is diagnostic of macular ischemia and indicates poor visual prognosis in patients with DME.

Risk Factors

Several risk factors have been associated with the prevalence of diabetic retinopathy in general. A recent meta-analysis suggested a greater burden of DME among non-Hispanic blacks, individuals with high concentrations of hemoglobin A1c, and those with longer duration of diabetes.[11]

Duration of Diabetes. The duration of diabetes is the most consistently associated risk factor for the development of diabetic retinopathy, as shown by all major population-based epidemiologic studies. Nearly all type 1 diabetic persons and 80% of type 2 diabetic persons develop some retinopathy after 20 years of diabetes.[12,13] However, in contrast with the literature, the 50-year Medalist Study, a study of patients with type 1 diabetes at the Joslin Diabetes Center who survived more than 50 years of diabetes, reported contrary observations.[14] In that study, only approximately 50% of those with a diabetes duration of 50 to 60 years presented with diabetic retinopathy. There was no association between glycemic control and prevalence of reported microvascular complications in these subjects. Such a protection from retinopathy in this population was attributed to the presence of specific advanced glycation endproduct combinations, high plasma carboxyethyl-lysine, and pentosidine.[15]

Hyperglycemia. The incidence of DME over the 10-year period in the WESDR study was found to be associated with higher concentrations of glycosylated hemoglobin.[1] Three large randomized clinical trials have shown the benefits of systemic control of blood glucose on the development and progression of retinopathy. The DCCT study of type 1 diabetic persons showed that tight glucose control prevented the development of diabetic retinopathy by 76% and slowed the progression of diabetic retinopathy by 54%.[16] The United Kingdom Prospective Diabetes Study (UKPDS) of type 2 diabetic persons also reported similar benefits of tight glucose control in progression of diabetic retinopathy.[17] Approximately 10% of the patients in the tight control arm of the DCCT study showed "worsening of retinopathy" in the form of cotton-wool spots in the first 2.5 years, and this has been attributed to increased levels of insulin-like growth factor (IGF)-1 or increased levels of insulin that can further upregulate VEGF, resulting in cotton-wool spots and blot hemorrhages.[18] When the DCCT patients were followed up after 10 years in another study, Epidemiology of Diabetes Interventions and Complications, in which the glycated hemoglobin (HbA1c) values became similar for both groups, the benefits in terms of reduction of progression of retinopathy were still seen in the original tight control group.[19] Ten years after the end of the DCCT study, the benefit of early tight control persisted, and the risk of retinopathy progression was reduced by 53%. These prolonged beneficial effects of intensive glucose control have been ascribed to a phenomenon called "metabolic memory," and one of the possible mechanisms could be epigenetic histone posttranslational modification by acetylation or methylation. Such an epigenetic modification was explained by an association between HbA1c level and H3 lysine-9 acetylation in a recent study.[20]

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study recently revealed that tight glucose control in type 2 diabetic persons (HbA1c level of 6.4% in the intensive group vs. 7.5% in the conventional group) reduced progression of diabetic retinopathy (3 steps on the ETDRS scale) by 35% over a 4-year span.[21] This randomized controlled clinical trial was designed to examine the benefits of systemic therapy (reduction of HbA1c <6%, reduction of systolic blood pressure to <120 mmHg, and lipid control with fenofibrate plus simvastatin) in type 2 diabetic persons. The trial phase of blood glucose control in this study was discontinued after 3.7 years because of higher mortality in the tight glucose control group. Although tight control helps slow the progression of diabetic retinopathy, too tight control resulting in hypoglycemic episodes may be detrimental, with other serious cardiovascular consequences.

Hypertension. The UKPDS study of type 2 diabetic persons showed a significant benefit of controlling blood pressure (targeting a systolic blood pressure <150 vs. <180 mmHg with standard control) by angiotensin-converting enzyme inhibitors or β-adrenergic blockers.[17] Both drugs slowed the progression of diabetic retinopathy and reduction of vision loss. However, this benefit of

controlling blood pressure was not observed in the ACCORD Eye Study.[21] If the patients were normotensive at the onset, there was little benefit noted in reduction of retinopathy in decreasing systolic blood pressure to <120 mmHg. Another study, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, also did not show a beneficial effect of intensive blood pressure control on progression of diabetic retinopathy.[22]

Hyperlipidemia. Low-density lipoprotein and triglyceride concentrations are directly related to the incidence and severity of diabetic retinopathy, whereas the high-density lipoprotein concentration has an indirect relation.[23] The ETDRS reported that diabetic persons who responded poorly with laser treatment and had diffuse edema with hard exudates had higher levels of blood lipids.[24] The Fenofibrate Intervention and Event Lowering in Diabetes study showed less need for laser treatment in those who were treated with fenofibrate (200 mg/day).[25] The ACCORD Eye Study further confirmed these findings by showing that fenofibrate added to simvastatin therapy in type 2 diabetic persons slowed the progression of diabetic retinopathy at 4 years.[21] The beneficial effects of fenofibrate in diabetic retinopathy are probably due to its agonist action on the peroxisome proliferator-activated receptor alpha pathway.[26] Hyperglycemia in diabetes downregulates this pathway, with damaging effects on vascular cells. In an uncontrolled study, oral atorvastatin (lisinopril) therapy in patients with DME with dyslipidemia reduced the severity of hard exudates and fluorescein leakage. Thus, atorvastatin therapy was suggested as an adjuvant therapy in the management of DME,[27] but such a beneficial effect may not be apparent in those with a normal lipid profile.[28]

Genetic Factors. That only 50% of diabetic patients develop PDR in their lifetime suggests that diabetic retinopathy may have genetic factors associated. Familial clustering of severe diabetic retinopathy was described among first-degree relatives of subjects in the DCCT study.[29] A promoter polymorphism of the erythropoietin gene was significantly associated with PDR and end-stage renal disease in 3 European-American cohorts.[30] However, genome-wide association studies conducted in different type 1 or type 2 diabetic patients revealed borderline or weak associations of diabetic retinopathy in these Mexican-American, Chinese, and white populations.[31] However, no genetic factor association has been reported in patients with DME.

In Vitro and In Vivo Models for Diabetic Macular Edema Studies

In vitro systems for DME studies mostly use bovine and human retinal endothelial cells in culture with or without supporting cells, such as pericytes and astrocytes. Transendothelial electrical resistance that can be quantitated by an electrical cell substrate impedance-sensing system has been used as a measure of the tightness of the barrier in these differentiated cells with tight and adherens junctions.[32] The permeability in these cells also has been measured by fluorescein isothiocyanate (FITC)−dextran transport through this cell layer.

For in vivo studies, streptozotocin-induced diabetic mice and rats have been widely used as a model for early diabetic retinopathy. The BRB is altered in these animals as early as 1 week after induction of diabetes, and the change in permeability of retinal vessels is commonly measured by the Evans Blue dye test or FITC-dextran test after 4 weeks of diabetes. An equally reproducible new technique of measuring extravasated albumin by Western blot in these animals has been used to avoid the cumbersomeness of the dye injection techniques.[33] All of these techniques aim to measure the leakage of an exogenous marker due to alteration of the BRB. Insulin Akita mice, in which there is a defect in folding of the insulin molecule, develop increased retinal vascular permeability and retinal ganglion cell layer loss by 3 months and have been used for studying the effects of neuroprotective drugs in diabetes.[34] A marmoset model fed galactose for 2 years developed many features of diabetic retinopathy, including microaneurysms, mild retinal edema, and retinal vascular leakage.[35]

There has been a lack of animal models and techniques that can measure increased retinal thickening in vivo so that the effect of drugs can be tested in live animals. Although increased retinal vascular permeability has been described in animal models, these models do not actually develop intraretinal thickening because the eye has mechanisms to correct retinal fluid imbalance.[36] Techniques such as dye or tracer injection used involve killing the animals after the intended study. Fluorescein angiography has not been widely used in animal models to measure BRB alteration because early cataract formation and small curved globes in these animals prevent light rays from focusing into the retina.[37] High-resolution OCT was reported to measure increased retinal thickening in diabetic rats,[36] and magnetic resonance imaging in 4-month-old diabetic rats demonstrated a persistent and diffuse retinal edema in vivo.[38]

Pathophysiology of Diabetic Macular Edema

Although hyperglycemia is the strongest risk factor contributing to the pathogenesis of DME, as evidenced by large prospective clinical studies, the exact mechanism it acts through is unclear. The hyperglycemia-induced pathogenesis of diabetic retinopathy is related to 4 major biochemical pathways: (1) polyol pathway, (2) advanced glycation endproducts pathway, (3) protein kinase C (PKC) pathway, and (4) hexosamine pathway.[39] All of these pathways lead to increased oxidative stress, inflammation, and vascular dysfunction. Oxidative stress and inflammation result in upregulation of growth factors and cytokines, such as VEGF, angiopoietins, tumor necrosis factor (TNF), interleukins (ILs), and matrix metalloproteinases (MMPs), which contribute to breakdown of the BRB and development of DME.

Alteration of Blood−Retinal Barrier. The BRB maintains the tight regulation of the fluid electrolyte balance in the retina. The breakdown of this barrier results in fluid accumulation in the layers of the retina, as seen in DME.

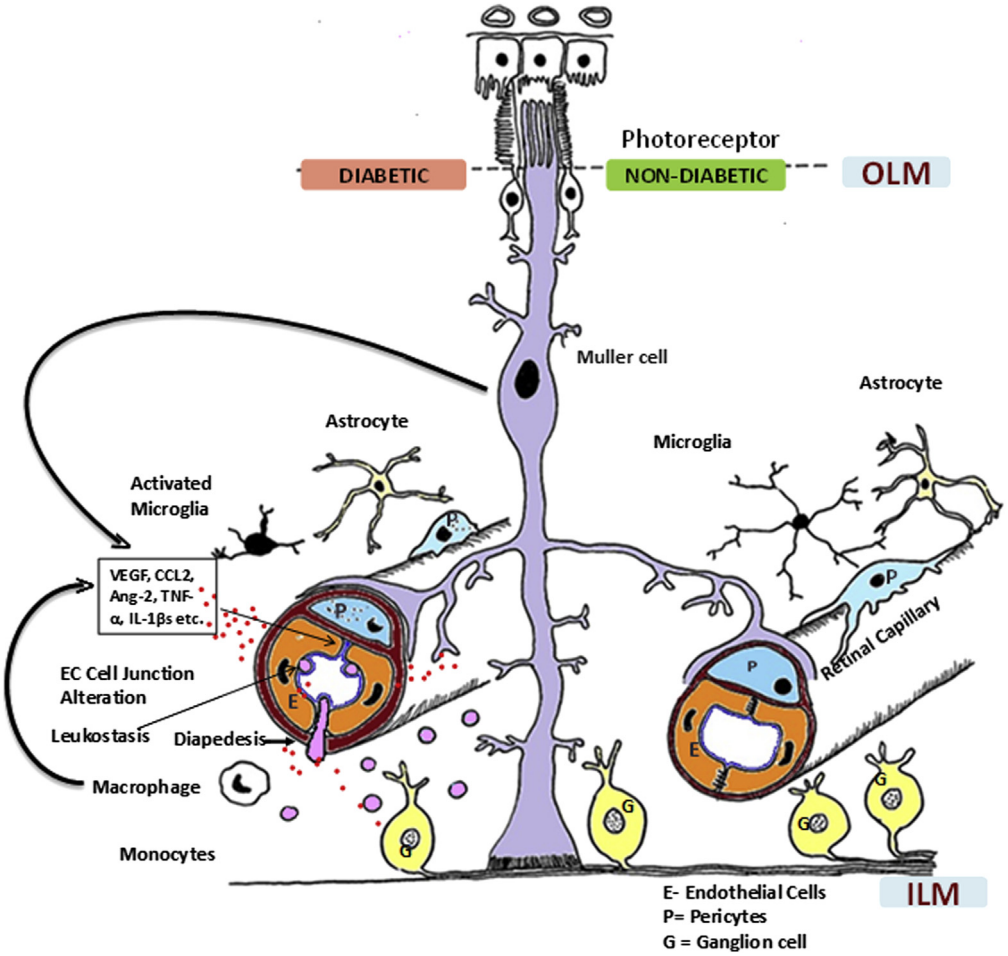

Figure 1. Neurovascular unit of the retina in nondiabetic and diabetic conditions. Normally, pericytes and endothelial cells constitute the blood–retinal barrier (BRB) (retinal capillary) that is covered intimately by multiple processes of the Müller cells (*right*). Astrocytes and microglia with long processes also surround the capillaries, maintaining the normal homeostasis for neuronal signaling and synaptic transmission. In diabetes, chronic inflammation sets in, contributing to the breakdown of the BRB (*left*). Müller cells and endothelial cells produce chemokines (including monocyte chemoattractant protein-1) that lead to increased leukostasis, diapedesis, and influx of monocytes into the retina and increased production of cytokines, including vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF)-α, interleukin (IL)-1β, matrix metalloproteinase, and angiopoietin (Ang)-2. These inflammatory mediators then result in the breakdown of endothelial cell–cell junctions. Microglia become activated, and there is increased apoptosis of ganglion cells and amacrine cells, which deranges synaptic degeneration. In retinal capillaries, pericyte dropout and thickening of the basement membrane also occur as a result of hyperglycemia, all contributing to increased leakage from vessels. Photoreceptors contribute to production of superoxide and inflammatory proteins in this process. CCL-2 = chemokine ligand 2; EC = endothelial cell; ILM = inner limiting membrane; OLM = outer limiting membrane.

The outer BRB consists of retinal pigment epithelium (RPE) cells between the fenestrated choriocapillaris and the outer retina, and the inner BRB consists of endothelial cells of retinal capillaries in the inner retina. The tightness of the inner BRB that prevents leakage of molecules from retinal capillaries depends on the integrity of the endothelial cell–cell junctions, a normal basement membrane, and pericytes sitting in the outer wall (Fig 1). Three important alterations of the BRB that occur in diabetes are breakdown of cell–cell junctions, pericyte loss, and thickening of the basement membrane (Fig 2).[18]

Endothelial Cells. The endothelial cells form a tight monolayer and are joined to each other by tight junctional complexes and adherens junctions.[40] In diabetes, breakdown of the cell–cell junction has occurred through a decrease in occludin and vascular endothelial-cadherin levels in the retinal microvessels in diabetic animals.[41,42] Intravitreal injection of VEGF in rats results in increased phosphorylation of occludin and zona occluding.[43] Apart from the breakdown of the cell–cell junction, capillary endothelial cells also undergo apoptosis, along with apoptosis of pericytes, resulting in the formation of acellular capillaries, which is an advanced lesion seen in diabetic retinopathy.[44] However, this lesion is not unique to diabetic retinopathy.

Pericytes. The original trypsin digestion technique has described pericytes as "mural cells,"[45] which are modified smooth muscle cells and have contractile properties.[46] Pericytes regulate the retinal capillary blood flow, and this function is lost during pericyte dropout that occurs in diabetic retinopathy. Pericyte loss is the classic histologic

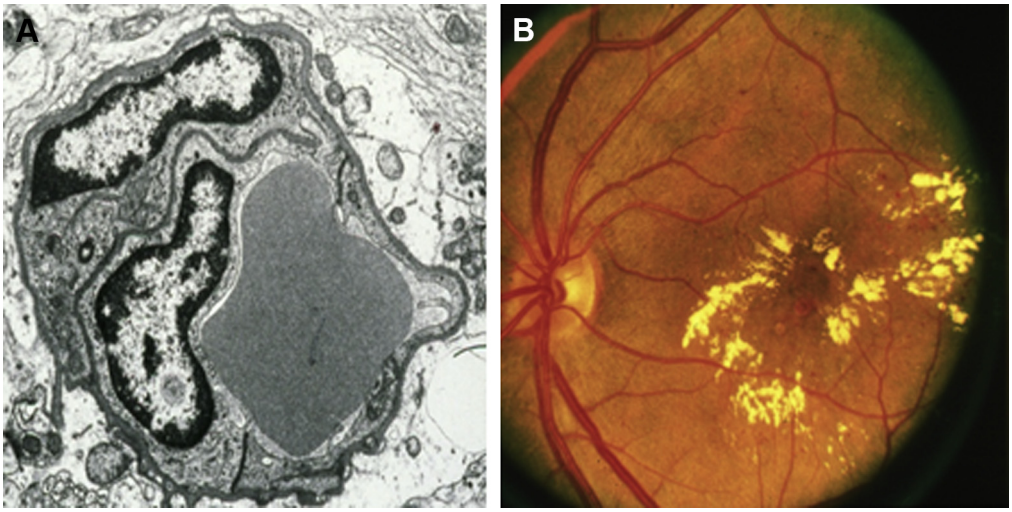

Figure 2. Blood–retinal barrier alteration in diabetes. **A,** Electron microscopic view of a monkey retinal capillary showing endothelial cells joined by tight junctions and surrounded by pericytes and a thin basement membrane between cells. **B,** Fundus photograph of a diabetic patient showing microaneurysms, retinal hemorrhages, and hard exudates in the macula. There is also exudation of plasma in the macula, leading to clinically significant macular edema.

lesion in early diabetic retinopathy in the human retina.[45] It is possible that alterations in the platelet-derived growth factor (PDGF)-B in early diabetes affect pericyte viability and may lead to pericyte loss.[47] Normally, PDGF-B promotes proliferation and migration of pericytes. Mice deficient in PDGF-B show pericyte loss and microaneurysm formation, as seen in diabetic persons.[48] Pericytes in contact with endothelial cells release and activate the transforming growth factor-β that is responsible for the inhibition of endothelial cells.[49] Pericyte loss as seen in diabetic retinopathy results in focal endothelial cell proliferation and probably contributes to the formation of microaneurysms in the weakened wall of retinal capillaries.

Basement Membrane. The basement membrane surrounds the endothelial cells on the abluminal side and splits to enclose pericytes completely. Apart from providing structural support or rigidity, basement membranes also act as filtration barriers and regulate cell proliferation and differentiation. Increased thickening of the capillary basement membrane is a well-described lesion of diabetic retinopathy. However, it is not clear how the thickening of the basement membrane would allow more diffusion of molecules and "leakage." An alteration of the molecular structure of the basement membrane or the distribution of negatively charged heparin sulfate proteoglycan molecules probably contributes to the increased porosity of this barrier in diabetes.[50]

The normal homeostasis in the retinal capillary is maintained by the balance of intravascular hydrostatic and extravascular oncotic forces, as explained by Starling's law. Conditions that increase hydrostatic forces (hypertension, congestive heart failure, renal failure) or conditions that decrease oncotic pressure (hypoalbuminemia) can further damage the already altered BRB in diabetes and compromise the barrier function.

Alterations in the Neurovascular Unit. Although diabetic retinopathy is considered primarily a vascular phenomenon with alteration of the BRB, recent work suggests that the pathology lies in alteration of the neurovascular unit.[51] The intimate dynamic interaction of retinal neurons and glia that surround the retinal capillaries controls fluid transport and metabolite transfer in the neural tissue. A similar concept about the blood–brain barrier explains the homeostasis imbalance in neurodegenerative disorders such as stroke and Alzheimer's disease.[52] The neurovascular unit consists of Müller cells, astrocytes, ganglion cells, amacrine cells, retinal vascular endothelial cells, and pericytes. Müller cells send out an extensive network of villi or processes that surround the vessels intimately. The level of glial fibrillary acidic protein has been described to be significantly increased in Müller cells in diabetic human donor retinas, thus providing evidence for selective biochemical changes of Müller glial cells in diabetes.[53] Müller cells release factors that induce the formation of tight junctions in retinal vessels. Abnormalities in Müller cells in diabetes probably affect this barrier property in the retinal vessels. The neuronal dysfunction in diabetic retinopathy is probably due to many biochemical changes, including impaired glutamate metabolism, loss of synapses and dendrites, and apoptosis of ganglion cells. Visual functional changes, such as loss of color, loss of contrast sensitivity, abnormalities in electroretinogram (oscillatory potential), and visual field defects seen in early diabetic retinopathy even before the vascular lesions appear, might be explained by these neuronal changes.[54] Two basic hypotheses have been proposed to explain the neuronal loss in diabetes.[55] First, the BRB alteration leads to edema, change in the extracellular fluid composition, and subsequent neuronal cell loss. Second, hyperglycemia can directly cause an increase in apoptosis, which then results in breakdown of the BRB. It is uncertain which mechanism leads to the other.

Photoreceptors. Oxidative stress has been shown to play an important role in the pathogenesis of diabetic retinopathy

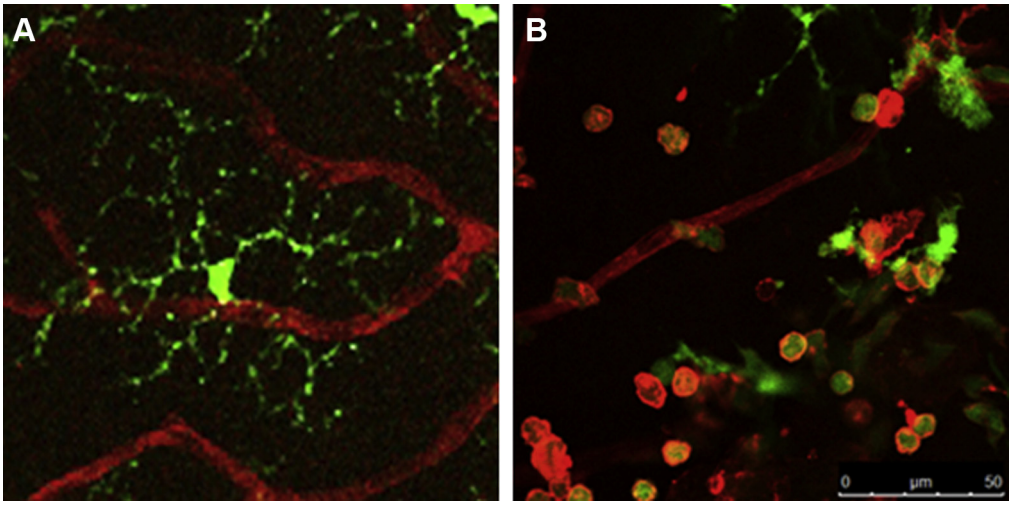

Figure 3. Increased monocyte trafficking into the retina of diabetic mice. Confocal images of retinal whole mounts from CxCr1-green fluorescent protein (GFP) mice counterstained with isolectin to label the retinal vessels and activated monocytes red. **A,** Nondiabetic animals show stained red vessels and green inactive microglia uniformly distributed with long, ramifying processes. **B,** Diabetic animals show several round monocytes (colocalized with GFP protein and lectin) GFP in the extravascular space. Monocytes become activated, with round amoeboid morphology with less branching of processes.

because it regulates the expression of proinflammatory proteins. Photoreceptors are the most prevalent cells in the retina and are highly metabolically active. Diabetic mice lacking photoreceptors have lower vascular density, indicating that photoreceptors influence diabetes-induced retinal capillary degeneration.[56] In a series of 55 diabetic patients with retinitis pigmentosa, none of them had any retinopathy despite the long duration of diabetes.[57] Such a clinical observation points out that retinitis pigmentosa, by an unknown mechanism, protects against the development of diabetic retinopathy. A recent study unveiled this mechanism by showing that deletion of photoreceptors inhibits a diabetes-induced increase in superoxide and inflammatory proteins in the remaining retina.[58]

Retinal Pigment Epithelium Cells. The diabetes-induced outer BRB alteration has been described in diabetic humans and animals.[59] An alteration in the c-wave of electroretinography has been reported in diabetic rats. The current FA technique cannot detect outer BRB-mediated leakage because the fluorescent material leaking from the retinal vessels may obscure the leakage from the outer BRB. A new microscopic imaging assay using FITC-dextran has been able to directly visualize macromolecules leaked through the outer BRB in diabetic rodents.[60]

Inflammation. Many features of inflammation, such as tissue edema, increased vascular permeability and blood flow, upregulation of cytokines, complement activation, microglial activation, and macrophage infiltration, have been described in both human and animal models of diabetic retinopathy.[61] Increased retinal leukostasis is an early event that was significantly increased in an animal model of diabetic retinopathy.[62] Instead of an acute vasculitis, this inflammation has been described as a sustained, chronic inflammation. This increased leukostasis results in upregulation of retinal intercellular adhesion molecule (ICAM)-1 and increased vascular permeability. Administration of antibodies to CD-18 or ICAM-1, or genetic knockout of these molecules, inhibits retinal leukostasis and BRB breakdown.[63] Elevated numbers of neutrophils have been described in retinal and choroidal vessels of human diabetic subjects and diabetic monkeys.[64,65] Our laboratory reported increased monocyte/macrophages trafficking into the extravascular retinal tissues in diabetic mice (Fig 3).[66] Quantification by flow cytometry demonstrated a 2-fold increase of $CX3CR1^{+}$/$CD11b^{+}$ (monocyte/macrophage and microglia) cells in retinas of wild-type diabetic animals in comparison with control nondiabetic animals.

The increased monocyte trafficking into the retina in early diabetes probably is regulated by the levels of monocyte chemoattractant protein (MCP)-1 also known as "chemokine ligand 2." Gene expression array results indicate that MCP-1 is remarkably upregulated (~16-fold) compared with other angiogenic factors, such as VEGF, angiopoietin (Ang)-2, and TNF-α.[66] Similar increases of MCP-1 levels have been reported in the vitreous of patients with DME.[67] A significant reduction in retinal vascular leakage and monocyte infiltration after induction of diabetes was shown using MCP-1 knockout mice.[66] Activated monocytes differentiate into macrophages that secrete cytokines and growth factors, including VEGF, Ang-2, TNF-α, ILs, MMP-2, and MMP-9, all of which have been shown to alter the BRB.

Management of Diabetic Macular Edema

Control of Systemic Factors. All of the major clinical trials (DCCT, UKPDS, and ACCORD) have shown the benefits of tight blood glucose control in preventing and slowing the progression of diabetic retinopathy. However, because of increased mortality and cardiovascular risks in the tight control group in the ACCORD Study, "too tight control" with reduction of HbA1c level to ≤6% is not recommended in these patients.[68] In regard to blood pressure control, the

UKPDS found the benefits of controlling blood pressure in reducing vision loss, but the ACCORD Eye Study did not show any benefit of blood pressure control in the progression of retinopathy or cardiovascular events. The ACCORD Study targeted a systolic blood pressure level <140 mmHg in the standard treatment arm and <120 mmHg in the intensive treatment arm, whereas in the UKPDS Study, the mean systolic pressure of patients was >140 mmHg. Of note, the addition of fenofibrate (160 mg/day) to simvastatin in the ACCORD Study significantly reduced the progression of diabetic retinopathy, but there was no beneficial effect on the cardiovascular outcome. In view of all these data, the question remains: Is there any benefit of systemic factor control on the progression of DME? The ACCORD Study concluded that there was no benefit of control of blood glucose, blood pressure, or lipid on DME or visual acuity.[69] The study had only approximately 8% patients with DME, and it was mostly mild. Neither the DCCT Study nor the UKPDS Study examined the effect of systemic factor control in patients with DME.

Although we have no definitive evidence of the role of systemic factor control in DME itself, it is still recommended that the ophthalmologist should be in close consultation with the internist regarding tight control of blood glucose, blood pressure, and blood lipids. One should target an HbA1c level of 7% and systolic blood pressure of <140 mmHg. The addition of fenofibrates in patients with DME merits further consideration in a larger trial. It is also important to inquire whether patients with DME are taking any glitazones because peripheral edema and fluid retention have been reported in patients using glitazones. This fluid retention associated with glitazone use may lead to worsening of DME. However, this visual loss is reversible because discontinuation of glitazones improves resolution of DME.[70]

Laser in Diabetic Macular Edema. Since the publication of the results from the ETDRS in 1985, focal/grid laser using small, light-intensity laser burns (50−100 μm in diameter) to microaneurysms or diffuse area of thickening in a grid pattern has been the gold standard treatment for clinically significant macular edema (CSME). The procedure resulted in a 50% reduction in severe vision loss.[7] Proposed mechanisms behind this therapy include increased intraocular oxygen tension; a decreased production of vasoactive cytokines, primarily VEGF; and increased phagocytosis by RPE cells and glial cells. A recent study showed that RPE cells at the margins of laser burns modulate various cytokines via photoreceptors.[71] With the approval of 2 anti-VEGF agents by the U.S. Food and Drug Administration (FDA) in recent years, the indication of focal/grid laser is now limited to patients with noncenter-involving DME. A recent DRCR study examined whether prompt laser treatment strategy along with anti-VEGF therapy was better in achieving superior visual outcome than anti-VEGF therapy alone.[72] The rationale was that the prompt reduction of edema with an anti-VEGF agent would provide functional benefits from laser treatment, and the effect might be longer lasting that that of anti-VEGF agents alone, thus reducing number of anti-VEGF injections.

However, recent 3-year results of this study showed that focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better, and possibly worse for vision outcomes, than deferring laser treatment for ≥24 weeks in eyes with center-involving DME, although fewer injections are likely to be given when prompt laser treatment is combined with ranibizumab.[73] The study continues with this protocol for 5 years. The DRCR points out that other strategies based on individual decisions may be beneficial because the study results are based on a specific group.

Some of the laser-treated patients experience vision loss because of thermal complications such as subretinal fibrosis or enlargement of laser scars. Selective application of subthermal intensity to RPE cells, while sparing the neurosensory retina, reduces these iatrogenic side effects. Longer wavelength 810-nm diode lasers reduce burn intensity and avoid absorption to macular chromophores. Also, micropulsar techniques increase the delay between pulses and reduce the size of retinal lesions by eliminating heat diffusion and lesion growth after treatment. A pilot study of the subthreshold diode micropulsar laser showed that subthreshold diode micropulsar laser photocoagulation was comparable to previous argon laser treatments in efficacy and did not have any adverse effects or iatrogenic retinal damage.[74]

Vitrectomy in Diabetic Macular Edema. In patients with significant vitreomacular traction in DME, vitrectomy with peeling of the inner limiting membrane can be combined with or without indocyanine green dyes. In a recent DRCR study of patients with DME and vitreomacular traction, most patients' eyes showed reduction of retinal thickening, but improvement of visual acuity by 10 letters occurred in only 38% of patients.[75]

Vitreolysis Agents. Microplasmin (ThromboGenics NV, Iselin, NJ) is a proteolytic enzyme that can induce posterior vitreous detachment through the liquefaction of the vitreous and weaken adhesions at the vitreoretinal interface. A multicenter phase II study to compare multiple doses of intravitreal microplasmin versus sham injection for the treatment of patients with DME (MIVI-II) was completed, and the results showed that microplasmin was able to induce release of vitreomacular adhesion in some patients with DME only.[76]

Pharmacotherapies in Diabetic Macular Edema

Although several biochemical mechanisms for the pathogenesis of diabetic retinopathy have been described, and the effects of drugs to block these pathways have been effective in animal models, none of these drugs have been approved by the FDA on the basis of clinical trial results. Both aldose reductase inhibitors, Sorbinil (Pfizer Inc., New York, NY) and Tolrestat (Wyeth-Ayerst, Princeton, NJ), did not show any benefit in large controlled clinical trials.[77] A large trial of aminoguanidine (inhibitors of glycation pathway) was conducted in patients with diabetic nephropathy, but the results have not been published. The failure of these trials does not rule out the role of these pathways in the pathogenesis of diabetic retinopathy. It is possible that the drugs did not reach the retinas in effective concentrations, or the biochemical pathway targeted might not be as important in human retinopathy as it was in animal models.

Protein Kinase C Inhibitor. Hyperglycemia activates the enzyme PKC by inducing de novo synthesis of

diacylglycerol of diabetic microvascular complications in the eyes, nerves, and kidneys. Increased PKC β-isoform activity induces retinal vascular permeability and neovascularization in animal models. The Protein Kinase Cβ Inhibitor Diabetic Macular Edema Study, a multicenter, randomized, double-masked, parallel, placebo-controlled clinical trial evaluated the effect of 3 doses of orally administered ruboxistaurin mesylate (Eli Lilly, Indianapolis, IN), a PKCβ-isozyme–selective inhibitor on the progression of DME and the need for laser photocoagulation.[78] The delay in progression to the primary outcome (progression to sight-threatening DME or application of focal/grid photocoagulation for DME) was not statistically significant. The drug also did not prevent progression to PDR.

Anti–Vascular Endothelial Growth Factor Therapy. Vascular endothelial growth factor is a potent vasopermeability factor. That VEGF is essential in causing vascular leakage was shown in animals in which implantation of pellets that release VEGF in the vitreous or intravitreal injection of VEGF causes breakdown of the BRB.[79,80] Vascular endothelial growth factor 164 has been shown to be a proinflammatory cytokine. In streptozotocin-induced diabetic animals, VEGF mRNA increases in the retina by 3.2-fold in 1 week and is accompanied by increased expression of ICAM-1 and retinal vascular leakage, and injection of a VEGF receptor fusion protein can prevent all these changes. The VEGF levels are significantly elevated in vitreous of patients with DME when compared with nondiabetic eye conditions.[67] There are several anti-VEGF drugs that target the VEGF molecule. Direct inhibitors of the VEGF molecule include the anti-VEGF aptamer pegaptanib (Macugen; OSI Pharmaceuticals, Long Island, NY), the monoclonal antibody fragment ranibizumab (Lucentis; Genentech, South San Francisco, CA), and the full-length antibody bevacizumab (Avastin; Genentech). Other anti-VEGF molecules include soluble VEGF receptor analogs, VEGF-Trap (Regeneron, Tarrytown, NY), and small interfering RNAs bevasiranib (Opko Health, Miami, FL) and rapamycin (Sirolimus, MacuSight, Union City, CA). Anti-VEGF drugs are delivered into the eye as intravitreal injections under topical anesthesia. It is important to note that the indication for use of anti-VEGF agents in DME is center-involving DME, whereas focal/grid laser is reserved for those with noncenter-involving DME.

Pegaptanib (Macugen; Eyetech Pharmaceuticals, Inc., and Pfizer Inc.) is a ribonucleic acid aptamer that selectively targets the VEGF 165 isoform. In a phase II/III, randomized, double-masked, 2-year trial in patients with DME, intravitreal pegaptanib sodium 0.3 mg was well tolerated and demonstrated superior efficacy over the sham.[81]

Ranibizumab is a monoclonal antibody that blocks all isoforms of VEGF-A and is "affinity-enhanced" to provide stronger affinity to bind to VEGF-A. This drug has been approved by the FDA for use in patients with DME. Two large studies showed the benefits of intravitreal ranibizumab injections in patients with DME. In the RIDE/RISE study, in which patients were randomized to 2 different doses of intravitreal ranibizumab (0.3 and 0.5 mg) or sham injection, 37% to 40% of patients in the ranibizumab arm showed a >15-letter improvement compared with 19% in the sham group after 3 years.[82] An interesting observation in this study was that progression of diabetic retinopathy was slowed and the severity of retinopathy improved in the ranibizumab-treated patients. The clinical significance of retinopathy improvement is not clear, and it is yet to be determined how long this beneficial effect of anti-VEGF therapy lasts after its cessation. The DRCR clinical trial Protocol I showed similar results and concluded that intravitreal ranibizumab with prompt or deferred laser was more effective in vision improvement through 3 years compared with prompt laser alone for center-involving DME.[73]

Bevacizumab (Avastin; Genentech) is a full-length humanized monoclonal antibody, approximately 3 times the size of the ranibizumab molecule, that also blocks all isoforms of VEGF-A. It has been used as an "off-label" drug for the treatment of DME. Because of its lower cost compared with other anti-VEGF drugs, it has become an affordable, popular drug in the treatment of retinal vascular diseases and age-related macular degeneration (ARMD). The Bevacizumab or Laser Therapy study compared intravitreal injections of bevacizumab (1.25 mg, 6 weekly) with focal/grid laser treatment for 2 years and showed a visual improvement of 8.6 letters with bevacizumab injections, whereas the laser-treated patients experienced visual loss of 0.5 letters.[83] The median number of treatments was 13 for bevacizumab-treated patients and 4 for laser-treated patients.

Aflibercept (Eylea; Regeneron) is a soluble protein that contains extracellular VEGF receptor 1 and 2 sequences fused to the Fc domain of a human immunoglobulin-G1 molecule and blocks all isoforms of VEGF and the placental growth factor. It has approximately 100-fold greater binding affinity to VEGF-A than bevacizumab or ranibizumab. The prolonged half-life of this drug offers the advantage of injections every other month rather than monthly injections. In the phase III VIVID-DME and VISTA-DME trials, patients receiving aflibercept (2 mg monthly or every other month) had a mean vision change from baseline of 12.5 and 11.1 letters, respectively, after 2 years compared with a mean change from baseline in best-corrected visual acuity of 0.2 letters in patients receiving laser therapy.[84] The DRCR Protocol T, in a head-to-head comparison of the efficacy and safety of the 3 anti-VEGF drugs, ranibizumab, bevacizumab, and aflibercept, in the treatment of patients with DME, showed that in eyes with better visual acuity (≥20/40), there was no difference among these 3 drugs, but at baseline visual acuity of 20/50 or worse, aflibercept was more effective at improving vision.[85]

Although anti-VEGF injections have become the first-line gold standard treatment in center-involving DME, there are many patients who respond poorly to anti-VEGF therapies, and the resolution of fluid is transient and not complete.[86] In fact, in the DRCR Protocol I study, 50% of patients had persistent macular thickening even after 1 year of monthly injections. In these patients, the VEGF-independent pathways may be more important and need to be targeted for treatment of DME.

Anti-Inflammatory Therapy

Steroids in Diabetic Macular Edema. Inflammation plays an important role in the pathogenesis of diabetic

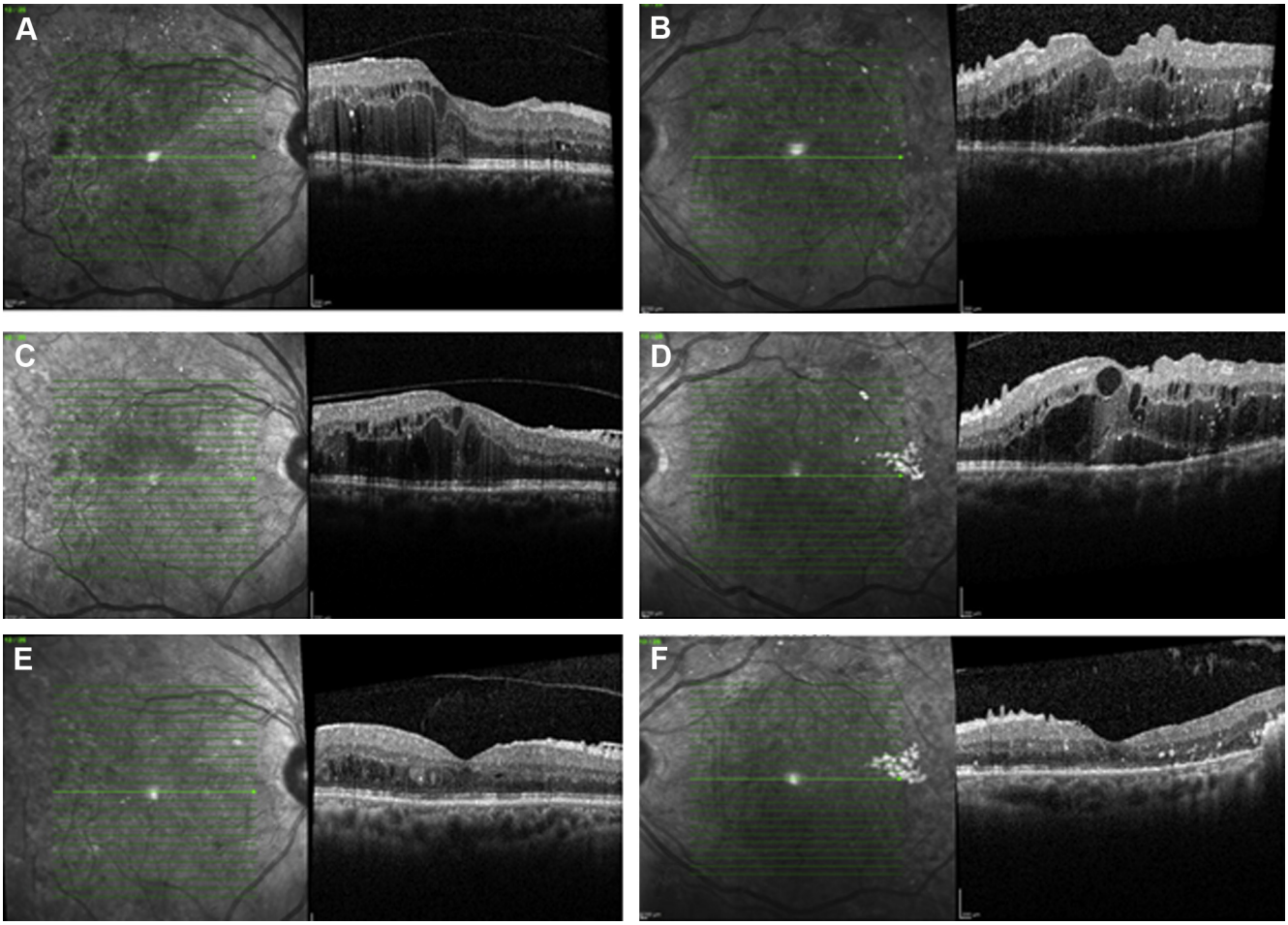

Figure 4. Optical coherence tomography (OCT) images of a patient with diabetic macular edema (DME) who responds poorly to anti–vascular endothelial growth factor (VEGF) drugs and shows good response to steroids. Right eye **(A, C, E)**. Left eye **(B, D, F)**. **A, B,** Fundus and OCT images of a 62-year-old diabetic patient with type 1 diabetes and hypertension had visual acuity of 20/50 and central retinal thickness (CRT) of 404 μm in the right eye **(A)** and visual acuity of 20/200 and CRT of 638 μm in the left eye **(B)**. **C, D,** The patient was treated with 6 monthly intravitreal injections of bevacizumab in both eyes. After 6 injections, there was little improvement, and his visual acuity and CRT were 20/70 and 634 μm in the right eye and 20/200 and 950 μm in the left eye. **E, F,** The patient was then treated with intravitreal triamcinolone injection in both eyes. The response was dramatic, and his visual acuity and CRT improved to 20/40 and 326 μm in the right eye and 20/100 and 256 μm in the left eye.

retinopathy, and several cytokines and chemokines (VEGF, TNF-α, MCP-1, IL-β) are elevated in DME.[87] Steroid injections can inhibit inflammatory cytokine production, leukostasis, and phosphorylation of cell-junction proteins. Steroids are effective in DME, as shown in the DRCR trial Protocol I. In this trial, the effect of intravitreal triamcinolone and laser in terms of visual improvement and reduction of central retinal thickness (CRT) was similar to that of ranibizumab and laser up to 24 weeks, and then the effect of triamcinolone gradually diminished because of increased rates of cataract formation.[72] In a subgroup analysis of pseudophakic patients, the triamcinolone plus laser group was found to be superior to the laser alone treatment and equivalent to the ranibizumab group.[72]

Similar benefits of steroids in DME have been described in 2 randomized clinical trials. In the Macular Edema: Assessment of Implantable Dexamethasone in Diabetes (MEAD) Study, dexamethasone intravitreal implant (Ozurdex; Allergan, Irvine, CA) caused visual improvement of >15 letters in 22% of patients (0.7 mg) and 18% (0.35 mg) compared with 12% in the sham group.[88] Rates of cataract formation were high in up to 68% of treated patients, and increases in intraocular pressure (IOP) could be controlled with medication or no therapy. The mean number of treatments was approximately 4 over 3 years. The dexamethasone implant has been recently approved by the FDA for DME treatment. In another randomized, multicenter, 3-year-long trial, the Fluocinolone Acetonide for Macular Edema (FAME) study, intravitreal inserts of fluocinolone acetonide (releasing 0.2 and 0.5 μg/day) provided substantial benefit of visual improvement in patients with DME.[89] However, almost all patients receiving fluocinolone acetonide had cataract formation. The dexamethasone implant had a lower incidence of increases in IOP compared with the fluocinolone implant, because only 0.3% to 0.6% of treated patients required incisional glaucoma surgery in the dexamethasone implant study, and the incidence of incisional glaucoma surgery was

4.8% (low dose) and 8.1% (high dose) in the fluocinolone implant study. Dexamethasone is less lipophilic and accumulates in the trabecular meshwork and lens less than fluocinolone or triamcinolone, which explains the lower incidence of side effects with dexamethasone.[90] The FDA has approved the fluocinolone implant for patients with DME who have been treated with a course of corticosteroids and did not show a significant IOP increase.

Because of side effects, the use of intravitreal steroids in clinical practice in patients with DME is currently reserved as the second line of therapy in those who poorly respond to intravitreal anti-VEGF therapy (after 4–6 monthly injections) (Fig 4). The combination of anti-VEGF agents and steroids may be more effective in certain patients with DME whose disease is difficult to control with anti-VEGF agents alone.

Nonsteroidal Anti-Inflammatory Drugs. Because of known side effects of steroids, nonsteroidal anti-inflammatory drugs seem to be an attractive strategy to treat DME. These drugs lack the steroid nucleus and are inhibitors of cyclooxygenase enzymes and prostaglandins. They are used for treatment of pseudophakic cystoid macular edema and during and after cataract surgery for control of inflammation. In diabetic rats, high-dose aspirin can suppress the breakdown of the BRB and reduce expression of ICAM-1 and leukostasis in retina.[91] However, this dose of aspirin is equivalent to the dose of 50 mg/kg/day in an average human being and can result in severe side effects in humans. There is much clinical evidence of the role of aspirin in slowing the progression of retinopathy. The first clue of the effects of aspirin in diabetic retinopathy came from the clinical observation that diabetic persons who are receiving high doses of salicylates have a lower incidence of diabetic retinopathy.[92] The Dipyridamole Aspirin Microangiopathy of Diabetes study further showed the benefit of aspirin in high doses (990 mg/day) in slowing the development of retinal microaneurysms.[93] However, the ETDRS Study found no effect of using aspirin (650 mg/day) in the prevention of vision loss in DME or severe non-PDR, nor did it show increase the incidence of vitreous hemorrhage.[94] In diabetic rats, topical nepafenac eye drops were shown to inhibit acellular capillaries and diabetes-induced alterations in retinal vascular metabolism, with no effects on ganglion cell survival.[95] However, a recently completed placebo-controlled phase II study (DRCR Protocol R) using nepafenac 0.1% eye drops for 1 year showed no meaningful difference in visual outcome or CRT in patients with noncenter-involving DME.[96]

Future Strategies: Vascular Endothelial Growth Factor and Beyond Vascular Endothelial Growth Factor

Anti–Vascular Endothelial Growth Factor Therapy

Higher Dose of Anti–Vascular Endothelial Growth Factor. Because there is a wide range of VEGF level in the vitreous in patients with DME, it is possible that poor responders with anti-VEGF therapy may need higher doses of anti-VEGF drugs because of higher levels of VEGF (Table 1, Fig 5). With this rationale, a new study, Ranibizumab for Edema of the mAcula in Diabetes (READ-3)–Protocol 3, has examined the efficacy of ranibizumab at 2 different doses (0.5 and 2.0 mg) in patients with DME. However, 2-year results from this study showed that the 0.5-mg dose was associated with a greater gain in vision compared with the 2.0-mg dose.[97] The higher dose (2 mg) of ranibizumab did not have an additional benefit over 0.5 mg ranibizumab. In the RIDE/RISE trials, the efficacy of ranibizumab was equivalent between 0.3 and 0.5 mg doses.[82] Because the use of a 0.3-mg dose has a lesser chance of potential risks related to systemic VEGF suppression, the FDA has approved the dose of 0.3 mg ranibizumab in patients with DME.

Long-Acting Anti–Vascular Endothelial Growth Factor Delivery. Monthly intravitreal injections are a treatment burden because many office visits are involved. Different long-acting anti-VEGF delivery systems are being investigated using bioerodable implants and microspheres, and encapsulated cells. A phase I clinical trial using a refillable, nonbiodegradable, long-term drug-delivery implant of ranibizumab has been completed on 20 patients with wet macular degeneration. This implant, placed under the conjunctiva in the pars plana, involves a 3.2-mm surgical incision without sutures and is refilled in as-needed intervals in a minimally invasive office procedure. Results showed a constant, maintained improvement of visual acuity of 10 letters throughout 1 year.[98]

Vascular Endothelial Growth Factor Designed Ankyrin Repeat Protein. Designed ankyrin repeat proteins (DARPins) are genetically engineered antibody mimetic proteins that show highly specific and high-affinity target protein binding. Newly developed anti-VEGF-A DARPins (both intravitreal and topical) based on the DARPin technology exhibit single-digit picomolar potency and, compared with currently approved anti-VEGF compounds, display a significantly increased potency in animal models of angiogenesis and vascular leakage. The longer half-life of DARPins allows prolonged VEGF suppression and probably needs less frequent injections.[99] A single intraocular injection of 0.4 mg MP0112 in patients with DME resulted in levels greater than the half-maximal inhibitory concentration and neutralization of VEGF in the aqueous humor for 8 to 12 weeks. A double-masked phase II study of the DARPin (abicipar pegol) for wet ARMD has shown that the drug provides equal or potentially higher vision gains compared with ranibizumab, with fewer injections. A randomized phase II trial (Allergan) of abicipar pegol in patients with DME is in progress.

Inhibitor of Multiple Growth Factors

Sirolimus. Sirolimus, also known as "rapamycin," is an immunosuppressive and antiproliferative agent that inhibits the mammalian target of rapamycin, which regulates multiple intracellular signaling pathways. It downregulates hypoxia-inducible factor 1α and inhibits the expression and signaling of VEGF, and thus retinal vascular hyperpermeability. It also

Table 1. Novel Pharmacotherapies for Diabetic Macular Edema Based on Mechanisms of Action

Drug	Target/Mechanism	Route of Administration	Clinical Development
Anti-VEGF			
Pegaptanib	VEGF 165	IVT	Phase III
Bevacizumab	VEGF-A all isoforms	IVT	Phase III
Ranibizumab	VEGF-A all isoforms	IVT	Phase III; FDA approved
Aflibercept	VEGF-A, VEGF-B, placental growth factor	IVT	Phase III; FDA approved
VEGF DARPin	VEGF	IVT	Phase II
Inhibitor of multiple growth factors			
Sirolimus (MacuSight, Union City, CA)	mTOR (VEGF, HIF-α)	SC, IVT	Phase II
PF-655 (Quark Pharmaceuticals, Fremont, CA)	*RTP801* gene (small interfering RNA)	IVT	Phase II (DEGAS and MATISSE)
iCo-007 (iCo Therapeutics, Vancouver, BC)	cRaf kinase mRNA Blocks VEGF, IGF-1, HGF	IVT	Phase II (iDEAL)
Src kinase inhibitors	VEGF, PDGF, bFGF	Topical	Preclinical
Squalamine	VEGF, PDGF, bFGF	Topical	Phase II IIT in DME (phase II wet ARMD)
Anti-inflammatory			
I. Steroids	Inhibits cytokines, inhibits leukostasis, enhances TJ		
Triamcinolone	(above as steroid)	IVT	
Dexamethasone implant	(above as steroid)	IVT Implant	Phase III; FDA approved
Dexamethasone-cyclodextrin	(nano drug delivery)	Topical	
Fluocinolone acetonide	(above as steroid)	IVT implant	Phase III; FDA approved
Betamethasone microspheres	(above as steroid)	Subtenon	Phase II/III
Loteprednol	(above as steroid)	Topical	Phase II
Danazol	Improves TJ	Oral	Phase II
II. NSAIDs:			
Aspirin	COX-1 and 2	Oral	ETDRS, DAMAD
Nepafenac	COX-1 and 2	Topical	Phase III
Bromfenac	COX-1 and 2	Topical	Phase III
III. Chemokine and cytokine inhibitors			
Infliximab	TNF-α	IVT	Phase II
Ang-2 inhibitor (AKB9778)	VETP	SC	Phase III
LFA-1 (SAR 1118; SARcode Bioscience, Brisbane, CA)	LFA-1	Topical	Phase II
Chemokine inhibitor	CCR2/CCR5 (receptors)	Oral	Phase II
Darapladib (GlaxoSmithKline, Middlesex, UK)	LPA-2 (lipoxygenase)	Oral	Phase II
Minocycline	Microglia, MMP	Oral	Phase II
KK inhibitors	KK system	Oral, IVT	Phase III
MMP inhibitors	MMP (MMP-2 and -9)	Systemic	Preclinical
IL inhibitors	IL-6	IVT	Preclinical
IV. Anti-integrin agents			
VAP-1 inhibitor	VAP-1	Oral	Preclinical
aV integrin inhibitor (ALG-1001; Allegro Ophthalmics, LLC, San Juan Capistrano, CA)	Integrin	IVT	Phase II
Hormone modulators:			
Exenatide	GL1 receptor agonist	SC	
Lanreotide	GH, TSH, insulin, glucagon	SC	
Acetylcholine receptor blocker:			
Mecamylamine (CoMentis, Inc., South San Francisco, CA)	Nicotinic acetylcholine receptors	Topical	Phase I/II
IGF-1 receptor blocker			
Teprotumumab (Genmab, Princeton, NJ)	IGF-1 receptor	IV	Phase I
Neuroprotective/antiapoptotic agent			
Erythropoietin	Improves hypoxia	IM, IVT	

The clinical development column describes whether the drug is in a preclinical or clinical trial (phases).
Ang = angiopoietin; ARMD = age-related macular degeneration; bFGF = basic fibroblast growth factor; CCR = chemokine receptor; COX = cyclooxygenase; DAMAD = Dipyridamole Aspirin Microangiopathy of Diabetes; DARPin = designed ankyrin repeat proteins; DEGAS = Dose-ranging evaluation of intravitreal siRNA PF-04523655 for diabetic macular edema; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; FDA = Food and Drug Administration; GH = growth hormone; HGF = hepatocyte growth factor; HIF-α = hypoxia inducible factor alpha; IGF-1 = insulin-like growth factor-1; IIT = investigator initiated trial; IL = interleukin; IV = intravenous; IVT = intravitreal; KK = kallikrein-kinin; LFA-1 = lymphocyte function associated antigen-1; MMP = matrix metalloproteinase; mTOR = mammalian target of rapamycin; NSAID = nonsteroidal anti-inflammatory drug; PDGF = platelet-derived growth factor; SC = subcutaneous; TJ = tight junctions; TNF = tumor necrosis factor; TSH = thyroid-stimulating hormone; VAP-1 = vascular adhesion protein-1; VEGF = vascular endothelial growth factor; VETP = vascular endothelial protein tyrosine phosphatase.

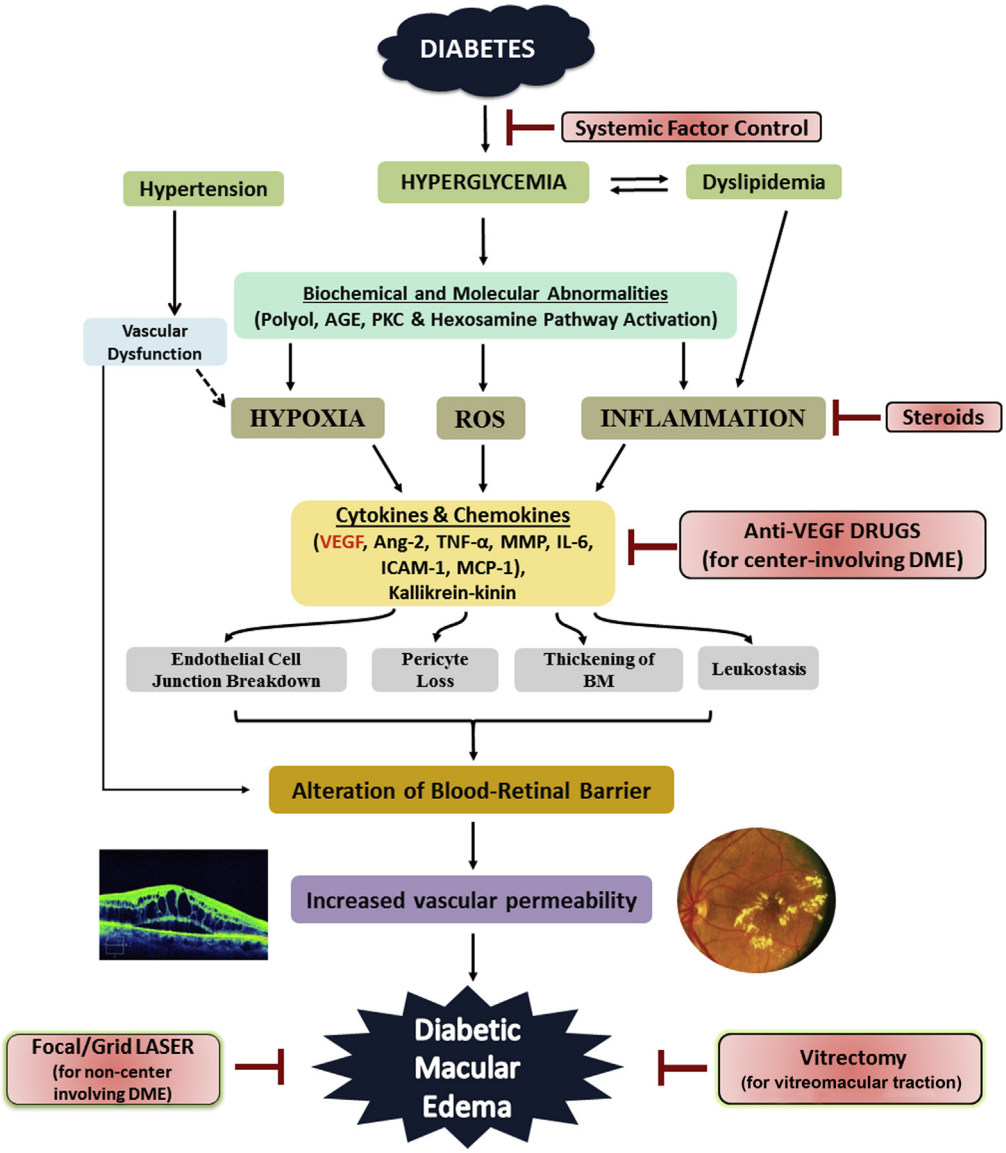

Figure 5. Pathophysiology of diabetic macular edema (DME) and different therapeutic strategies. Hyperglycemia in diabetes activates different biochemical pathways that lead to increased hypoxia, reactive oxygen species (ROS) formation, and inflammation with production of cytokines and chemokines. These mediators then cause endothelial cell junction breakdown and leukostasis, resulting in alteration of the blood–retinal barrier (BRB), increased retinal vascular permeability, and DME. Hyperglycemia also causes thickening of the basement membrane (BM) and pericyte dropout. Hypertension and hyperlipidemia, which coexist commonly in diabetic persons, further damage the already altered BRB. Currently, control of systemic factors, focal/grid laser (for noncenter-involving DME), anti–vascular endothelial growth factor (VEGF) therapies (for center-involving DME), steroids, and vitrectomy (in cases of vitreomacular traction) are the mainstays of management of DME. However, the current anti-VEGF therapies have limitations because they target only VEGF rather than other inflammatory molecules (e.g., angiopoietin [Ang]-2, matrix metalloproteinase [MMP], tumor necrosis factor [TNF]-α, interleukin [IL]-1β, kallikrein-kinin) present in the retina in diabetic persons. Many future therapies target these other mediators. AGE = advanced glycation end-products; ICAM = intercellular adhesion molecule; MCP = monocyte chemoattractant protein; PKC = protein kinase C.

inhibits expression of many inflammatory-associated genes, including *IL-8* and cyclooxygenase-1 and 2. A phase I study using a single subconjunctival or intravitreal injection of sirolimus formulation in patients with DME showed moderate improvement of vision and reduction of macular thickness.[100]

Squalamine. Squalamine is a small-molecule, anti-angiogenic drug that inhibits neovascularization through inhibition of multiple growth factors, including VEGF, platelet-derived growth factor (PDGF), and basic fibroblast growth factor. It does not block all intracellular VEGF pathways but inhibits specifically mitogen-activated protein kinase, p38 inflammatory, and vascular endothelial-cadherin and other signaling pathways. Preclinical studies have shown that squalamine eyes drops are safe and can reach the retina at effective concentrations. A randomized, placebo-controlled, multicenter, phase II clinical trial is currently evaluating the effect of squalamine (OHR-005; Ohr Pharmaceuticals, New York, NY) eye drops in patients with

DME. In a phase II, randomized, double-masked, placebo-controlled study (IMPACT) in patients with wet AMD, more than twice the proportion of patients achieved ≥3 line gains in visual acuity at 9 months with the combination of squalamine eye drops and ranibizumab compared with the ranibizumab monotherapy group.[101]

Src Kinase Inhibitors. Because Src kinase activity is critical for VEGF-induced permeability, Src kinase inhibitors may prevent VEGF-associated vascular permeability while maintaining its angiogenic and cell-survival activities. Two separate studies confirmed benefits of topical Src kinase inhibitors (TG 100081) in reducing retinal edema in animal models.[102,103] These inhibitors target multiple growth factors, including VEGF, basic fibroblast growth factor, and PDGF.

RTP801 Inhibitor. *RTP801* is a gene that is stimulated by oxidative stress and DNA damage and is expressed in patients with diabetic retinopathy and neovascular AMD. Intravitreal injections of a small interfering RNA (PF-655; Quark Pharmaceuticals, Fremont, CA) that targets *RTP801* reduced blood vessel leakage by 50% in diabetic mice. Currently, 2 phase II studies have examined the effects of PF-655 on patients with DME: the DEGAS (Dose-ranging evaluation of intravitreal siRNA PF-04523655 for diabetic macular edema) study (comparing with laser) and the MATISSE (Dose Escalation Study, and Evaluation of PF-04523655 With/Without Ranibizumab in Diabetic Macular Edema) study (comparing monotherapy with combination therapy with ranibizumab or laser).[104] This drug has been found to be safe, well-tolerated, and showed a dose-related tendency for improvement of visual acuity.

iCo-007. A second-generation antisense inhibitor targeting C-raf kinase mRNA (iCo-007; iCo Therapeutics, Vancouver, BC, Canada) can block neovascularization and retinal vascular permeability by inhibiting multiple growth factors, including VEGF, hypoxia-inducible factor (HIF-1), and hepatocyte growth factor. A randomized, phase II study is examining the safety, tolerability, and bioactivity of intravitreal injections of iCo-007 as monotherapy or in combination with ranibizumab or laser therapy in patients with DME (iCo-007 as monotherapy or in combination with Ranibizumab or laser photocoagulation in the treatment of diabetic macular edema [iDEAL] study). However, mean changes in visual acuity measures in the iDEAL Study at both month 4 and month 8 visits were found to be negative, and further analysis of the data is needed for 12-month visits.[105]

Anti-inflammatory Therapy

Tumor Necrosis Factor Inhibitor. TNF-α is one of the crucial mediators of retinal leukostasis, chemoattraction of monocytes, and upregulation of adhesion molecules, and intravitreal injection of TNF-α causes BRB breakdown. TNF-α has been implicated in many inflammatory diseases, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and Crohn's disease. A monoclonal antibody, infliximab, has been approved for treatment of these disorders. In diabetic rats, the TNF-α inhibitor etanercept has been shown to reduce leukocyte adhesion and retinal ICAM-1 expression and suppress BRB breakdown. However, TNF-α inhibition does not affect retinal VEGF levels, indicating other mechanisms are involved in the response to etanercept. Thus, there is some interaction between VEGF and TNF-α-mediated pathways that act independently in diabetes-related inflammation.[61] A double-blind, randomized, placebo-controlled crossover study of 11 patients with DME (persisting after 2 sessions of laser treatment) showed significantly improved visual acuity and reduction in retinal thickness with intravenous infliximab (5 mg/kg) (Janssen Biotech, Horsham, PA).[106] It is important to note that all TNF-α inhibitors behave the same way, and some of these agents are cytolytic, and intravitreal infliximab is toxic. Larger clinical trials for longer periods need to be performed to confirm the efficacy of systemic anti-TNF drugs for treatment of DME.

Angiopoietin-2 Inhibitor. Angiopoietins are a family of growth factors that bind to the endothelial receptor tyrosine kinase Tie-2 and regulate vascular development and function. The activity of Tie-2 is differentially regulated by 2 ligands, Ang-1 and Ang-2. Ang-2 has been shown to be upregulated in retinas in an animal model of diabetes, and increased Ang-2 leads to increased retinal vascular permeability.[107] The therapeutic role of Ang-1 in diabetic retinopathy has been clearly established by experiments showing that intravitreal Ang-1 injection in diabetic animals prevented retinal vascular leakage.[108] Vascular endothelial-protein tyrosine phosphatase, which negatively regulates Tie-2 activation, has been shown to be upregulated in hypoxic vascular endothelial cells in retinal neovascularization, and a small-molecule inhibitor of vascular endothelial-protein tyrosine phosphatase catalytic activity, AKB-9778, blocked VEGF-induced leakage from retinal vessels.[109] An ongoing phase II clinical trial with AKB 9778 (Aerpio Therapeutics, Blue Ash, OH) alone or in combination with ranibizumab is examining its efficacy in patients with DME.[110] The subcutaneous route for this drug offers a self-administered alternative in patients with DME.

Chemokine Inhibitor. As mentioned earlier, chemokines, especially MCP-1 (also known as "chemokine ligand 2"), play an important role in alteration of the BRB in diabetic animals.[66] Inhibition of the chemokine pathway (mechanisms of early leukocyte influx and reducing monocyte trafficking into the retina) is a potential novel approach of addressing a critical upstream target in the inflammatory cascade in DME. Several clinical trials targeting chemokines and their receptors are in progress in systemic diseases, such as atherosclerosis, chronic kidney diseases, diabetes, and diabetic nephropathy. A phase II randomized trial is currently comparing the efficacy and safety of an oral chemokine CCR2/5 receptor antagonist (PF-04634817; Pfizer Inc.) with that of ranibizumab in patients with DME.[111]

Antagonist of Lymphocyte Function Associated Antigen-1 (SAR 1118). Lymphocyte function-associated antigen-1 (LFA-1; $\alpha L\beta 2$), an integrin receptor expressed on leucocytes, interacts with its ligand ICAM-1, expressed on endothelial cells. Targeting the LFA-1/ICAM-1 interaction with a monoclonal antibody or by deletion of the gene

encoding ICAM-1 reduces leukostasis, vascular leakage, and endothelial cell death, preserving the integrity of the BRB. Topically administered SAR 1118 (SARcode Bioscience, Brisbane, CA), a small-molecule antagonist of LFA-1/ICAM-1 interaction, has been shown to reduce leukostasis and BRB breakdown in a diabetic rat model.[112]

Betamethasone Microsphere. A randomized, multicenter, sham-controlled, double-masked, phase II/III study assessing the efficacy and safety of sub-tenon injections of biodegradable, sustained-release betamethasone microspheres (DE-102; Santen Pharmaceuticals, Osaka, Japan) in patients with DME has been completed.[113]

Dexamethasone-Cyclodextrin. A new drug-delivery platform based on cyclodextrin microparticles that dissolve in the tear fluid to form water-soluble dexamethasone/cyclodextrin complex microparticles has been shown to effectively deliver the drug to the retina in animals. A short pilot study using topical 1.5% dexamethasone-cyclodextrin eye drops decreased central macular thickness and improved visual acuity in DME.[114]

Loteprednol. Another novel topical steroid preparation, loteprednol etabonate based on a Mucus Penetrating Particle delivery platform (Kala Pharmaceuticals, Waltham, MA), has been investigated for its better penetration through the mucus layer of the tear film. It causes less of an increase in IOP in patients than prednisolone acetate 1%. In a phase II, single-masked, randomized trial, Kala is investigating the efficacy and safety of 1% and 0.25% loteprednol dosed 4 times daily in patients with DME.[115]

Danazol. Danazol is a steroid and testosterone derivative that can improve tight junctions, thereby restricting leakage across the cell membrane. A phase II efficacy and safety study with 2 doses of oral danazol (DMI-5207; Ampio Pharmaceuticals, Englewood, CO) in adult subjects with DME has been completed, and a larger study has been initiated.[116]

Darapladib. Lipoprotein-associated phospholipase-A2 is an important enzyme involved in lipid metabolism and inflammation. In atherosclerosis, lipoprotein-associated phospholipase-A2 circulates with low-density lipoproteins into arterial walls and recruits macrophages. Darapladib (GlaxoSmithKline, Middlesex, UK) is an oral drug and a selective inhibitor of lipoprotein-associated phospholipase-A2. A phase II clinical trial with this drug has been completed in patients with DME, and this drug has been investigated in acute coronary syndrome.[117]

Minocycline. In diabetic retinas, microglia proliferate becomes activated with amoeboid morphologies and upregulates expression of inflammatory cytokines.

These cells represent a promising cellular target for inhibition of the inflammatory changes in diabetic retinopathy. Minocycline, a second-generation tetracycline, has been shown to have anti-inflammatory properties. In a mouse model of diabetes, minocycline decreased diabetes-induced inflammatory cytokines and reduced the release of cytotoxins from activated microglia. A phase I/II pilot proof-of-concept study in patients with DME showed that oral minocycline (100 mg twice per day for 6 months) improved visual function, central macular edema, and vascular leakage.[118] Oral minocycline has the advantages of high bioavailability and known safety profile, and seems to be a promising microglial-targeted therapy for diabetic retinopathy.

Kallikrein-Kinin Inhibitor. The plasma kallikrein-kinin system plays an important role in innate inflammation, blood flow, and coagulation. Vitreous proteomics in advanced stages of diabetic retinopathy have shown increased levels of plasma kallikrein-kinin system components, including plasma kallikrein, coagulation factor XII, and high-molecular-weight kininogen.[119] Preclinical studies in diabetic rats have reported activation of the intraocular kallikrein-kinin system, and administration of plasma kallikrein inhibitors and B1R antagonists to diabetic rats suppresses retinal vascular leakage and inflammation. A phase I single ascending dose study to investigate the safety and tolerability of the novel plasma kallikrein inhibitor KVD001 (intravitreal) (KalVista Pharmaceuticals, Porton Down, UK) in subjects with DME is in progress.[120]

Proteinase Inhibitors. The role of MMPs in the maintenance of systemic vessel integrity and remodeling has been well documented in animal models of angiogenesis. The MMPs are zinc-dependent proteinases that are capable of degrading numerous structural components of the extracellular matrix and a variety of nonextracellular matrix proteins.[87] In an animal model of diabetes, both MMP-2 and MMP-9 were elevated in the retinas, and the increased retinal vascular permeability was inhibited with an MMP inhibitor (BB-94; British Biotech, Oxford, England).[121] These preclinical studies suggest a possible mechanism by which diabetes contributes to BRB breakdown through the proteolytic degradation of vascular endothelial-cadherin, and a potential role of MMP inhibitors in DME.

Interleukin Inhibitors. Intravitreal administration of an antibody against human IL-6, EBI-029 (Eleven Biotherapeutics, Cambridge, MA), potently inhibits IL-6 cis- and trans-signaling and has been effective in an animal model of choroidal neovascularization. Further development of EBI-029 as a therapy for DME is in progress.[122]

Integrin Inhibitors

Integrins constitute a class of proteins that serve as cell surface receptors to the extracellular matrix and immunoglobulin molecules. They interact with growth factor receptors and regulate their functions. The process of leukostasis that is enhanced in diabetic retinopathy is dependent on specific integrins containing the beta 2 chain.

ALG-1001. An integrin antagonist, ALG-1001 (Allegro Ophthalmics, LLC, San Juan Capistrano, CA), that blocks all integrin a-b combinations rather than subunits has been shown to be effective in patients with wet ARMD and patients with DME. In a phase I study in patients with DME, after 3 monthly intravitreal injections of ALG-1001 (2 mg), there was significant visual improvement and reduction of CRT.[112] Apart from targeting integrin receptors involved in cell signaling and cell adhesion, this drug has the added advantage of inducing posterior vitreous detachment and vitreolysis. A phase II trial with Luminate (ALG-1001) is enrolling patients with DME for comparison with bevacizumab and focal laser therapy.[123]

Vascular Adhesion Protein-1 Inhibitor. Vascular adhesion protein-1 (VAP-1) is a unique endothelial adhesion molecule that is involved in leukocyte transmigration during inflammation. VAP-1 has been shown to be expressed on retinal vascular endothelial cells, where it functions in leukostasis in retinal vessels. In a streptozotocin-induced diabetic rat model, a highly potent VAP-1 inhibitor given orally was found to be effective in preventing retinal vascular permeability.[124]

Hormone Modulators

Exenatide. Exenatide is an inhibitor of the glucagon-like peptide-1 that has been approved by the FDA for type 2 diabetic patients who have not been able to control their blood glucose with metformin or a sulfonylurea drug. Subcutaneous injection of exenatide has been shown to reduce inflammatory markers (MCP-1 and C-reactive protein) and oxidative stress in diabetic persons.[125] A case report of regression of DME after several subcutaneous injections of this drug was reported.[126]

Lanreotide. Lanreotide is a synthetic analogue of somatostatin, a hormone that blocks the release of hormones such as growth hormone, thyroid-stimulating hormone, insulin, and glucagon. However, lanreotide has a longer half-life and produces far more prolonged effects, whereas somatostatin is metabolized quickly. Subcutaneous injections of lanreotide have been shown to be effective in visual improvement and reduction of macular edema in a case report.[127]

Acetylcholine Receptor Blocker

Mecamylamine. Vascular endothelial cells contain nicotinic acetylcholine receptors that, if stimulated, promote angiogenesis and vascular permeability in animal models. In a phase I/II trial, topical mecamylamine, a nonspecific nicotinic acetylcholine receptor blocker (CoMentis, Inc., South San Francisco, CA), showed variable results in visual improvement.[128] Identification of subtypes of these receptors that contribute to retinal vascular permeability may be an important step in further consideration of these drugs.

Insulin-Like Growth Factor-1 Receptor Blocker

Teprotumumab. Intraocular insulin-like growth factor-1 (IFG-1), but not systemic IGF-1, has been found to trigger BRB breakdown and increased retinal vascular permeability.[129] On the basis of this rationale, a phase I, open-label study of Teprotumumab (Genmab, Princeton, NJ), an IGF-1 receptor blocker given by intravenous infusion, is examining the safety and efficacy of this drug in patients with DME.[130]

Neuroprotective/Antiapoptotic Agents

Erythropoietin. Because hypoxia is one of the key factors in the pathogenesis of diabetic retinopathy, increasing the oxygen tension in tissues by administration of erythropoietin is an attractive approach to treatment of DME. Erythropoietin also acts as a neuroprotective, antioxidant, and antiapoptotic factor. In a case series, Friedman et al[131] published the results of erythropoietin use in anemic azotemic diabetic subjects who had improvement of macular edema. In another series, intravitreal injection of erythropoietin in patients with chronic DME resulted in improved visual acuity and clearing of hard exudates.[132]

Stem Cell Therapy. Endothelial progenitor cells (EPCs) are circulating cells that play a role in promoting the repair of blood vessels and reperfusion of ischemic areas. These cells may originate from hematopoietic stem cells in the bone marrow and specialized vascular stem cells in vessel walls or within the endothelium. Variable results using EPCs have been reported in preclinical and clinical studies. There are many challenges in stem cell therapy that need to be resolved before its clinical application. Selection of a well-defined, efficacious EPC, the correct dose (number of cells) and route of administration, and timing of treatment (stage of vascular damage in DME or precapillary dropout stage) need to be determined for an optimal effect for this potential therapy.[133,134]

Conclusions

Many patients with DME who receive intravitreal anti-VEGF injections as a first line of treatment do not show complete resolution of edema and vision improvement even after multiple injections. Focal/grid laser photocoagulation, which was the gold standard treatment, is now reserved for noncenter-involving DME and may be combined with anti-VEGF therapy for a complete response. Also, other approaches such as combination therapy of steroids and anti-VEGF agents, and switching to other anti-VEGF agents, have been considered.[85] It is also important to note that anti-VEGF drugs have a more robust effect in the angiogenesis process (PDR or neovascularization of iris) compared with that in DME. Although PDR seems to be a primarily VEGF-dependent disease, DME is a disease involving more than VEGF. So, what are the other targets beyond VEGF? More and more data are pointing toward an inflammatory disease process in DME. With multiple chemokines and cytokines known to be involved in the process, new pharmacotherapies targeting these inflammatory mediators are being developed. It is possible that in those poor responders to anti-VEGF therapy, the retina has a plethora of other inflammatory mediators that need to be targeted along with VEGF. Also, the response to anti-VEGF drug response seems variable, and one wonders whether genetic factors play a role in determining this response to these treatments. In the future, individualized treatment based on these genetic profiles and pharmacogenetic testing may have the potential to increase the efficacy of treatments and reduce treatment burden for patients. Novel drug delivery systems using nanotechnology, sustained-release medications, and stem cell therapy are on the horizon. Our field of ophthalmology is currently seeing a sudden explosion of various novel technologies and therapeutic approaches that are being developed to treat DME for visual improvement.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
ACCORD = Action to Control Cardiovascular Risk in Diabetes; **Ang** = angiopoietin; **ARMD** = age-related macular degeneration; **BRB** = blood–retinal barrier; **CRT** = central retinal thickness; **DARPin** = designed ankyrin repeat proteins; **DCCT** = Diabetes Control and Complications Trial; **DME** = diabetic macular edema; **DRCR** = Diabetic Retinopathy Clinical Research; **EPC** = endothelial progenitor cell; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FA** = fluorescein angiography; **FDA** = Food and Drug Administration; **FITC** = fluorescein isothiocyanate; **HbA1c** = glycated hemoglobin; **ICAM** = intercellular adhesion molecule; **IGF-1** = insulin-like growth factor-1; **IL** = interleukin; **IOP** = intraocular pressure; **LFA-1** = lymphocyte function-associated antigen-1; **MCP** = monocyte chemoattractant protein; **MMP** = matrix metalloproteinase; **OCT** = optical coherence tomography; **PDGF** = platelet-derived growth factor; **PDR** = proliferative diabetic retinopathy; **PKC** = protein kinase C; **RPE** = retinal pigment epithelium; **TNF** = tumor necrosis factor; **UKPDS** = United Kingdom Prospective Diabetes Study; **VAP-1** = vascular adhesion protein-1; **VEGF** = vascular endothelial growth factor; **WESDR** = Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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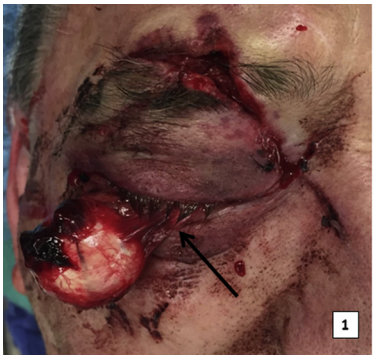
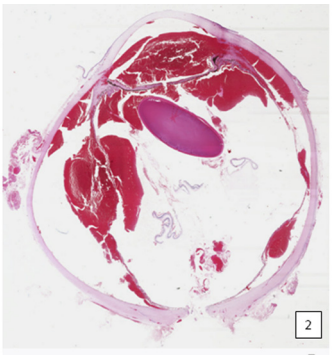
Pictures & Perspectives





Spring-Loaded Enucleation

Traumatic enucleation of the right eye. This 61-year-old man was attempting to fix a spring-loaded garage door when the spring broke and struck him in the face. The only remaining attachment between the globe and the orbit, seen in the clinical photo (Fig 1), was determined to be the inferior rectus muscle (arrow). There was a hyphema, vitreous hemorrhage, suprachoroidal hemorrhage, and an avulsion of the optic nerve seen on histopathologic examination (Fig 2).

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