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Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 1

Diabetic Retinopathy

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Over 135 million individuals are afflicted with diabetes across the world. In the U.S., diabetes affects over 18.2 million people (or 6.3% of the total population) and 800,000 new cases of type 2 diabetes are diagnosed each year (1). Retinopathy is the most common microvascular complication of diabetes, resulting in blindness for over 10,000 people with diabetes per year. Epidemiological studies have described the natural history of and treatment for diabetic retinopathy. There is evidence that retinopathy begins to develop at least 7 years before the clinical diagnosis of type 2 diabetes (2). Clinical trials have demonstrated the effectiveness of photocoagulation, vitrectomy, and control of hyperglycemia and hypertension for diabetic retinopathy (Table 1). The current review will discuss the pathophysiology, screening, medical treatment, and future research for diabetic retinopathy.

PATHOPHYSIOLOGY

Several biochemical pathways have been proposed to link hyperglycemia and microvascular complications. These include polyol accumulation, formation of advanced glycation end products (AGEs), oxidative stress, and activation of protein kinase C (PKC). These processes are thought to modulate the disease process through effects on cellular metabolism, signaling, and growth factors.

Polyol accumulation

Accumulation of polyol occurs in experimental hyperglycemia, which in rats and dogs is associated with the development of basement thickening, pericyte loss, and microaneurysm formation (3,4). High concentrations of glucose increase flux through the polyol pathway with the enzymatic activity of aldose reductase, leading to an elevation of intracellular sorbitol concentrations. This rise in intracellular sorbitol accumulation has been hypothesized to cause osmotic damage to vascular cells (5). Aldose reductase inhibitors (ARIs) have been evaluated for the prevention of retinal and neural damage in diabetes (6). However, three clinical trials of ARIs in humans have not shown efficacy in preventing the incidence or progression of retinopathy (7,8 and S. Feman [St. Louis University, St. Louis, MO], personal communication). The efficacy of new, more potent ARIs remains to be evaluated in clinical trials.

AGEs

Another well-characterized pathway is damage resulting from accumulation of AGEs. High serum glucose can lead to nonenzymatic binding of glucose to protein side chains, resulting in the formation of compounds termed AGEs (9,10). After 26 weeks of induced hyperglycemia, the retinal capillaries of diabetic rats have marked accumulation of AGEs as well as a loss of pericytes. Furthermore, diabetic rats treated with aminoguanidine (AGE formation inhibitor) have reduced AGE accumulation and reduced histological changes, including microaneurysm formation and pericyte loss (11). An ongoing clinical trial is investigating the effect of aminoguanidine in humans (12). Preliminary results suggest that aminoguanidine reduces the progression of retinopathy but is associated with anemia (13).

Oxidative damage

Diabetes and hyperglycemia can also lead to oxidative stress and formation of reactive oxygen species (ROS), leading to vascular damage. Production of ROS (free radicals) may result from glucose autooxidation, protein glycation, increased flux through the polyol pathway, and prostanoid production (14). Normalization of glucose-stimulated superoxide production has been found to block at least three independent pathways of hyperglycemia-induced vascular damage (15). Furthermore, animal studies suggest that antioxidants such as vitamin E may prevent some of the vascular dysfunction associated with diabetes (16). In one study of patients with diabetes who had no or minimal retinopathy ($n = 36$), treatment for 4 months with high-dose vitamin E (1,600 IU/day) was found to significantly reverse abnormalities of retinal blood flow ($P < 0.001$) (17,18). An 88% normalization of retinal blood flow was seen, despite an unchanged level of glycemic control.

The Heart Outcomes Prevention Evaluation (HOPE) trial is a randomized clinical trial with a 2×2 factorial design that evaluated the effects of vitamin E and ramipril in patients at high risk for cardiovascular events (19). Patients were eligible for the study if they were 55 years of age or older and if they had cardiovascular

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Abbreviations: ABCD, Appropriate Blood Pressure Control in Diabetes; ACCORD, Action to Control Cardiovascular Risk in Diabetes; AGE, advanced glycation end product; ARI, aldose reductase inhibitor; DCCT, Diabetes Control and Complications Trial; DIRECT, Diabetic Retinopathy Candesartan Trial; DME, diabetic macular edema; EDTRS, Early Treatment Diabetic Retinopathy Study; EUCLID, Eurodiab Controlled Trial of Lisinopril in Insulin Dependent Diabetes; FPG, fasting plasma glucose; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PEDF, pigment epithelium–derived growth factor; PKC, protein kinase C; QALY, quality-adjusted life-year; ROS, reactive oxygen species; SSF, seven standard field; SNMDP, single-field digital monochromatic nonmydriatic photography; TGF-β, transforming growth factor-β; UKPDS, U.K. Prospective Diabetes Study; VEGF, vascular endothelial growth factor; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 2

Table 1—*Outline of 1998 technical review (ref. 40)*

Epidemiology
Impact
Natural history
Causes of visual loss
Providers of eye care for patients with diabetes
Provider of medical care for patients with diabetes
Comprehensive eye evaluation
Initial eye evaluation and minimal follow-up
NPDR levels and disease progression
PDR levels and disease progression
Macular edema levels and disease progression
Treatment objectives
Determination of treatment efficacy
General treatment efficacy
Specific clinical trials outcomes
Management of diabetic retinopathy
Exercise
Aspirin therapy
Ancillary tests
Photography and retinal screening
Conclusions

disease or diabetes with at least one additional coronary risk factor. Patients were randomly allocated to daily treatment with 400 IU vitamin E and 10 mg ramipril or their respective placebos and were followed for an average of 4.5 years. The primary study outcome was the composite of myocardial infarction, stroke, or cardiovascular death. Secondary outcomes included total mortality, hospitalizations for heart failure or unstable angina, revascularizations, overt nephropathy, and laser therapy for diabetic retinopathy. In the 3,654 people with diabetes, vitamin E at this dose had a neutral effect on the primary study outcome (relative risk 1.03, 95% CI 0.88–1.21; $P = 0.70$), on each component of the composite primary outcome, and on all predefined secondary outcomes.

PKC activation

There is increasing evidence that PKC activation is related to hyperglycemia-induced microvascular dysfunction in diabetes (20). Activation of PKC results in numerous cellular changes, including increased expression of matrix proteins, such as collagen and fibronectin, and increased expression of vasoactive mediators, such as endothelin. The changes are seen as thickening of the basement membrane, increased retinal vascular permeability, and alterations in retinal blood flow. Although the activity of multiple PKC isoforms (α, β1, β2, and ε) is increased in vascular tissues in the diabetic state, studies suggest that the PKC-β2 isoform preferentially mediates the pathologic complications associated with hyperglycemia (21,22). Moreover, PKC-β has been shown to be an integral component of cellular signaling by vascular endothelial growth factors (VEGFs) (23), important mediators of ocular neovascularization, secondary to retinal ischemia and diabetic macular edema (DME) (24,25). Results from one clinical trial using a PKC inhibitor will be discussed in the section on future directions and PKC inhibitors.

Growth factors

The biochemical pathways described above are associated with production and signaling of growth factors such as VEFG, growth hormone, IGF-I, transforming growth factor-β (TGF-β), and pigment epithelium–derived growth factor (PEDF).

The VEGFs are a family of proteins that are mitogenic for vascular endothelial cells and increase vascular permeability. VEGF is important in fetal vascular development, with VEGF levels diminishing after birth. However, increased expression of VEGF has been demonstrated in diabetic retinopathy (26). In addition, VEGF has been shown to be upregulated by hypoxia, with increasing levels of VEGF in the vitreous associated with increasing retinal ischemia. In a mouse model of hyperoxic retinopathy, soluble VEGF-neutralizing VEGF receptor chimera was shown to suppress retinal neovascularization (27). There is increasing evidence that inhibition of PKC-β can prevent the neovascular and permeability effects of VEGF in animals (28).

Growth hormone and IGF-I have been suspected of playing a role in the progression of diabetic retinopathy. In a previous era, hypophysectomy was shown to lead to regression of proliferative retinopathy in a study of 100 patients (29). Similarly, diabetic dwarfs with low systemic IGF-I levels due to growth hormone deficiency have a reduced incidence of proliferative diabetic retinopathy (PDR) compared with age- and sex-matched diabetic patients. Other evidence includes observations of diabetic retinopathy progression in states of elevated IGF-I, such as puberty pregnancy (30), and upon rapid improvement of metabolic control (31). Such observations have raised interest in the use of growth hormone–inhibitory and antiproliferative somatostatin analogs to treat severe PDR (32,33). In a recent small-scale study of adults with diabetes and PDR, however, a growth hormone receptor antagonist, pegvisomant, failed to induce regression of neovascularization (34). This negative result may have occurred because the treatment was initiated too late; treatment may need to have started prior to the development of PDR. In another small-scale trial (23 patients), octreotide (a somatostatin analog) treatment reduced the requirement for laser photocoagulation compared with conventional treatment in patients with either severe nonproliferative diabetic retinopathy (NPDR) or early PDR (35). Over the 15-month study, only 1 of 22 octreotide-treated patients required photocoagulation compared with 9 of 24 conventionally treated patients. A large clinical trial of octreotide is ongoing. TGF-β is produced by pericytes and may inhibit endothelial proliferation. Active PDR and patients with rubeosis have lower levels of TGF-β (36). Lower levels may promote angiogenesis by removal of an inhibitor. Levels of TGF-β are usually high in the vitreous of normal eyes (37).

PEDF is produced by the retinal pigment epithelium and inhibits neovascularization (38). Systemic injection can reduce the development of retinal neovascularization in mouse retinopathy of a prematurity model (39). It has been postulated that reduced levels of PEDF may contribute to diabetic retinopathy; however, PEDF transgenic knockout mice do not show ocular pathology or altered neovascular responses.

DIAGNOSIS

A previous technical review published in *Diabetes Care* (40) provides an extensive review of the elements of comprehensive eye evaluation and levels of diabetic retinopathy, as well as management for diabetic retinopathy. The current review discusses *1*) techniques for diabetic retinopathy screening, *2*) intervals for evaluating patients without any retinopathy, *3*) a new classification of diabetic retinopathy severity, and *4*) optical coherence tomography.

Many techniques are used in the detection of diabetic retinopathy, including

Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 3

direct and indirect ophthalmoscopy, fluorescein angiography, stereoscopic digital and color film–based fundus photography, and mydriatic or nonmydriatic digital color or monochromatic single-field photography. Grading of stereoscopic color fundus photographs in seven standard fields (SSFs), as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) group, is a recognized standard for the detection of diabetic retinopathy (41). Although this approach is accurate and reproducible, it is labor intensive, requiring skilled photographers and photograph readers and sophisticated photography equipment, film processing, and archiving.

Ophthalmoscopy is the most commonly used technique to monitor for diabetic retinopathy. However, undilated ophthalmoscopy, especially by non–eye care providers has poor sensitivity compared with stereoscopic seven-field color photography (42). Under typical clinical conditions, direct ophthalmoscopy by nonophthalmologists has a sensitivity of ~50% for the detection of proliferative retinopathy (43).

Various systems using multiple-field photography have been reported. Three groups have reported their results using proprietary systems, and these systems seem to perform well. However, the systems are proprietary and require pupillary dilation and skilled photographers and may therefore be more complex than required for screening purposes.

The Joslin Vision Network (44) compared stereo nonmydriatic digital-video color and three-field fundus photographs in three fields with SSF photography in 54 patients (108 eyes) with type 1 or type 2 diabetes (level 1 evidence). They found substantial agreement ($\kappa = 0.65$) between the two techniques for determination of the clinical level of diabetic retinopathy. Agreement was excellent ($\kappa = 0.87$) for referral to an ophthalmologist for clinical examination. In addition, a retrospective review of a subset of patients that had Joslin Vision Network imaging showed good correlation with an examination by a retina specialist (45).

The Inoveon Diabetic Retinopathy system (46) compared SSF photographs of 290 diabetic patients recorded on 35-mm film and on their proprietary system. The sensitivity and specificity of the digital system in detecting threshold events were 98.2 and 89.7%, respectively. Although Inoveon's diabetic retinopathy-3DT system provides highly accurate diabetic retinopathy referral decisions, the requirement for dilation and the cost both reduce its usefulness as a screening tool.

The DigiScope is a semiautomated instrument that acquires fundus images, evaluates visual acuity, and transmits the data to a remote reading center through telephone lines (47). A pilot study in normal eyes of normal volunteers and 17 consecutive diabetic patients showed that the visualization of many retinal lesions present in diabetic retinopathy can be visualized by the DigiScope. Further studies are needed to evaluate the test characteristics of this technology.

The use of single-field fundus photography has also been used as a detection tool for diabetic retinopathy. Patients with type 1 or type 2 diabetes were sequentially photographed through a nonpharmacologically dilated pupil by single-field digital monochromatic nonmydriatic photography (SNMDP), pharmacologically dilated, examined by ophthalmoscopy by an ophthalmologist, and then had 30° color stereoscopic photographs taken in SSFs (48). There was excellent agreement ($\kappa = 0.97$) between the SNMDP and SSFs for degree of diabetic retinopathy using a "referral" (ETDRS level $\geq$35) or "no referral" (ETDRS level $\leq$20) dichotomization (level 1 evidence). The sensitivity and specificity of SNMDP compared with SSFs were 78 and 86%, respectively. SNMDP was superior to ophthalmoscopy through pharmacologically dilated pupils when compared with SSFs. SNMDP demonstrated 100% sensitivity and 71% specificity when compared with direct ophthalmoscopy. None of the patients identified by ophthalmoscopy for referral were missed by SNMDP. SNMDP demonstrated 25% overcalls (higher retinopathy levels diagnosed by the tested modality rather than by the standard) for referral compared with ophthalmoscopy. However, when adjudicated against SSFs, this difference was due to the reduced sensitivity of ophthalmoscopy. With a sensitivity of 78%, SNMDP did miss some patients requiring referral based on SSFs. The lack of stereopsis also diminishes the ability to diagnose clinically significant macular edema in the absence of hard exudates or retinal hemorrhages and microaneurysms. The authors emphasize that SNMDP is superior to dilated ophthalmoscopy. The effectiveness was confirmed in other studies (49,50).

Single-field photography is not a substitute for a comprehensive ophthalmic examination. However, there is evidence from well-designed comparative studies that single-field fundus photography can serve as an initial evaluation tool for diabetic retinopathy by identifying patients with retinopathy for referral to ophthalmic evaluation and management. The effectiveness is demonstrated by its ease of use (only one photograph is required), cost (the cost of one photograph in most cases), convenience, and ability to detect retinopathy. None of the above approaches, including the proprietary systems, are able to detect other diseases often present in older patients with diabetes. This inability reduces the value of using these approaches when compared with examination by a skilled eye care provider.

Mydriasis and single-field photography

Although most patients can be photographed without pharmacological dilation, lens opacities in older patients can result in photographs that are ungradeable. In the studies previously mentioned, Pugh et al. (50) found that 42 of 50 ungradeable photographs became gradable after dilation. Taylor et al. (49) and Joannou et al. (50a) evaluated only dilated single-field photography. Based on these studies, eyes with ungradeable pictures should have dilation and repeat photography. Eyes with photographs that remain ungradeable after dilation would be considered as screen positives and require referral to ophthalmic evaluation. With the advent of digital photography, the quality of the image taken can be reviewed by the photographer and retakes made if necessary, possibly reducing the high frequency of ungradeable photographs found in older subjects.

Screening interval

Regular dilated eye examinations are an effective approach to detecting and treating vision-threatening diabetic retinopathy (51). They can help prevent blindness and are cost effective (52,53). Guidelines for systematic evaluation have been developed because patients with retinopathy are often asymptomatic and because retinal photocoagulation treatment is more effective at reducing visual loss when ap-

Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 4

plied at specific, often asymptomatic, but advanced stages of retinopathy (54,55). However, despite the recommendations for regular evaluation and the availability of effective treatment, many patients at risk of visual loss due to severe retinopathy are not receiving dilated eye examinations and necessary photocoagulation treatments (56,57).

Guidelines for the frequency of dilated eye examinations have been based on the severity of the retinopathy (58,59). These recommendations are described in a previously published technical review (40). For patients with moderate to severe NPDR, frequent eye examinations are often necessary to determine when to initiate treatment. However, for patients without retinopathy or with only microaneurysms, the need for annual dilated eye examinations is less clear. For these patients, the annual incidence of either proliferative retinopathy or macular edema is low, suggesting that a reduced frequency of screening would decrease costs without increasing the risk of visual loss (60). Recently, some have suggested that annual screening for some patients may not be cost effective, and in some cases consideration should be given to increasing the screening interval (61). However, for patients where less frequent screening seems appropriate, there should be some oversight by the eye care professional to assure that the patient is not lost to follow-up. Before a less frequent screening schedule should be generally recommended or adopted, a better understanding of the total value of screening eye examinations, the potential indirect effects of less frequent eye examinations, and patient preference is needed.

Eye examinations may include other benefits. Older people often need eye exams for increasing presbyopia and are at higher risk for cataract, glaucoma, age-related macular degeneration, and more, which may result in vision loss. Discussion by ophthalmologists with their diabetic patients about medical as well as ophthalmic conditions certainly has value. For example, most primary care doctors tell their patients that it is important to control blood glucose, blood pressure, and serum lipids. During the eye exam these messages can be reinforced by the ophthalmologist at a time when patients are particularly aware of the implications of vision loss. Patients can also be reminded that controlling these parameters also will reduce the risk of neuropathy and nephropathy. Increased patient compliance will reduce the risks of these secondary complications of diabetes. Prevention of multiple complications is surely better than managing them after they have occurred, both for patient health and because of economic consequences. This value is difficult to measure and is often not incorporated into analyses of the costs and benefits of screening.

Less frequent examinations may also have indirect effects. Long intervals between follow-up visits may lead to difficulties in maintaining contact with patients. Also, patients may be unlikely to remember that they need an eye examination after several years have passed. Finally, a recommendation for follow-up visits at 2- or 3-year intervals may give a patient the impression that visual loss is very unlikely and therefore not a concern. All of these factors may result in longer-than-recommended intervals between examinations. Although automatic reminders from clinics can be helpful, they may be difficult to implement, especially when patients have relocated. Until we have empirical evidence to confirm that lengthening the follow-up interval is not harmful, maintaining an annual frequency seems conservative.

Patient expectations also should be considered. Blindness and visual loss is a major fear of most patients with diabetes. Visual loss leads to emotional distress and reduces functionality in daily life. The magnitude of this fear, the effect of blindness on functionality, and the economic value of these factors are hard to quantify. One way to assess the worth of these factors is to determine the value of blindness in terms of quality-adjusted life-years (QALYs). Investigators have suggested values of 0.48–0.36 (52,62) for blindness, but there are no QALY values for visual impairment that are less than blindness. Changes in QALY values significantly affect the cost-effectiveness of screening. Analyses should include a sensitivity analysis for different values of QALYs before making generalized recommendations.

Physicians may elect to individually reduce the frequency of follow-up for certain patients without retinopathy or nephropathy who are very compliant and have very good control of their blood glucose, blood pressure, and serum lipids. However, they should not assume that aggregate medical care costs can be reduced and efficiency increased by simply decreasing the frequency of screening examinations for entire groups of patients. Until empirical data are available to show otherwise, the general recommendation that individuals with diabetes should have a yearly eye examination seems safe, conservative, and reasonable. Deviations from this guideline are appropriate in certain low-risk groups but with caveats. Even with the current guideline, too many people with diabetes are needlessly losing vision because the opportunity to treat them in a timely fashion was missed. Relaxing the guidelines will not solve this problem. We think the guideline for a regular dilated eye examination should remain at 1 year rather than at 2 or 3 years. It is appropriate for the guideline to be conservative, and deviations from it should only be made after considering all of the risks.

New classification

The ETDRS severity scale was based on the modified Airlie House classification of diabetic retinopathy and was used to grade fundus photographs (63). Although it is recognized as the gold standard for grading the severity of diabetic retinopathy in clinical trials, its use in everyday clinical practice has not proven to be easy or practical. The photographic grading system has more levels than may be necessary for clinical care, and the specific definitions of the levels are detailed, require comparison with standard photographs, and are difficult to remember and apply in a clinical setting. In addition, in the past there has been no common practical clinical standard terminology that has been accepted for the worldwide exchange of information and data (64–66) until a new diabetic retinopathy severity scale was developed by the Global Diabetic Retinopathy Group at the International Congress of Ophthalmology in Sydney, Australia, in April 2002 (67).

The levels in this new diabetic retinopathy disease severity scale are listed in Table 2 and consist of five scales with increasing risks of retinopathy. The first level is "no apparent retinopathy," and the second level, "mild NPDR," includes ETDRS stage 20 (microaneurysms only). The risk of significant progression over several years is very low in both groups. The third level, "moderate NPDR," includes eyes with ETDRS levels 35–47, and the risk of

Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 5

Table 2—*International Clinical Diabetic Retinopathy Disease Severity Scale (ref. 63)*

Proposed disease severity level	Findings observable upon dilated ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR	Microaneurysms only
Moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any of the following: >20 intraretinal hemorrhages in each of 4 quadrants Definite venous beading in 2+ quadrants Prominent intraretinal microvascular abnormalities in 1+ quadrant And no signs of proliferative retinopathy
PDR	One or more of the following: Neovascularization Vitreous/preretinal hemorrhage

progression increases significantly by level 47. Still, the fourth level, "severe NPDR" (ETDRS stage 53), carries with it the most ominous prognosis for progression to PDR. The fifth level, "PDR," includes all eyes with definite neovascularization or vitreous/preretinal hemorrhage. There was no attempt to subdivide level 5 as a function of ETDRS "high-risk characteristics" because significant rates of progression are expected to occur in all of these cases.

DME disease severity scale is listed in Table 3. The initial and most important designation is to separate eyes with apparent DME from those with no apparent thickening or lipid in the macula. Because there are significant variations in examiner education and availability, a two-tiered system was recommended. The first level is determined by the presence or absence of apparent retinal thickening or lipid in the posterior pole. A second level evaluation documents details related to the distance of retinal thickening and/or lipid from the fovea. Eyes with obvious foveal involvement by edema or lipid are categorized as "severe DME." Eyes with edema and/or lipid relatively distant from the macula are graded as "mild DME." "Moderate DME" was used to identify cases in which retinal thickening and/or lipid are close to (or "threatening") the fovea.

The clinical disease severity scale is intended to be a practical and valid method of grading severity of diabetic retinopathy and DME and will allow observers to recognize and categorize levels of retinopathy and the presence of most DME. The identification of specific severity levels should result in more appropriate and consistent referrals to treatment centers.

Optical coherence tomography

Optical coherence tomography provides images by projecting a pair of near-infrared light beams into the eye. The resulting interference pattern from these beams is dependent of the thickness and reflectivity of the retinal structures and is detected by the measuring system (68). The images produced appear to be cross-sections of the retina and allow the thickness of the retina to be measured. The thickness of the retina may allow DME to be followed in a quantitative manner (69). An ongoing clinical trial will investigate the relationship between optical coherence tomography measurements and visual acuity.

TREATMENT

The technical review published in 1998 (40) discusses the efficacy of laser photocoagulation for PDR and DME and vitrectomy surgery for vitreous hemorrhage and active PDR. The current review discusses medical management and experimental therapies.

Glycemic control

At present, the most effective medical treatment to slow the progression of diabetic retinopathy is glycemic control. The relationship between hyperglycemia and retinopathy has been reported in well-conducted observational studies (70). The Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) are two randomized clinical trials that conclusively showed the efficacy of glycemic control in preventing diabetic retinopathy (71–73).

The DCCT (74) investigated whether intensive treatment of glycemia would prevent or delay the progression of early NPDR (primary prevention) and whether intensive glycemic control would prevent the progression of early retinopathy to more advanced forms of retinopathy (secondary intervention) (1). Patients eligible for the primary prevention cohort had type 1 diabetes for 1–5 years and no retinopathy by seven-field photography and for secondary intervention had type 1 diabetes for 1–15 years and very mild to

Table 3—*International Clinical Diabetic Macular Edema Disease Severity Scale (ref. 63)*

Proposed disease severity level	Findings observable upon dilated ophthalmoscopy*
DME apparently absent	No apparent retinal thickening or hard exudates in posterior pole
DME apparently present	Some apparent retinal thickening or hard exudates in posterior pole
DME present	Mild DME (some retinal thickening or hard exudates in posterior pole but distant from the center of the macula) Moderate DME (retinal thickening or hard exudates approaching the center of the macula but not involving the center) Severe DME (retinal thickening or hard exudates involving the center of the macula)

*Hard exudates are a sign of current or previous macular edema. DME is defined as retinal thickening requiring a three-dimensional assessment that is best performed by a dilated examination using slit-lamp biomicroscopy and/or stereo fundus photography.

Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 6

moderate NPDR. Patients were randomized to either conventional or intensive treatment. Conventional treatment was comprised of one to two daily injections of insulin, without daily adjustment in insulin dosage. The goals of the treatment were absence of symptoms from glycosuria and hyperglycemia, absence of ketonuria and frequent serious hypoglycemia, and normal growth and development of ideal body weight. Patients assigned to intensive treatment received more than three injections of insulin or insulin by an external pump with the goal of achieving normal glycemia. The main outcome measure was a three-step change in retinopathy level on fundus photography that was sustained for 6 months. Of the 1,441 patients in the DCCT, followed for a mean of 6.5 years, 99% completed the study and 95% of all scheduled examinations were completed.

In the primary prevention cohort, the cumulative incidence of a three-step increase in retinopathy level sustained over 6 months was quite similar between the two groups during the first 36 months. From that point on, there was a persistent decrease in the intensive group. From 5 years onward, the cumulative incidence was ~50% less in the intensive than in the conventional group. During a mean follow-up of 6 years, retinopathy developed in 23 patients in the intensive group and in 91 patients in the conventional group. Intensive therapy reduced the mean risk of retinopathy by 76% ($P < 0.002$). In the secondary intervention cohort, the intensive group had a higher cumulative incidence of sustained progression during the 1st year. However, by 36 months the intensive group had lower risks of progression. Intensive therapy reduced the risk of progression by 54% ($P = 0.011$). The protective effect of intensive therapy for retinopathy was investigated and found to be consistent in all subgroups (e.g., groups divided by age, sex, duration, percentage of ideal body weight, level of retinopathy, blood pressure, clinical neuropathy, baseline HbA_{1c}, and albuminuria).

Analysis for early worsening was conducted and noted to be present at the 6- and/or 12-month visit in 13.1% of 711 patients assigned to intensive treatment and in 7.6% of 728 patients assigned to conventional treatment ($P < 0.001$). By the 18-month visit, there was recovery in 51% of the intensive and 55% of the conventional groups ($P = 0.39$). The risk of three-step or greater progression from the retinopathy level present 18 months after entry into the trial was greater in patients who had previously had early worsening than in those who had not, but there was a large long-term risk reduction with intensive treatment. Patients who developed early worsening as a result of the intensive treatment were similar to or had more favorable outcomes than those in the conventional group who did not have early worsening. Analysis did not suggest reduction of early worsening with more gradual reduction of glycemia.

The Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group followed patients for 4 years after the conclusions of the DCCT and found that the benefits of intensive diabetes control persisted even with increasing hyperglycemia (HbA_{1c} increased from 7.2 to 7.9%). This increase in HbA_{1c} in the intensive group combined with a reduction in HbA_{1c} in the group originally assigned to standard care has resulted in essentially equal blood glucose in the two groups for the previous 5 years. Despite the absence of a difference in blood glucose for this period, the benefit in retinopathy prevention between the original standard control group and intensive control group continued to grow (75).

In the U.K. Prospective Diabetes Study (UKPDS), 3,867 newly diagnosed patients with type 2 diabetes (median age 54 years) were randomly assigned to an intensive treatment with a sulfonylurea (chlorpropamide, glibenclamide, or glipizide) or insulin or a conventional policy with diet (76). The aim in the intensive group was a fasting plasma glucose (FPG) level <6 mmol/l, and the aim in the conventional group was the best achievable FPG with diet alone and drugs added only if there were hyperglycemic symptoms or an FPG level >15 mmol/l. Three aggregate end points were used to assess differences between conventional and intensive treatment: any diabetes-related end point (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction), diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia, or sudden death), and all-cause mortality. Over 10 years, HbA_{1c} was 7.0% (6.2–8.2) in the intensive group compared with 7.9% (6.9–8.8) in the conventional group, an 11% reduction. There was no difference in HbA_{1c} among agents in the intensive group. Compared with the conventional group, the risk in the intensive group was 12% lower (95% CI 1–21, $P = 0.029$) for any diabetes-related end point, 10% lower (−11 to 27, $P = 0.34$) for any diabetes-related death, and 6% lower (−10 to 20, $P = 0.44$) for all-cause mortality. Most of the risk reduction in the any diabetes-related aggregate end point category was due to a 25% risk reduction (7–40, $P = 0.0099$) in microvascular end points, including the need for retinal photocoagulation.

Both the DCCT and the UKPDS showed that glycemic control is protective for all levels of control; there is no glycemic threshold below which a reduction in microvascular complications is not observed (77,78). Currently, the recommendation is for maintenance of glucose levels as near normal as possible. There does not appear to be a level below which there is not a reduction of microvascular complications.

However, there are risks to intensive control. The incidence of severe hypoglycemia was three times higher (62 vs. 100 severe hypoglycemic episodes per 100 patient-years) in the DCCT intensive group compared with the conventional group. There were 54 hospitalizations for treatment of severe hypoglycemia in 40 patients in the intensive group and 36 in 27 patients in the conventional treatment group. Some of the serious adverse experiences in that study, such as hospitalizations and possibly deaths while operating motor vehicles, were associated with hypoglycemia. In addition, a less severe side effect of intensive glycemic control was increased weight gain. There was a 33% increased risk of becoming 120% over ideal body weight. At 5 years, patients receiving intensive therapy gained an average of 4.6 kg more than those in the conventional group.

In the UKPDS, patients in the intensive group had more hypoglycemic episodes than those in the conventional group on both types of analysis (both $P < 0.0001$). The rates of major hypoglycemic episodes per year were 0.7% with conven-

Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 7

Table 4—*American Diabetes Association recommendations for glycemic control*

Glycemic control	Level
HbA_{1c}	<7.0%
Preprandial plasma glucose	90–130 mg/dl (5.0–7.2 mmol/l)
Postprandial plasma glucose	<180 mg/dl (<10.0 mmol/l)

tional treatment, 1.0% with chlorpropamide, 1.4% with glibenclamide, and 1.8% with insulin. Weight gain was significantly higher in the intensive group (mean 2.9 kg) than in the conventional group ($P < 0.001$), and patients assigned insulin had greater weight gain (4.0 kg) than those assigned chlorpropamide (2.6 kg) or glibenclamide (1.7 kg).

The American Diabetes Association recommendations for glycemic control are listed in Table 4 (79). However, the practitioner should individualize the glycemic target with the understanding that more stringent glycemic goals, i.e., a normal A1C (<6%), may further reduce complications but with an increased risk of hypoglycemia (particularly in those with type 1 diabetes). In patients with severe or frequent hypoglycemia, less intensive glycemic goals may be indicated. In addition, certain populations (children, pregnant women, and elderly) may require special considerations.

Blood pressure control

Epidemiological observations suggest that hypertension increases the risk and/or progression of diabetic retinopathy and macular edema. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), progression of retinopathy was associated with higher diastolic blood pressure at baseline and an increase in diastolic blood pressure over a 4-year follow-up period (80). Among older-onset patients in the WESDR, increased diastolic blood pressure was associated with a higher incidence of macular edema (81).

In 1998, the UKPDS Study Group reported the effectiveness of tight blood pressure control (82–84). The UKPDS randomized 1,148 hypertensive patients with type 2 diabetes to less tight (<180/105 mmHg) and tight (<150/85 mmHg) blood pressure control with the use of an ACE inhibitor or a β-blocker. With a median follow-up of 8.4 years, a mean blood pressure of 144/82 was achieved in the tight and 154/87 in the less tight control group. Patients in the tight control group had a 34% reduction in progression of retinopathy and a 47% reduced risk of deterioration in visual acuity of three lines compared with the less tight control group. In addition, there were reductions in deaths related to diabetes and stroke. Unlike tight glycemic control, there were no clear adverse reactions to tight blood pressure control. Like glycemic control, tight blood pressure control does require significant effort; almost one-third of patients required three or more medications to control blood pressure. The UKPDS data showed no difference in the efficacy of ACE inhibitors or β-blockers with regard to progression of diabetic retinopathy in type 2 diabetic subjects, suggesting that blood pressure control and not the type of medication is most important in those with hypertension (85).

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial was a prospective randomized trial comparing the effects of intensive and moderate blood pressure control in hypertensive type 2 diabetic subjects (86). The study also compared nisoldipine with enalapril as a first-line antihypertensive agent in terms of the prevention and progression of complications of diabetes. Analysis of the 470 patients in the trial who had hypertension (baseline diastolic blood pressure ≥90 mmHg) showed similar control of blood pressure, blood glucose and lipid concentrations, and smoking behavior in the nisoldipine (237 patients) and enalapril (233 patients) groups throughout 5 years of follow-up. Using a multiple logistic regression model with adjustment for cardiac risk factors, nisoldipine was associated with a higher incidence of fatal and nonfatal myocardial infarctions (a total of 24) than enalapril (a total of 4) (risk ratio 9.5, 95% CI 2.7–33.8). The authors concluded that in patients with diabetes and hypertension, those assigned to calcium channel blockers had a significantly higher incidence of fatal and nonfatal myocardial infarction compared with those assigned to enalapril. Over a 5-year follow-up period, there was no difference between the intensive and moderate groups with regard to the progression of diabetic retinopathy and neuropathy. In addition, the use of nisoldipine versus enalapril had no differential effect on diabetic retinopathy and neuropathy.

To investigate the effect of blood pressure lowering in normotensive subjects, the ABCD randomized 480 patients (blood pressure <140/90 mmHg) to intensive versus moderate diastolic blood pressure control. Patients in the moderate therapy group were given placebo, and patients randomized to intensive therapy received either nisoldipine or enalapril. The primary end point was change in creatinine clearance, with progression of retinopathy as a secondary end point. At 5 years, there was no difference in creatinine clearance ($P = 0.43$), but patients in the intensive group were less likely to progress to microalbuminuria ($P = 0.012$) and to overt albuminuria ($P = 0.028$). In addition, progression of diabetic retinopathy ($P = 0.019$) was less frequent in the intensive group (87).

The Eurodiab Controlled Trial of Lisinopril in Insulin Dependent Diabetes (EUCLID) Study Group investigated the effect of lisinopril in patients with type 1 diabetes who were normotensive and normo- or microalbuminuric (88). After 2 years, the clinical trial showed a statistically significant 50% ($P = 0.02$) reduction in retinopathy progression by at least one level: 13.2% of 159 patients on lisinopril progressed versus 23.4% of 166 patients on placebo. After adjusting for center and glycemic control, the protective effect (0.55, $P = 0.06$) was similar but not statistically significant. The borderline effect in this study and the findings from ABCD may be due to the small benefit of incremental lowering of blood pressure in normotensive patients.

The Diabetic Retinopathy Candesartan Trial (DIRECT), a large randomized controlled clinical trial, has recently begun with the aim of examining the efficacy of ACE inhibitors in preventing the incidence and progression of retinopathy in type 1 and type 2 diabetic subjects (89). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is a randomized, multicenter, double 2 × 2 factorial design study in 10,000 patients with type 2 diabetes (90). It is designed to test the effects on major cardiovascular disease of intensive glycemia control,

Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 8

treatment to increase HDL cholesterol and lower triglycerides (in the context of good LDL cholesterol and glycemia control), and intensive blood pressure control (in the context of good glycemic control). All 10,000 participants will be in the glycemia trial. In addition, one 2 × 2 trial will also address the lipid question in 5,800 of the participants, and the other 2 × 2 trial will address the blood pressure question in 4,200 of the participants. The primary outcome of the ACCORD Eye Study is progression of diabetic retinopathy of at least three stages on the ETDRS scale, photocoagulation, or vitrectomy.

Management of impaired renal function

Retinopathy and nephropathy are two important microvascular complications in diabetic patients with hyperglycemia and hypertension (91). The Microalbuminuria Collaborative Study Group found that retinopathy was not an independent predictor of albuminuria, but the WESDR found that the presence and severity of diabetic retinopathy are still indicators of the risk of developing proteinuria (92,93). Conversely, proteinuria is a known predictor of the development of PDR in type 1 diabetic subjects (94), and gross proteinuria is also associated with a 95% increased risk of developing DME among type 1 diabetic subjects (95). There is controversy as to whether this association is due to hyperglycemia or whether nephropathy is an independent risk factor for diabetic retinopathy.

ACE inhibitors slow the progression of nephropathy. Serum prorenin concentrations have recently been directly correlated with the severity of diabetic retinopathy, and components of the renin-angiotensin system have been found in the eye. These observations imply that the use of ACE inhibitors may also protect against the development and progression of diabetic retinopathy (96). However, the association between the renin-angiotensin system and the development and progression of diabetic retinopathy is not straightforward, and initial results looking at the influence of ACE inhibitors on diabetic retinopathy in normotensive diabetic subjects have had equivocal results. Two recent studies examining the relationship between vitreous and plasma VEGF concentrations and the use of ACE inhibitors demonstrated differing results (97,98). In one study, it was found that the use of ACE inhibitors decreased levels of vitreous VEGF, possibly protecting against the development of PDR, while circulating plasma VEGF levels were not affected by ACE inhibitors in the other.

The EUCLID study, the most recent randomized clinical trial, found that the use of lisinopril in normotensive type 1 diabetic subjects decreased the progression of retinopathy (88). Other studies examining the use of ACE inhibitors in type 1 diabetic subjects have shown nonsignificant benefits upon the progression of diabetic retinopathy (23,24,99,100).

In normotensive type 2 diabetic subjects, treatment of diabetic retinopathy with ACE inhibitors has also had mixed results. One study that used the development of albuminuria as an end point found that ACE inhibitors was beneficial in delaying the progression of retinopathy (14). A recent study looking at the use of ACE inhibitors in normotensive type 2 diabetic subjects used progression to PDR as an end point and was ended prematurely because an interim analysis failed to identify a beneficial effect (19). Given these mixed results, the DIRECT study, a large randomized, double-masked, placebo-controlled trial examining the efficacy of ACE inhibitors (and ACE receptor blockers) in both type 1 and type 2 diabetic subjects is currently underway. Patients with refractory retinopathy and macular edema should have an evaluation of their renal status.

Serum lipid control

A sometimes forgotten systemic risk factor is lipid control. Dyslipidemia is a known risk factor for diabetic renal disease, but the effect of serum lipids on diabetic retinopathy and macular edema is still under investigation (101–105). There is observational evidence that elevated lipids may increase the morbidity of macular edema and affect the severity of diabetic retinopathy. Among insulin-using patients in the WESDR, the presence of retinal hard exudates was significantly associated with increased serum cholesterol levels (106). Likewise, patients in the ETDRS who had elevated serum cholesterol or LDL levels at baseline were more likely to have retinal hard exudates than those with normal levels (107). Development of retinal hard exudates was also 50% more likely in those patients with elevated serum total cholesterol or triglyceride levels. Because the risk of loss in visual acuity was correlated with the degree of retinal hard exudates, reducing serum lipid levels in patients with diabetes and retinopathy may be particularly important. In addition, severe hard exudates can lead to the development of subretinal fibrosis, a complication that can lead to permanent loss of vision (108). Whether intensive lipid-lowering therapy will reduce the severity of retinopathy or the resultant losses in visual acuity remains to be tested in prospective trials.

FUTURE DIRECTIONS

PKC inhibitors

Two PKC inhibitors are being developed to reduce microvascular complications in patients with diabetes. One of these, Ruboxistaurin (LY333531), is a specific inhibitor of PKC-β (109) and has been found to block vascular complications of diabetes, including abnormalities in retinal blood flow, neovascularization, and VEGF-mediated effects on permeability in animal models (110–112). In a small trial ($n = 29$) of diabetic patients with no or minimal retinopathy, the drug was well tolerated with no adverse events noted and normalized mean circulation time and retinal blood flow abnormalities (113). The PKC-β Inhibitor Diabetic Macular Edema Study (PKC-DMES) was a multicenter, multinational, double-masked, placebo-controlled trial with patients followed for up to 52 months. The trial included 686 patients with DME and mild-to-moderate NPDR. There was no statistically significant reduction in progression of retinopathy or incidence of macular edema found in this trial. However, Ruboxistaurin, when given at 32 mg, displayed a trend ($P = 0.041$) toward a positive effect on the secondary outcome of occurrence of DME involving or imminently threatening the center of the macula. When patients with poor glycemic control at baseline were excluded (defined as $HbA_{1c} \geq 10\%$), Ruboxistaurin displayed a borderline positive effect ($P = 0.019$) on the occurrence of DME involving or imminently threatening the center of the macula. Additional clinical trials are under way to assess whether LY333531 can delay or stop the progression of diabetic retinopathy and macular edema at their earliest stages.

The second PKC inhibitor, PKC412,

Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 9

is under development for treatment of diabetic retinopathy and other indications. This compound inhibits multiple PKC isoforms (α, β, and γ) and at least two other receptor kinases (114). Orally administered PKC412 effectively inhibited retinal and choroidal neovascularization in a mouse model (115). The broader inhibitory potential of this drug, however, suggests that it may impede other physiologic processes. In a phase 1 trial of cancer patients, PKC412 was found to be generally tolerable at the doses tested (116), but further studies are needed to investigate the utility of PKC412 in preventing diabetic retinopathy/macular edema.

Macugen

Pegaptanib (Macugen) is a 28-base oligonucleotide (aptamer) that binds VEGF (117). Preliminary analyses suggest that this agent is effective against the neovascular form of age-related macular degeneration. Macugen is currently in being investigated in a phase 3 clinical trial on DME.

Lucentis

Lucentis (ranibizumab) is an antibody fragment directed against VEGF. There are plans to investigate this product in the treatment of DME.

Corticosteroids

Corticosteroids, a class of substances with anti-inflammatory properties, have been demonstrated to inhibit the expression of the VEGF gene (118). In a study of cultured human aortic vascular smooth muscle cells, corticosteroids have been shown to inhibit platelet-derived growth factor–induced expression of the VEGF gene. Corticosteroids also have been shown to reduce the induction of VEGF by proinflammatory mediators in a time- and dose-dependent manner (119).

Triamcinolone acetonide (4 mg/0.1 ml) was injected into the vitreous cavity of 16 eyes with macular edema due to diabetic retinopathy (120). Baseline central foveal thickness averaged 540 μm for the 16 enrolled eyes when measured by optical coherence tomography. At 3 months, 14 eyes (2 eyes did not have 3-month follow-up) showed a reduction in mean foveal thickness from 528 to 224 μm. Mean Snellen visual acuity improved by 2.4, 2.4, and 1.3 lines at the 1-, 3-, and 6-month follow-up intervals, respectively. In another study of intravitreal triamcinolone acetonide injection, best-corrected visual acuity improved from a mean of 20/165 at baseline to a mean of 20/105 at the end of follow-up (121). In comparison, 16 patients followed in a control group that received grid laser photocoagulation showed no improvement in visual acuity. In a study of patients with bilateral diffuse DME refractory to photocoagulation, one eye served as a control and the other received intravitreal triamcinolone acetonide (4 mg/0.1 ml) (122). Baseline central macular thickness measured on optical coherence tomography averaged 510 μm for the 12 eyes injected with triamcinolone acetonide and 474 μm for the 12 eyes in the control group. At 12 weeks of follow-up, 9 of the 12 injected eyes had normal (<206 μm) central macular thickness. No eyes in the control group had normal thickness, and seven eyes had an increase from baseline. Mean ETDRS best-corrected visual acuity scores improved in injected eyes from 47.8 letters at baseline to 52.7 letters at 12 weeks. Control eyes averaged 51.9 letters at baseline and 50.8 letters at 12 weeks.

Although intravitreal triamcinolone appears to have efficacy in these case series, elevated intraocular pressure and cataract formation are important side effects, and their long-term effect on functional outcome is still unknown. In a study by Martidis et al. (120), the average intraocular pressure increased 45, 20, and 13% from baseline at the 1-, 3-, and 6-month follow-up intervals, respectively. Cataract progression that did not require surgery was noted in one eye at the 6-month follow-up. In a study by Jonas et al. (121), the mean intraocular pressure increased from 16.9 mmHg at baseline to a maximal value of 21.3 mmHg during follow-up and decreased to 18.3 mmHg at the 7-month follow-up. No glaucomatous optic nerve damage was detected in any of these eyes, and the intraocular pressure was normalized in all of these eyes. No significant posterior subcapsular cataract or nuclear sclerosis was identified in any of the 18 phakic eyes. In a study by Massin et al. (122), the mean intraocular pressure increased from a mean of 18.2 mmHg at baseline to 20.8 mmHg at 4 weeks and to 20.5 mmHg at 12 weeks. None of the 10 phakic eyes experienced cataract progression.

Oculex is developing a biodegradable, implantable, extended-release product (Posurdex) that delivers the corticosteroid dexamethasone directly to the posterior segment for a period of 35 days. A phase 2 clinical trial was conducted in patients with macular edema due to diabetic retinopathy, retinal vascular occlusive disease, Irvine-Gass syndrome, or uveitis. Patients receiving the 700-μg implant had a statistically significant improvement in visual acuity of two or more lines on the ETDRS chart when compared with patients who did not receive the implant ($P = 0.02$). Patients receiving the 350-μg implant also demonstrated statistically significant decreases in retinal thickness and fluorescein leakage, with a trend toward improvement in visual acuity, indicating a dose response to the treatment. An intraocular pressure elevation to 25 mmHg or more was noted at some point in 32 eyes but all were readily controlled with topical antiglaucoma medication. There was no difference in cataract progression between the study groups, but follow-up was short.

To investigate the safety and efficacy in DME, the National Institutes of Health is sponsoring a clinical trial investigating intravitreal triamcinolone for DME (123).

Vitrectomy

Vitrectomy surgery has been demonstrated to be effective for the treatment of nonclearing vitreous hemorrhage, tractional detachments, and active progressive PDR. There are now reports in the literature suggesting that vitrectomy surgery may be helpful in eyes with refractory macular edema. In some eyes not responsive to laser photocoagulation, tangential tractional forces from the vitreous may be the reason for continued visual loss. The role of the vitreous has been described in cystoid macular edema secondary to uveitis, retinitis pigmentosa, and aphakia (124). Diabetic eyes with macular edema may have a lower rate of posterior vitreous separation (20%) than those without macular edema (55%) (125). In one study of 82 eyes with clinically significant macular edema followed over 6 months, macular edema was more likely to resolve in eyes with posterior vitreous detachment (126). Clinically significant macular edema is defined as one or more of the following: any retinal thickening within 500 μm of the center of the macula, hard exudates associated with retinal

Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 10

Table 5—*Published reports of vitrectomy for diffuse macular edema*

Study (ref. no.)	Eyes	Vitreous findings	Previous focal photocoagulation	Resolution of edema	>2 lines of Snellen acuity increase
Lewis et al. (127)	10	Thickened hyaloid	90%	80%	60%
Van Effenterre et al. (133)	22	Thickened hyaloid	64%	45%	86%
Harbour et al. (128)	7	Thickened hyaloid	57%	57%	57%
Tachi and Ogino (130)	58	Attached hyaloid	19%	98%	53%
Pendergrast et al. (134)	55	Attached and taut hyaloid	85%	82%	49%

thickening within 500 μm of the center of the macula, or one disc area of thickening within one disc diameter of the center of the macula. Tangential vitreomacular traction may arise from contraction of the premacular hyaloidal membrane and cause increased permeability of the retinal vasculature or retinal detachment. In a recent study (127) using optical coherence tomography to evaluate the macula in eyes with DME and thickened posterior hyaloid, a shallow macular traction detachment was observed in eight of nine eyes.

These observations have led some investigators to recommend vitrectomy for patients with refractory DME (Table 5). In several small case series, vitrectomy in eyes with diffuse DME associated with posterior hyaloidal traction was shown to lead to resolution of macular edema (128–130). More recent larger series have confirmed these earlier observations that vitrectomy along with stripping of posterior hyaloid can lead to resolution of macular edema (131,132). Resolution of macular detachment from removal of tangential traction by vitrectomy may explain why vision improves when vitrectomy is performed (127). In every series, eyes that improved with vitrectomy had an intact/attached macular posterior vitreous hyaloid attachment. In all of the series, the authors report impressive visual acuity gains.

However, one cannot conclude that eyes with diffuse macular edema undergoing vitrectomy had a more favorable clinical course than eyes that did not undergo vitrectomy. The natural history of these eyes is unknown because the study did not provide a comparison group. The efficacy of vitrectomy surgery will likely require investigation with a randomized clinical trial.

CONCLUSIONS — Diabetic retinopathy is still a leading cause of blindness. However, our understanding of the pathophysiology of the disease is increasing as new biochemical pathways are identified. Our ability to diagnosis and classify retinopathy is also improving. In addition, the treatment of diabetic retinopathy involves not just laser photocoagulation and vitrectomy surgery but now also includes control of blood glucose, hypertension, and serum lipids. In the near future, clinical trials of several pharmacologic agents may lead to the introduction of additional treatments and reduction in the frequency of visual loss.

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Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 11

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Samsung et al. v. Regeneron IPR2023-00884
Regeneron Pharmaceuticals, Inc. Exhibit 2120 Page 15