Anti-vascular endothelial growth factor therapy for diabetic macular edema

David S. Boyer, J. Jill Hopkins, Jonathan Sorof and Jason S. Ehrlich

Abstract: Diabetes mellitus is a serious health problem that affects over 350 million individuals worldwide. Diabetic retinopathy (DR), which is the most common microvascular complication of diabetes, is the leading cause of new cases of blindness in working-aged adults. Diabetic macular edema (DME) is an advanced, vision-limiting complication of DR that affects nearly 30% of patients who have had diabetes for at least 20 years and is responsible for much of the vision loss due to DR. The historic standard of care for DME has been macular laser photocoagulation, which has been shown to stabilize vision and reduce the rate of further vision loss by 50%; however, macular laser leads to significant vision recovery in only 15% of treated patients. Mechanisms contributing to the microvascular damage in DR and DME include the direct toxic effects of hyperglycemia, sustained alterations in cell signaling pathways, and chronic microvascular inflammation with leukocyte-mediated injury. Chronic retinal microvascular damage results in elevation of intraocular levels of vascular endothelial growth factor A (VEGF), a potent, diffusible, endothelial-specific mitogen that mediates many important physiologic processes, including but not limited to the development and permeability of the vasculature. The identification of VEGF as an important pathophysiologic mediator of DME suggested that anti-VEGF therapy delivered to the eye might lead to improved visual outcomes in this disease. To date, four different inhibitors of VEGF, each administered by intraocular injection, have been tested in prospective, randomized phase II or phase III clinical trials in patients with DME. The results from these trials demonstrate that treatment with anti-VEGF agents results in substantially improved visual and anatomic outcomes compared with laser photocoagulation, and avoid the ocular side effects associated with laser treatment. Thus, anti-VEGF therapy has become the preferred treatment option for the management of DME in many patients.

Keywords: diabetic macular edema, diabetic retinopathy, intravitreal anti-VEGF therapy, vascular endothelial growth factor A

Epidemiology, socioeconomic burden and natural history of diabetic retinopathy and diabetic macular edema

Diabetes epidemic
Diabetes mellitus is a global health problem associated with serious long-term micro- and macrovascular complications and premature death [Centers for Disease Control and Prevention, 2011; International Diabetes Federation, 2011]. In 2011, an estimated 366 million individuals worldwide had diabetes [International Diabetes Federation, 2011], and by 2030, this number is expected to increase to 552 million [International Diabetes Federation, 2011]. According to 2010 estimates, diabetes is the seventh leading cause of death in the USA [Murphy *et al.* 2012], and affects approximately 25.8 million Americans or 8.3% of the population [Centers for Disease Control and Prevention, 2011]. An additional 79 million American adults aged 20 years and over are considered prediabetic based on fasting blood glucose or hemoglobin A1c levels [Centers for Disease Control and Prevention, 2011]. The estimated total cost of diabetes in the USA was US$245 billion in 2012; US$176 billion (72%) was associated with direct medical costs, while US$69 billion (28%) was attributable to indirect

Correspondence to:
David S. Boyer, MD
Retina Vitreous Associates Medical Group, 1127 Wilshire Boulevard, Suite 1620, Los Angeles, CA 90017, USA
vitdoc@aol.com

J. Jill Hopkins, MD
Jonathan Sorof, MD
Jason S. Ehrlich, MD, PhD
Genentech, Inc., South San Francisco, CA, USA

costs (e.g. work-related absenteeism, chronic disability leading to unemployment, and premature mortality) [American Diabetes Association, 2013]. The estimated worldwide healthcare cost attributable to diabetes is projected to total at least US$490 billion in 2030 [Zhang *et al.* 2010a].

Diabetic retinopathy (DR) is the most common microvascular complication of type 1 and type 2 diabetes [Fong *et al.* 2004; American Diabetes Association, 2012], and is more prevalent in patients who have had diabetes for a longer duration [American Diabetes Association, 2012]. In the USA, DR is the leading cause of incident blindness in working-aged adults aged 20−74 years [Centers for Disease Control and Prevention, 2011]. An estimated 28.5% of Americans with diabetes aged over 40 years have DR and one in 12 patients with diabetes has advanced vision-threatening DR [Kempen *et al.* 2004; Centers for Disease Control and Prevention, 2011]. A nationally representative sample of adults in the USA with diabetes aged 40 years and over participating in the National Health and Nutrition Examination Survey found that the prevalence of DR and vision-threatening DR is especially high among racial/ethnic minorities, particularly non-Hispanic black individuals [Zhang *et al.* 2010b]. The World Health Organization has identified DR as a priority eye disease with respect to the prevention of blindness and visual impairment in industrialized countries [World Health Organization, 2010].

Diabetic macular edema (DME) is an advanced, vision-limiting manifestation of DR in which swelling of the central retina causes loss of central vision [Frank, 2004; Johnson, 2009]. The Wisconsin Epidemiologic Study found that the prevalence of DME increases from 0−3% in recently diagnosed individuals to 28−29% in those living with type 1 or 2 diabetes for at least 20 years [Klein *et al.* 1984]. The long-term incidence of DME (over a 10-year period) in the Wisconsin study was highest (25.4%) in older-onset patients (diagnosed with diabetes at ≥30 years of age) with type 2 diabetes who required insulin and lowest (13.9%) in older-onset patients with type 2 diabetes who did not take insulin [Klein *et al.* 1995].

The microvascular complications associated with DR and DME are thought to be caused by chronic hyperglycemia, which results in damage to, and dysfunction of, capillary endothelial cells located in the retina, as well as the other metabolic abnormalities common in diabetes, such as diabetic dyslipidemia, hypertension, and vascular inflammation [Bloomgarden, 2007; Morello, 2007]. Over time, ongoing microvascular damage triggers a well defined succession of pathogenic events in the retina, including capillary nonperfusion and inner retinal ischemia, upregulation of vascular endothelial growth factor A (VEGF), macular edema, and retinal neovascularization; these events can cause loss of vision and, eventually, blindness [Burditt *et al.* 1968; Kohner, 1972; 1991; Morello, 2007; American Academy of Ophthalmology, 2008].

Pathogenesis and natural history of diabetic retinopathy

DR is classified into several stages based on the level of disease severity (Figures 1 and 2) [Ulbig and Hamilton, 1993; American Academy of Ophthalmology, 2008]. Preretinopathy is characterized by hemodynamic changes and vascular permeability with no apparent retinopathy on clinical examination [Ulbig and Hamilton, 1993; American Academy of Ophthalmology, 2008]. Mild nonproliferative DR (NPDR) is characterized by the appearance of microaneurysms, which at moderate stages can develop into intraretinal microvascular abnormalities (IRMAs), intraretinal hemorrhages, and cotton-wool spots, which represent focal infarcts of the retinal nerve fiber layer [Ulbig and Hamilton, 1993; American Academy of Ophthalmology, 2008]. Increased permeability of the retinal vasculature can lead to retinal edema and the formation of protein and lipid-rich deposits, referred to as hard exudates [American Academy of Ophthalmology, 2008]. In severe NPDR, the retinal vasculature gradually closes, which impairs perfusion and leads to retinal ischemia, characterized by venous caliber abnormalities, IRMAs (essentially, neovascularization within the retina), and widespread vascular leakage [Kempen *et al.* 2004; American Academy of Ophthalmology, 2008]. Neovascularization on the surface of the retina, optic nerve, and other structures (such as the iris, in severe cases) characterizes the most advanced stage of DR, known as proliferative DR (PDR; Figure 2) [Morello, 2007]. The abnormal new vessels are fragile and can bleed into the vitreous, causing sudden loss of vision. In some cases, spontaneous contraction of the retinal neovascular membranes detaches the retina from its support structures, a condition known as tractional retinal detachment [Morello, 2007]. Although surgery can be performed to
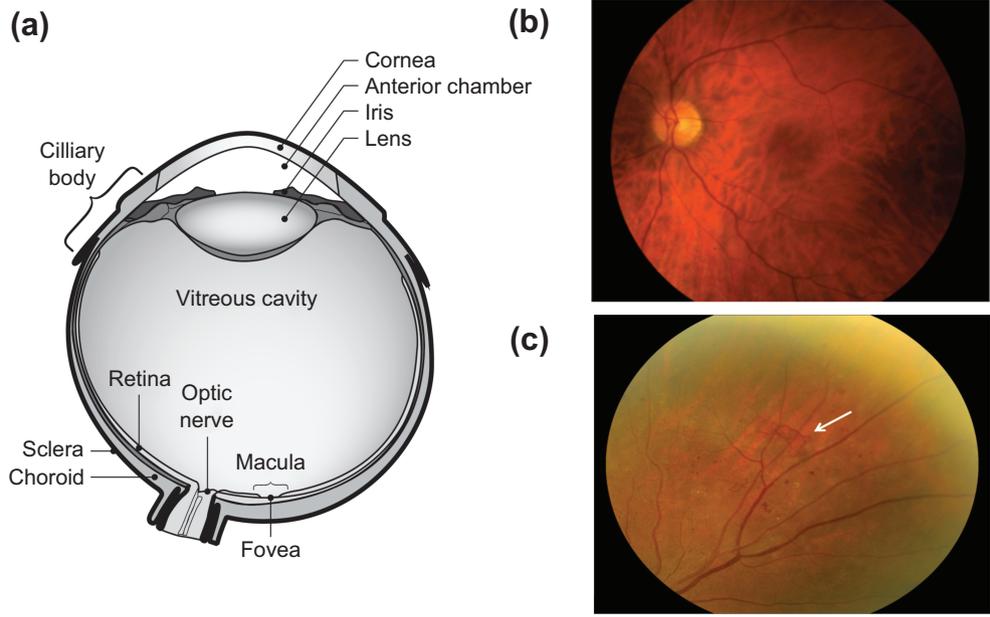
Figure 1. Fundus photographs of a normal retina and a retina with diabetic retinopathy. (a) Normal eye anatomy. (b) Fundus photograph of a normal retina. (c) Fundus photograph of a patient with mild proliferative diabetic retinopathy. Arrow indicates area of neovascularization at baseline. Fundus photographs provided by the University of Wisconsin Fundus Photograph Reading Center.

Pre-retinal neovascularization
Inner retinal ischemia triggers the formation of tortuous leaky vessels prone to causing serious vision-threatening complications such as vitreous hemorrhages and tractional retinal detachment.

Inner retinal ischemia
In DR retinal capillary leukostasis, endothelial damage and capillary closure lead to capillary nonperfusion and inner retinal ischemia.

Microaneurysms
Microaneurysms can result from 'pouching' of the basement membranes of abnormal vessels and tend to surround areas of non-perfusion.

Fundus photograph of patient with PDR

Figure 2. Pathogenesis of diabetic retinopathy (DR). BM, Bruch's membrane; CH, choroid; DR, diabetic retinopathy; GL, ganglion layer; INL, inner nuclear layer; IPL, inner plexiform layer; NF, optic nerve fibers; ONL, outer nuclear layer; OPL, outer plexiform layer; PDR, proliferative diabetic retinopathy; RA, retinal artery; RC, rods and cones; RPE, retinal pigment epithelium; RV, retinal vein.
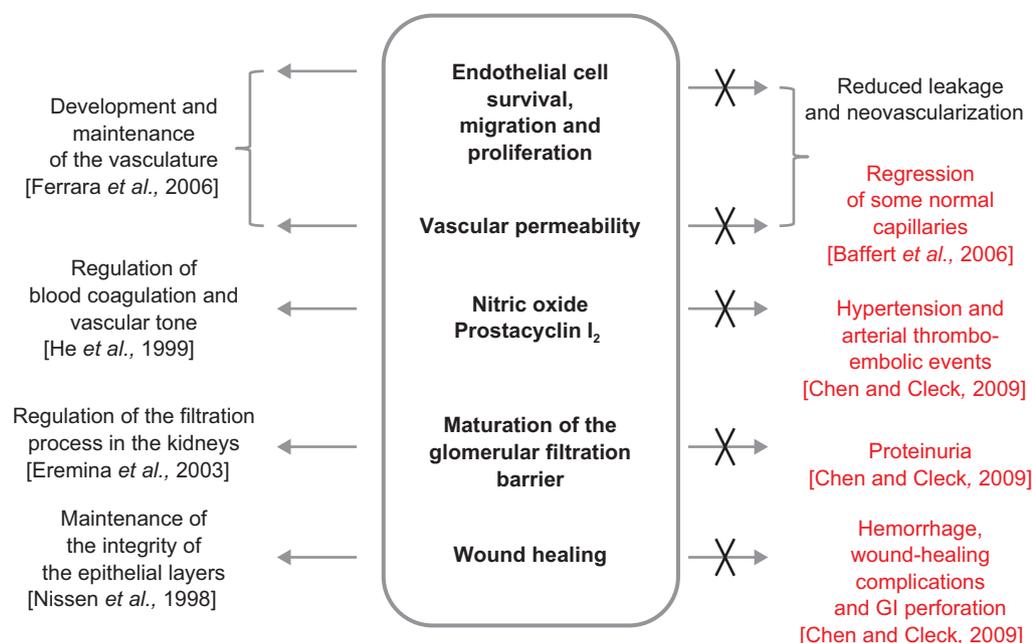
Figure 3. Physiology of vascular endothelial growth factor inhibition. GI, gastrointestinal.

attempt to reattach the retina, vision loss in such cases is frequently significant and irreversible.

Pathogenesis of diabetic macular edema: role of vascular endothelial growth factor

The microvascular injury discussed previously may lead to retinal vascular leakage with accumulation of excess extracellular fluid manifested as DME [Miller *et al.* 2012]. While the molecular pathogenesis of DME is not fully elucidated, it appears that VEGF plays a critical role. VEGF is a potent, diffusible, endothelial-specific mitogen typically found as a homodimer with a molecular weight of approximately 45 kDa [Miller *et al.* 2012]. It mediates many important physiologic processes (Figure 3), including the development and maintenance of the vasculature [Ferrera *et al.* 2003], regulation of blood coagulation and vascular tone through the production of nitric oxide and prostacyclin I_2 [He *et al.* 1999], regulation of the podocytes necessary for glomerular filtration by the kidneys [Eremina *et al.* 2003], and maintenance of integrity of epithelial cell layers during normal wound repair [Nissen *et al.* 1998].

The human VEGF family comprises five related glycoproteins: VEGF-A (commonly known as VEGF), VEGF-B, VEGF-C, VEGF-D and placental growth factor [Ferrera *et al.* 2003, 2006; Papadopoulos *et al.* 2012; Stewart, 2012]. VEGF-A is the best characterized, and is mainly responsible for the angiogenic and vasopermeability activities in adults [Papadopoulos *et al.* 2012; Stewart, 2012]. Alternative splicing and/or proteolytic cleavage of the eight-exon VEGF-A gene gives rise to four main VEGF-A isoforms: $VEGF_{121}$, $VEGF_{165}$ (which appears to be the most abundant), $VEGF_{189}$, and $VEGF_{206}$ [Ferrera *et al.* 2003; Miller *et al.* 2012; Stewart, 2012]. All VEGF family members signal through three trans-membrane tyrosine kinase receptors (VEGFRs): VEGFR-1, VEGFR-2, and VEGFR-3 [Ferrera *et al.* 2003; Papadopoulos *et al.* 2012; Stewart, 2012]. Most of the mitogenic, angiogenic and vascular-hyperpermeability responses to VEGF-A are mediated through VEGFR-2, which is expressed by the vascular endothelium [Miller *et al.* 2012]. Neuropilin 1, an isoform-specific receptor for $VEGF_{165}$, is widely expressed in human adult tissues and has been demonstrated to promote the binding of $VEGF_{165}$ to VEGFR-2 [Miller *et al.* 2012].

In patients with diabetes, chronic hyperglycemia leads to the upregulation of VEGF, resulting in angiogenesis, increased vascular permeability, and the production of proinflammatory cytokines (e.g. intracellular adhesion molecule 1 and tumor necrosis factor α) [Stewart, 2012]. Thickening of the basement membrane and pericyte loss, which are key hallmarks of DR, as well as sheer stress on endothelial cells, may further stimulate VEGF
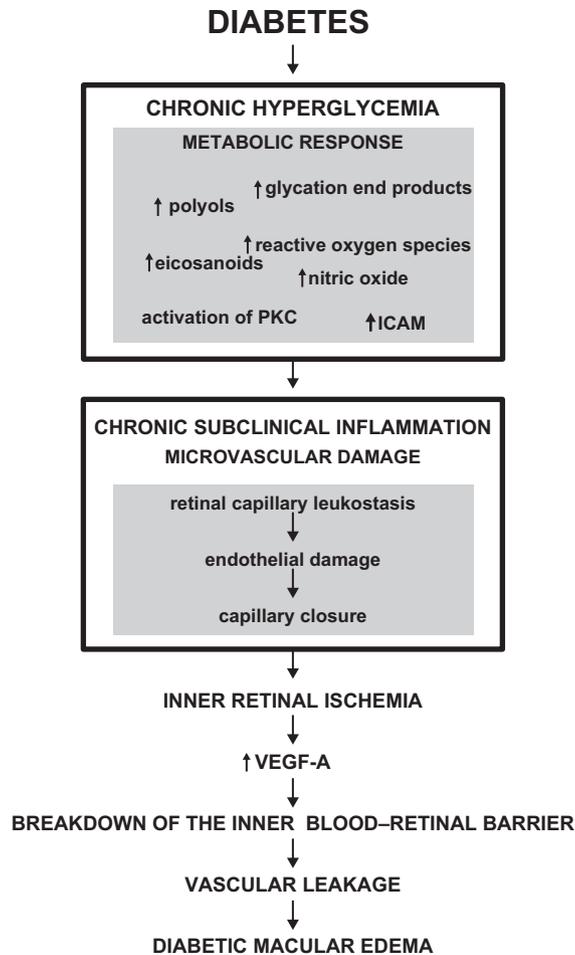
DIABETES

Figure 4. Pathogenesis of diabetic macular edema. ICAM, intercellular adhesion molecule; PKC, protein kinase C; VEGF, vascular endothelial growth factor.

production [Stewart, 2012]. DME occurs when the retinal circulation deteriorates as a result of DR and the resultant ischemia, together with the breakdown of the blood–retinal barrier, leads to extravascular accumulation of serum resulting in macular thickening (Figure 4) [Do *et al.* 2012; Stewart, 2012]. DME is considered clinically significant (CSME) if it involves or threatens to spread to the center of the macula, the portion of the retina responsible for sharp, central vision [Early Treatment Diabetic Retinopathy Study Research Group, 1985; Ryan, 2007].

Data supporting the key role of vascular endothelial growth factor in diabetic retinopathy and diabetic macular edema
VEGF and its receptors, VEGFR-1 and VEGFR-2, are constitutively expressed in normal vascularized intraocular tissues, including the conjunctiva, iris, retina, and choroid-retinal pigment epithelium (RPE) complex [Kim *et al.* 1999]. *In vitro* and *in situ* studies have demonstrated that human RPE cells can synthesize and secrete VEGF [Adamis *et al.* 1993], and VEGF is upregulated in human RPE cells in response to hypoxia [Shima *et al.* 1995]. In multiple nonhuman primate models of ocular angiogenesis, VEGF expression is associated temporally and spatially with development of intraocular neovascularization [Miller *et al.* 1994]. In addition, injections of recombinant human $VEGF_{165}$ into the vitreous of a nonhuman primate are sufficient to produce intraocular neovascularization [Tolentino *et al.* 1996], while inhibition of VEGF by intravitreal administration of a neutralizing anti-VEGF monoclonal antibody [Adamis *et al.* 1996] or antigen binding fragment [Krzystolik *et al.* 2002] prevents neovascularization in this nonhuman primate model.

Intraocular levels of VEGF are elevated in patients with DR and DME. A study evaluating undiluted vitreous samples from 20 eyes of 20 patients (8 with PDR, 12 with other conditions requiring vitrectomy) found that VEGF levels were significantly higher ($p = 0.006$) in the eyes of patients with PDR compared with the eyes of patients without PDR [Adamis *et al.* 1994]. Furthermore, the vitreous concentrations of VEGF in patients with PDR were considered to be physiologically relevant and most likely produced by retinal ischemia [Adamis *et al.* 1994]. In a comparative, cross-sectional study of undiluted aqueous humor samples taken from 54 eyes of 54 patients with DME undergoing cataract surgery, the aqueous levels of VEGF were significantly ($p < 0.001$) associated with the severity of DME [Funatsu *et al.* 2002]. These results demonstrate that VEGF is produced in the intraocular tissues of patients with diabetes and is involved in the pathogenesis of DME [Funatsu *et al.* 2002].

Management of diabetic retinopathy and diabetic macular edema

Management of blood sugar levels, blood pressure, and blood lipids
Intensive glycemic control, blood pressure control, and blood lipid level control are widely accepted ways to reduce the risk of DME [Diabetic Retinopathy Clinical Research Network, 2008]. This concept was illustrated in the Steno-2

study, in which intensive management of hyperglycemia, hypertension, dyslipidemia, and microalbuminaria, together with secondary prevention of cardiovascular disease, significantly reduced the risk of developing DR compared with conventional treatment in accordance with national guidelines (hazard ratio 0.42; 95% confidence interval 0.21−0.86) [Gaede *et al.* 2003]. The importance of hyperglycemia as a risk factor for DR has been demonstrated in an analysis of the Diabetes Prevention Program cohort [Diabetes Prevention Program Research Group, 2007]. In this analysis, 7.9% of patients with elevated fasting glucose and impaired glucose tolerance, and no known history of diabetes developed retinopathy consistent with DR. Among patients with new-onset diabetes (< 3 years in duration), the prevalence of DR was significantly higher at 12.6%. The results from this analysis suggest that retinopathy may occur over a wide range of glucose levels, even in the absence of a diagnosis of diabetes [Diabetes Prevention Program Research Group, 2007]. The importance of strict glucose control was further demonstrated in the 9-year multicenter, randomized Diabetes Control and Complications Trial (DCCT), which found that maintaining near-normal blood glucose levels substantially reduced the risk of DR development or progression in patients with type 1 diabetes compared with conventional therapy [Diabetes Control and Complications Trial Research Group, 1995]. Follow up of the DCCT cohort showed that intensive insulin therapy was associated with a significantly lower incidence of DR progression compared with conventional treatment, and these benefits were maintained for 10 years [White *et al.* 2008].

Controlling hyperglycemia in patients with type 2 diabetes is also associated with slowing DR progression, as has been demonstrated in the UK Prospective Diabetes Study (UKPDS) [UK Prospective Diabetes Study (UKPDS) Group, 1998a]. This randomized, controlled clinical trial in which a sulfonylurea or insulin was used to tightly control blood glucose levels (< 108 mg/dl) in 3,867 patients with newly-diagnosed type 2 diabetes showed that both agents decreased the risk of microvascular complications [UK Prospective Diabetes Study Group, 1998a]. A subset of these patients with diabetes who also had hypertension (*n* = 1148) were randomized to receive the antihypertensive agents captopril or atenolol [UK Prospective Diabetes Study Group, 1998b]. Tight blood pressure regulation
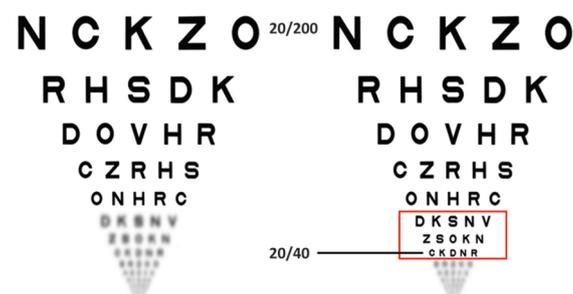
Figure 5. Standard ETDRS chart: example of 15-letter gain (three lines on the ETDRS chart) and 20/40 BCVA Snellen equivalent (minimum driving vision). BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

(< 150/85 mmHg) with either agent resulted in clinically meaningful reductions in the risk of DR progression by at least two-step progression from baseline [34% reduction (*p* = 0.004) by a median of 7.5 years of follow up] and a 47% reduction (*p* = 0.004) in the risk of worsening visual acuity by 15 letters (three lines) on the Early Treatment of Diabetic Retinopathy Study (ETDRS) eye chart (Figure 5) at 9 years of follow up [UK Prospective Diabetes Study Group, 1998b].

Focal/grid laser photocoagulation
Historically, the primary technique used to treat vision-threatening complications of DR was laser photocoagulation surgery [Bloomgarden, 2007; American Academy of Ophthalmology, 2008]. Panretinal (scatter) photocoagulation (PRP), which is one type of laser treatment that places laser burns at the back of the eye to the peripheral retina to promote the regression of abnormal blood vessels, is the current standard of care for PDR [Bloomgarden, 2007; American Academy of Ophthalmology, 2008]. PRP and vitrectomy have been shown to improve the oxygenation of the inner retina [Stefánsson, 2001], and the efficacy of PRP in the treatment of intraocular neovascularization has been studied extensively. Data from large prospective randomized clinical trials support the use of these techniques in the treatment of neovascularization associated with PDR [Diabetic Retinopathy Vitrectomy Study Research Group, 1985, 1988; Diabetic Retinopathy Study Research Group, 1987]. While PRP reduces the rate of severe vision loss by 50% [Diabetic Retinopathy Study Research Group, 1987], the technique is associated with adverse effects due to the destructive nature of laser photocoagulation;

these include peripheral visual field loss, abnormal color and night vision, and reduced central acuity from exacerbation of concomitant DME [Early Treatment Diabetic Retinopathy Study Research Group, 1991; American Academy of Ophthalmology, 2008].

Macular (focal/grid) photocoagulation has typically been used to manage DME; the exact mechanism by which macular laser has an effect remains poorly understood. The ETDRS randomized trial established focal/grid photocoagulation as the standard of care treatment by demonstrating that patients with clinically significant DME treated with macular laser experienced a 50% reduction in moderate vision loss after 3 years compared with untreated patients [Early Treatment Diabetic Retinopathy Study Research Group, 1985]. Patients treated with laser in this study also had an increased chance of gaining vision, and a decreased frequency of persistent DME compared with their untreated counterparts. However, less than 3% of patients treated with laser therapy experienced vision improvement of 15 letters from baseline, or three lines on the ETDRS eye chart [Early Treatment Diabetic Retinopathy Study Research Group, 1985]. While randomized, multicenter trials have demonstrated significant improvements in best-corrected visual acuity (BCVA) in eyes with center-involved DME and visual acuity (VA) up to 20/32 (Snellen equivalent) after laser treatment, these improvements tended to occur slowly (i.e. over a 2-year period) [Diabetic Retinopathy Clinical Research Network, 2008; Elman *et al.* 2011]. Although laser photocoagulation can reduce the risk of further vision loss in patients with DME, the procedure may also cause macular scarring over time with repeated treatment [Bloomgarden, 2007; Ryan, 2007].

Corticosteroids
The pathophysiology of DME provides a rationale for the use of treatments designed to counter anti-inflammatory and anti-VEGF effects within the retina. Intraocular corticosteroids have been evaluated for the treatment of DME because they have anti-inflammatory properties and have been shown to inhibit both VEGF and VEGF gene expression [Diabetic Retinopathy Clinical Research Network, 2008; Stewart, 2012]. Intravitreal administration of triamcinolone (off label) has been shown to reduce DME and improve vision [Stewart, 2012]; however, in randomized, prospective trials, this agent has not demonstrated better outcomes in patients with DME compared with laser photocoagulation [Diabetic Retinopathy Clinical Research Network, 2008; Elman *et al.* 2010].

Sustained delivery systems releasing either dexamethasone (DEX) (Ozurdex, DEX intravitreal implant, Allergan, Inc., Irvine, CA, USA) or fluocinolone acetonide (FA) (Iluvien, FA intravitreal implant, Alimera Sciences, Alpharetta, GA, USA) have also been, and continue to be, evaluated [Campochiaro *et al.* 2011, 2012; Callanan *et al.* 2013]. The Ozurdex DEX implant is a biodegradable copolymer that is placed in the vitreous cavity by intravitreal injection and releases DEX gradually for up to 6 months [Callanan *et al.* 2013]. The DEX implant is approved by the US Food and Drug Administration (FDA) for the treatment of macular edema following branch or central retinal vein occlusion (RVO) and for the treatment of noninfectious posterior segment uveitis (Ozurdex package insert). In the phase II PLACID trial, patients with diffuse DME experienced similar visual improvements (≥10 letters; two lines on the ETDRS chart) from baseline at month 12 whether treated with the DEX implant plus laser or sham implant plus laser [Callanan *et al.* 2013]. However, elevations of intraocular pressure and cataract-related adverse events (AEs) were more common in the DEX plus laser treatment group compared with sham.

The FA implant is a nonbiodegradable cylindrical polymide tube that is injected into the vitreous cavity and releases FA gradually for up to 3 years [Campochiaro *et al.* 2011, 2012; Alimera Sciences, 2013]. Iluvien is available in the UK for use in patients with chronic DME whose condition is considered refractory to existing therapies; however, it is not currently approved by the US FDA for this indication [Alimera Sciences, 2013]. In the phase III FAME study, a higher proportion of patients with persistent DME who were treated with the FA implant experienced vision improvements of at least 15 letters from baseline (three lines on the ETDRS chart) at month 24 [Campochiaro *et al.* 2011] and month 36 [Campochiaro *et al.* 2012] compared with patients receiving sham injection. However, serious AEs (SAEs), including cataract surgery, increased intraocular pressure, and glaucoma requiring incisional surgery, were more frequent in patients receiving the FA insert compared with sham treatment [Campochiaro *et al.* 2011, 2012]. Because of the AEs associated with

corticosteroids, they are not routinely used for the treatment of DME in most patients at this time.

Inhibitors of vascular endothelial growth factor signaling

VEGF inhibitors have been shown to significantly improve vision and restore retinal anatomy in many patients [Nguyen *et al.* 2012a]. Additionally, an exploratory (*post hoc*) analysis suggests that VEGF inhibitors may also prevent or slow the further worsening of DR in many patients with DME [Ip *et al.* 2012]. Four anti-VEGF drugs, administered by intravitreal injection, have been tested in prospective, randomized clinical trials in adult patients (aged ≥ 18 years) with type 1 or type 2 diabetes (Table 1).

Ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA, USA) is currently approved by the US FDA for the treatment of neovascular age-related macular degeneration (wet AMD), macular edema secondary to RVO, and DME (Lucentis package insert). It is the only VEGF inhibitor approved for the treatment of DME. Ranibizumab is a 48 kDa humanized monoclonal anti-VEGF antigen binding fragment specifically designed and manufactured for use in the eye [Ferrara *et al.* 2006; Yu *et al.* 2011] (Lucentis package insert). Amino acid substitutions in the complementarity-determining region (i.e. the antigen-binding site) of ranibizumab enhanced its binding affinity to VEGF-A isoforms [Ferrara *et al.* 2006]. The ranibizumab molecule also lacks a Fc region, which allows for shorter systemic circulation and faster clearance [Ferrara *et al.* 2006]. Ranibizumab potently inhibits the biologic activity of all known isoforms of VEGF [Ferrara *et al.* 2006; Yu *et al.* 2011].

Bevacizumab (Avastin, Genentech, Inc.) is a 149 kDa, full-length, recombinant, humanized monoclonal anti-VEGF antibody that binds all isoforms of VEGF-A [Ferrara *et al.* 2006; Stewart, 2012]. Bevacizumab is neither designed nor manufactured for use in the eye; however, it is used off label, by intravitreal injection, for the treatment of intraocular vascular diseases, including wet AMD, RVO, and DME [Stewart, 2012].

Pegaptanib sodium injection (Macugen, OSI Eyetech, Inc., Cedar Knolls, NJ, USA) is a 28-base RNA aptamer covalently linked to two branched 20 kDa polyethylene glycol moieties (molecular weight of ~50 kDa) that binds potently and specifically to $VEGF_{165}$ [Gragoudas *et al.* 2004] (Macugen package insert) Pegaptanib is approved for the treatment of wet AMD by the US FDA (Macugen package insert).

Aflibercept (Eylea, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) is a 115 kDa recombinant fusion protein consisting of portions of the human VEGFR-1 and VEGFR-2 fused to the Fc domain of human immunoglobulin G1 domain [Holash *et al.* 2002] (Eylea package insert). Aflibercept binds all isoforms of VEGF-A, VEGF-B, and placental growth factor [Holash *et al.* 2002; Papadopoulos *et al.* 2012]. The drug is currently approved in the USA and Europe for the treatment of wet AMD and macular edema following central RVO (Eylea package insert; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002392/WC500135815.pdf).

Investigational agents targeting pathways beyond vascular endothelial growth factor

Although beyond the scope of this review, it is worth noting that many of the novel therapeutics for DME offer alternative entry points into pathways promoting angiogenesis and vascular permeability, and may complement existing anti-VEGF therapies to further improve vision. Ongoing, early clinical trials are investigating therapeutic agents with a variety of targets, such as a kinase downstream of multiple growth factors (including VEGF) [Afzal *et al.* 2007] [ClinicalTrials.gov identifier: NCT01565148], a suppressor of a vascular endothelial receptor tyrosine kinase [Moss, 2013] [ClinicalTrials.gov identifier: NCT01702441], a hypoxia-induced activator of a cellular stress pathway [Nguyen *et al.* 2012b] [ClinicalTrials.gov identifier: NCT01445899], integrins that mediate cell adhesion [Santulli *et al.* 2008] [ClinicalTrials.gov identifier: NCT01749891], and steroid hormone receptors that regulate endothelial cell permeability [Thomas *et al.* 2012] [ClinicalTrials.gov identifier: NCT01821677].

Key clinical trials of intravitreal anti-vascular endothelial growth factor inhibitors in diabetic macular edema

Assessment of efficacy

Assessments of efficacy in key clinical trials of ranibizumab, bevacizumab, pegaptanib, and aflibercept for the management of DME typically

Table 1. Key phase II and phase III clinical trials of anti-vascular endothelial growth factor agents in diabetic macular edema.

Clinical trial (number enrolled)	Treatment: Intervention	Frequency	Duration	Results: Primary outcome measure	Outcome or proportion with outcome (p value for comparison against control)	VA ≥20/40 Snellen equivalent (sufficient for being able to drive)
DRCRnet (n = 691) [Elman *et al.* 2010]	Ranibizumab 0.5 mg + prompt laser	As needed*	3 years	Mean change in BCVA at 1 year	9 letters (p < 0.001)	72%
	Ranibizumab 0.5 mg + deferred laser	As needed*			9 letters (p < 0.001)	70%
	Triamcinolone 4 mg + prompt laser	As needed*			4 letters (p = 0.31)	51%
	Sham injection + prompt laser	As needed*			3 letters	51%
RESOLVE (n = 151) [Massin *et al.* 2010]	Ranibizumab 0.3 mg$	As needed‡	1 year	Mean change in BCVA at 1 year	10.3 letters§ (p < 0.0001)	
	Ranibizumab 0.5 mg$	As needed‡				
	Sham injection	As needed‡			−1.4 letters	
RESTORE (n = 395) [Mitchell *et al.* 2011]	Ranibizumab + laser	As needed*	1 year	Mean change in BCVA at 1 year	5.9 letters (p < 0.0001)	44.9%
	Sham injections + laser	As needed*			0.8 letters	23.6%
READ-2 (n = 126) [Nguyen *et al.* 2009]	Ranibizumab 0.5 mg‖	As needed**	3 years	Mean change in BCVA at 6 months	7.24 letters (p = 0.01)	
	Macular laser photocoagulation¶	As needed**			−0.43 letters	
	Ranibizumab 0.5 mg + macular laser photocoagulation#	As needed**			3.8 letters (p = 0.08)	
RISE (n = 377) [Nguyen *et al.* 2012a]	Ranibizumab 0.3 mg	4 weeks	3 years	Gaining ≥15 ETDRS letters at 24 months	44.8% (p < 0.0001)	60%
	Ranibizumab 0.5 mg	4 weeks			39.2% (p < 0.001)	63.2%
	Sham injection	4 weeks			18.1%	37.8%
RIDE (n = 382) [Nguyen *et al.* 2012a]	Ranibizumab 0.3 mg	4 weeks	3 years	Gaining ≥15 ETDRS letters at 24 months	33.6% (p < 0.0001)	54.4%
	Ranibizumab 0.5 mg	4 weeks			45.7% (p < 0.0001)	62.2%
	Sham injection	4 weeks			12.3%	34.6%
BOLT (n = 80) [Michaelides *et al.* 2010]	Bevacizumab 1.25 mg	As needed‡‡	2 years	Difference in BCVA at 12 months	61.3 letters (p = 0.0006)	
	Macular laser therapy	As needed			50.0 letters	

(Continued)

Table 1. (Continued)

Clinical trial (number enrolled)	Treatment			Results		
	Intervention	Frequency	Duration	Primary outcome measure	Outcome or proportion with outcome (p value for comparison against control)	VA ≥20/40 Snellen equivalent (sufficient for being able to drive)
Macugen DR Study (n = 172) [Cunningham et al. 2005]	Pegaptanib 0.3 mg	As needed$$	36 weeks	Mean change at week 36 in BCVA and CRT, and additional therapy with photocoagulation between weeks 12 and 36	+4.7 letters (p = 0.04) / −68 μm (p = 0.02)	39%
	Pegaptanib 1 mg	As needed$$			+4.7 letters (p = 0.05) / −22.7 μm (p = 0.44)	
	Pegaptanib 3 mg	As needed$$			+1.1 letters (p = 0.55) / −5.3 μm (p = 0.81)	
	Sham injection	As needed$$			−0.4 letters / +3.7 μm	20%
Macugen phase II/III study (n = 260) [Sultan et al. 2011]	Pegaptanib 0.3 mg	6 weeks§§	2 years	Gaining ≥ 10 letters of VA at 1 year	36.8% (p = 0.0047)	
	Sham injection	6 weeks§§			19.7%	
DA VINCI (n = 221) [Do et al. 2011]	Aflibercept 0.5 mg	4 weeks	52 weeks	Mean change in VA and CRT at 24 weeks	+8.6 letters (p ≤ 0.0054) / −144.6 μm (p = 0.0002)	
	Aflibercept 2.0 mg	4 weeks			+11.4 letters (p < 0.00001) / −194.5 μm (p < 0.0001)	
	Aflibercept 2.0 mg	8 weeks||||			+8.5 letters (p ≤ 0.0085) / −127.3 μm (p = 0.0066)	
	Aflibercept 2.0 mg	As needed||||			+10.3 letters (p ≤ 0.0004) / −153.3 μm (p < 0.0001)	
	Macular laser photocoagulation¶¶				+2.5 letters / −67.9 μm	

* After baseline laser treatment (active or sham) and three loading injections administered monthly.

$ Patients initially randomized to ranibizumab 0.3 mg or 0.5 mg treatment groups. After month 1, double dosing was allowed (i.e. 0.3–0.6 mg or 0.5–1.0 mg).

‡ Three initial monthly doses, then PRN treatment through 1 year. Laser photocoagulation was given as rescue therapy using protocol-defined criteria.

§ Results from the pooled ranibizumab treatment groups (0.3–0.6 mg and 0.5–1.0 mg) were reported.

|| Injections at baseline and at months 1, 3, and 5.

¶ Laser treatments at baseline and again at month 3 if center subfield thickness was at least 250 μm.

Injections at baseline and month 3 followed by laser therapy 1 week later.

** After month 6, ranibizumab or laser was administered PRN if center subfield thickness was at least 250 μm.

‡‡ Three loading injections were administered at baseline, week 6, and week 12.

$$ Injections at study entry, week 6, and week 12 with additional injections and/or focal photocoagulation PRN for an additional 18 weeks.

§§ For the first year, then up to every 6 weeks per prespecified criteria.

|||| Three initial monthly doses. Patients received sham injections during visits in which an active dose was not given.

¶¶ By the modified ETDRS protocol. Patients in the laser arm received sham injections at each visit.

BCVA, best corrected visual acuity; CRT, central retinal thickness; ETDRS, Early Treatment of Diabetic Retinopathy Study; PRN, pro re nata (as needed); VA, visual acuity.
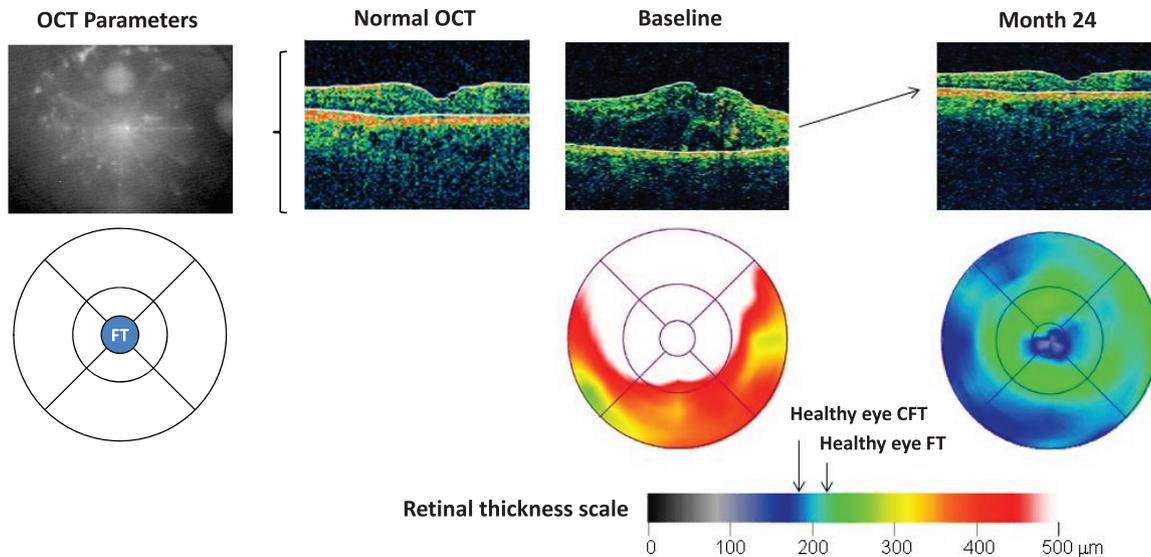
Figure 6. Retinal thickness measured by optical coherence tomography. CFT, central foveal thickness (mean thickness at the point of intersection of six radial scans) on the OCT; FT, foveal thickness (mean thickness in the central 1000 μm diameter area); OCT, optical coherence tomography. Images provided by the University of Wisconsin Fundus Photograph Reading Center.

measure changes in a patient's ability to distinguish detail (VA), measured using the standardized ETDRS eye chart (Figure 5). The most common measure used is BCVA, which corresponds to the best possible VA achieved using corrective lenses. Improved BCVA is indicated by the ability to distinguish individual letters in the rows further down the eye chart.

Common VA-based measures of clinical efficacy used in these studies include mean change from baseline in BCVA, clinically significant BCVA gain of at least 15 letters (three lines) based on the ETDRS eye chart, achievement of a Snellen equivalent of 20/40 or better (Figure 5), and maintenance of vision (i.e. loss of <15 ETDRS letters). An improvement of at least 15 letters on the ETDRS eye chart is considered clinically significant and has also been shown to correlate with clinically meaningful improvements in patient-perceived visual function as measured by the National Eye Institute standardized Visual Function Questionnaire (NEI VFQ-25) [Suñer *et al.* 2009]. Similarly, achievement or maintenance of a Snellen equivalent of 20/40 or better has important quality of life implications, as this is the minimum requirement (in at least one eye) for a driver's license in most states in the USA [Steinkuller, 2010]. The change in retinal thickness from baseline measured by optical coherence tomography (OCT) is also

commonly used to assess efficacy, as reductions in central retinal thickness (CRT) indicate resolution of macular edema (Figure 6).

Review of efficacy findings

Ranibizumab. Several prospective clinical studies in patients with DME, including READ-2, RESOLVE, RESTORE, DRCR.net Protocol I, and RISE/RIDE have demonstrated that intravitreal ranibizumab reduces macular edema and sustainably improves vision in this patient population (Table 1) [Nguyen *et al.* 2009, 2010, 2012a, Elman *et al.* 2010, 2011, 2012; Massin *et al.* 2010; Mitchell *et al.* 2011; Do *et al.* 2013]. In several of these studies, ranibizumab was found to be significantly superior to macular laser therapy [Nguyen *et al.* 2009, 2010; Elman *et al.* 2010, 2011; Mitchell *et al.* 2011].

In the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I phase III study, ranibizumab combined with prompt or deferred (by ≥24 weeks) focal/grid laser generated significantly greater mean changes from baseline in BCVA after months 12 and 24 than laser alone or combined with corticosteroid (triamcinolone) (Table 1) [Elman *et al.* 2010, 2011]. These vision gains were generally maintained at month 36 in ranibizumab-treated patients, although prompt laser treatment provided no added benefit, and

possibly worsened visual outcomes over time compared with deferred laser treatment [Elman *et al.* 2012]. Similarly, in the 12-month, phase III RESTORE study there was a significantly greater mean change in BCVA from baseline at month 12 for ranibizumab treatment alone or combined with laser therapy compared with laser monotherapy (Table 1) [Mitchell *et al.* 2011]. A significantly greater percentage of patients achieved a Snellen equivalent of 20/40 or better in the ranibizumab groups compared with laser alone, and demonstrated significantly greater reductions from baseline in CRT. Patients in the two ranibizumab groups also reported better health-related quality of life changes from baseline at month 12 *versus* laser alone, as assessed by the NEI VFQ-25 [Mitchell *et al.* 2011].

More recently, two parallel, methodologically identical, 3-year phase III clinical trials (RISE and RIDE) compared monthly ranibizumab 0.3 mg and 0.5 mg with sham injection [Nguyen *et al.* 2012a]. In both studies, significantly more ranibizumab-treated patients gained at least 15 letters from baseline at month 24 compared with the sham-treated group, and the percentage of patients achieving a Snellen equivalent of 20/40 or better was also significantly greater in ranibizumab-treated patients at month 24 *versus* sham (Table 1) [Nguyen *et al.* 2012a]. Macular edema was also significantly improved on time-domain OCT compared with sham treatment, while retinopathy was less likely to worsen and more likely to improve. Ranibizumab-treated patients also required significantly fewer macular laser procedures than sham-treated patients [Nguyen *et al.* 2012a]. The importance of early treatment with ranibizumab was highlighted at the month 36 endpoint of the RISE and RIDE trials, in which lesser BCVA gains were observed in patients who crossed over from sham to ranibizumab 0.5 mg after month 24 compared with the vision gains observed in patients who had been randomized to receive ranibizumab from the beginning of the studies [Brown *et al.* 2013].

Bevacizumab. Intravitreal bevacizumab has been compared to modified ETDRS macular laser therapy in 80 patients (80 eyes) with center-involved CSME in a 2-year single-center study (BOLT) [Michaelides *et al.* 2010; Rajendram *et al.* 2012]. Mean BCVA at month 12 (the primary endpoint) was significantly better in the group receiving bevacizumab compared with the macular laser-treated group (Table 1). Bevacizumab-treated patients also gained significantly more letters and had 5.1

times higher odds of gaining at least 10 letters (two lines on the ETDRS chart) over the 12-month study period compared with the macular laser arm [Michaelides *et al.* 2010]. There was also a greater reduction in central macular thickness at month 12 in the bevacizumab group, although this was not statistically significant [Michaelides *et al.* 2010]. The visual and anatomic improvements seen with bevacizumab treatment were maintained at 24 months [Rajendram *et al.* 2012].

Pegaptanib. In the 36-week, phase II, dose-ranging Macugen DR study, patients with diabetes with center-involved DME who received pegaptanib 0.3 mg every 6 weeks for a minimum of three injections had a significantly better gain in BCVA from baseline at 36 weeks compared with sham-injected controls and a significantly greater reduction in mean CRT compared with baseline (Table 1) [Cunningham *et al.* 2005]. However, while both the percentage of patients who gained at least 15 letters in BCVA at week 36 and the percentage of patients achieving a VA of 20/40 or better were numerically higher in the pegaptanib 0.3 mg group compared with sham-injected patients, these results were not statistically significant. Patients who received the pegaptanib 1.0 or 3.0 mg doses showed no statistically significant improvements *versus* the sham-treated group (Table 1) [Cunningham *et al.* 2005]. In a 2-year phase II/III clinical trial in 260 patients comparing pegaptanib 0.3 mg every 6 weeks with sham treatment, significantly more pegaptanib-treated patients gained at least 10 letters in BCVA compared with sham (Table 1), although there was no significant difference between the two groups in the percentage of patients with at least a 15-letter BCVA gain [Sultan *et al.* 2011]. After 102 weeks, change in BCVA from baseline was significantly greater in the pegaptanib group, while significantly fewer patients treated with pegaptanib required salvage grid laser photocoagulation at weeks 54 and 102 [Sultan *et al.* 2011].

Aflibercept. An exploratory study demonstrated that a single intravitreal injection of aflibercept improved VA and reduced retinal thickness in five patients with DME [Do *et al.* 2009]. More recently, four different doses and dosing regimens of intravitreal aflibercept were evaluated *versus* focal/grid laser photocoagulation in eyes with center-involved DME in the 1-year, phase II DA VINCI study (Table 1) [Do *et al.* 2011, 2012]. After 6 months of treatment, the mean change from baseline in BCVA was significantly greater in all the aflibercept dose groups compared with

laser-treated patients (Table 1), as was the change from baseline in CRT [Do *et al.* 2011]. These benefits were maintained to 12 months [Do *et al.* 2012]. However, while the percentage of patients treated with aflibercept who gained at least 15 letters from baseline was numerically superior compared with laser, this difference was not significant at either 6 or 12 months [Do *et al.* 2011].

Two phase III, similarly designed, randomized, double-masked, active control studies of aflibercept for DME (VIVID-DME and VISTA-DME) are currently ongoing and the 1-year results were recently reported [ClinicalTrials.gov identifier: NCT01331681, NCT01783886; Regeneron, 2013]. In these studies, patients received either aflibercept 2.0 mg monthly or every 2 months following five monthly loading doses, or laser photocoagulation [Regeneron, 2013]. After 1 year of treatment, the mean change from baseline in BCVA was significantly greater with either aflibercept regimen compared with laser treatment alone [Regeneron, 2013].

Review of safety findings

All currently available ocular anti-VEGF treatments are administered via intravitreal injection. Effective treatment generally requires repeated injections over a prolonged period (months to years), leading to the potential for ocular complications. Commonly reported ocular AEs include endophthalmitis (which is usually a result of the injection procedure), subconjunctival hemorrhage, increased intraocular pressure, and intraocular inflammation. However, data from clinical trials to date indicate that ocular AE rates in patients treated with anti-VEGF agents are generally low and comparable to sham treatment, with most AEs being mild or moderate and self-limiting [Cunningham *et al.* 2005; Nguyen *et al.* 2009, 2012a; Elman *et al.* 2010, 2011, 2012; Massin *et al.* 2010; Michaelides *et al.* 2010; Do *et al.* 2011, 2012; Sultan *et al.* 2011; Rajendram *et al.* 2012; Brown *et al.* 2013]. The reported rates of ocular SAEs are also low [Cunningham *et al.* 2005; Nguyen *et al.* 2009, 2012a; Elman *et al.* 2010, 2011, 2012; Massin *et al.* 2010; Michaelides *et al.* 2010; Do *et al.* 2011, 2012; Sultan *et al.* 2011; Rajendram *et al.* 2012; Brown *et al.* 2013]. Furthermore, in patients with DME, rates of procedure-related complications are to a certain extent balanced by decreased rates of VEGF-mediated ocular complications of diabetes, such as proliferative retinopathy, vitreous hemorrhage,

and neovascular glaucoma [Ip *et al.* 2012]. Patients with diabetes are more susceptible to systemic infections, so a potentially increased rate of endophthalmitis was a concern when DME studies were initiated; however, endophthalmitis has been reported infrequently, and at per-injection rates of around 0.05%/injection, were identical to those seen with intravitreal injections of anti-VEGF agents for wet AMD [Cunningham *et al.* 2005; Nguyen *et al.* 2009, 2012a; Elman *et al.* 2010, 2011, 2012; Massin *et al.* 2010; Michaelides *et al.* 2010; Do *et al.* 2011, 2012; Sultan *et al.* 2011; Rajendram *et al.* 2012; Brown *et al.* 2013].

The use of intravenous VEGF inhibitors in patients with various forms of cancer suggests that systemic inhibition of VEGF signaling may be associated with various AEs, including regression of some normal capillaries [Baffert *et al.* 2006], as well as hypertension and arterial thromboembolic events (myocardial infarction and cerebrovascular accidents), proteinuria, hemorrhage, wound-healing complications, and gastrointestinal perforation [Chen and Cleck, 2009]. Patients with DME are typically at higher risk of myocardial infarction and cerebrovascular accidents than patients with diabetes without DME [Hirai *et al.* 2008]. However, in general, rates of these categories of AEs were low in patients with DME treated with intravitreal anti-VEGFs, although the rates of AEs potentially related to systemic VEGF inhibition were higher in patients treated with intravitreal anti-VEGF than in sham-treated patients [Cunningham *et al.* 2005; Do *et al.* 2011; Sultan *et al.* 2011; Nguyen *et al.* 2012a; Brown *et al.* 2013].

A benefit–risk analysis of pooled 36-month efficacy and safety data from the RISE and RIDE trials in which patients were treated with intravitreal ranibizumab monthly for 36 months found both the ranibizumab 0.3 mg dose (approved by the US FDA; Lucentis package insert) and the 0.5 mg dose (approved by the European Medicines Agency) [European Medicines Agency, 2013] to be comparably effective [Brown *et al.* 2013]. Both doses demonstrated an acceptable overall risk–benefit profile; however, the incidence of several categories of AEs potentially related to systemic VEGF inhibition were higher in the 0.5 mg group compared with the 0.3 mg group [Brown *et al.* 2013]. The incidences of SAEs potentially related to systemic VEGF inhibition in the ranibizumab 0.3 mg and 0.5 mg groups, and the sham group through 24 months of treatment were 5.6%, 11.9%, and 10.6% in RISE and 9.6%, 5.6%, and 9.4% in RIDE respectively [Nguyen

et al. 2012a]. The US product labeling for ranibizumab includes appropriate warnings and precautions regarding the rates of these events in patients with DME (Lucentis package insert).

An important question is the comparative efficacy, intraocular safety, and systemic safety of the three most commonly used anti-VEGF agents for DME because these molecules differ in design, potency of VEGF inhibition, and systemic exposure when administered intravitreally. The safety profiles of ranibizumab and bevacizumab in wet AMD have been directly compared in three major randomized trials [Martin *et al.* 2011, 2012; Chakravarthy *et al.* 2012; Krebs *et al.* 2013], and in large-scale analyses of Medicare claims databases [Gower *et al.* 2011; Curtis *et al.* 2012]. In the CATT trial, patients treated with bevacizumab experienced a significantly higher rate of SAEs through 2 years of follow up compared with patients treated with ranibizumab: 234/586 (39.9%) *versus* 190/599 (31.7%) respectively, $p = 0.004$ [Martin *et al.* 2011, 2012]. Data from the IVAN trial indicate that bevacizumab suppresses systemic VEGF levels to a greater extent than ranibizumab [Chakravarthy *et al.* 2012]. However, there is uncertainty whether such suppression has any link to the rates of SAEs. An ongoing, independent DRCR.net comparative effectiveness study will compare the efficacy and safety of intravitreal ranibizumab, bevacizumab, and aflibercept in patients with DME [ClinicalTrials.gov identifier: NCT01627249].

Summary of efficacy and safety findings

Taken together, the results from these key clinical trials in patients with DME demonstrate that intravitreal anti-VEGF inhibitors improve visual and anatomic outcomes better than the historic standard of care (i.e. macular laser) and represent an effective treatment option for the management of DME. Currently, ranibizumab is the only VEGF inhibitor approved by the US FDA and the European Medicines Agency for the treatment of DME.

Importance of screening, patient education, and compliance in the detection and management of diabetic retinopathy and diabetic macular edema

DR is often asymptomatic until vision loss develops [Bragge *et al.* 2011; Bursell *et al.* 2012]. Therefore, early referral to an eye care provider is critically important for preserving the vision of patients with diabetes. The American Diabetes Association recommends that patients with type 1 diabetes receive their first dilated and comprehensive eye examination performed by an ophthalmologist or optometrist within 5 years after diabetes onset, with yearly follow up thereafter [American Diabetes Association, 2012]. For patients with type 2 diabetes, the first dilated and comprehensive eye examination should take place shortly after diagnosis, with exams repeated annually thereafter [American Diabetes Association, 2012]. Follow-up exams can occur less frequently (every 2−3 years) following at least one normal exam, but are required more often if retinopathy is progressing [American Diabetes Association, 2012]. In particular, recent screening data from the UK suggest that patients with established DR in both eyes may worsen at higher rates compared with other patients and may require particularly close follow up [Stratton *et al.* 2012]. However, despite these guidelines, it is estimated that nearly 50% of patients with diabetes do not receive eye examinations on a regular basis [Bursell *et al.* 2012].

The detection and management of DR and DME requires prompt and effective communication and cooperation between primary care physicians, diabetologists, and ophthalmologists [Haas *et al.* 2012]. It also requires that healthcare providers educate their patients with diabetes about the need for annual preventative care (e.g. eye, foot, and dental examinations), which is effective in reducing the risk of diabetes-related complications, including vision loss [Bragge *et al.* 2011; American Diabetes Association, 2012; Yuen, 2012]. However, a recently published survey of patients with type 2 diabetes found that nearly 30% of respondents (44/147) had not received a dilated eye examination in the past year; approximately 23% of these individuals (10/44) were unaware that a dilated eye exam was recommended [Crosby and Shuman, 2011]. A separate study conducted by the Joslin Vision Network to evaluate patient awareness of their DR and timeliness of follow up ($n = 2795$) demonstrated that over 82% of patients with DR and over 78% of patients with vision-threatening DR did not know they had retinopathy despite continued eye care [Soliman *et al.* 2011].

Educating patients about the need for annual preventative care does increase patient compliance. A study among adults with diabetes ($n =$

253) found that patients were 4.3 times more likely to have an eye examination in the past 12 months if a healthcare professional recommended that they have their eyes checked once a year ($p < 0.05$) [Yuen, 2012]. Prevention programs geared toward improving eye care for patients with diabetes have been shown to result in substantial cost savings to the US federal budget and to help reduce the economic burden to society [Javitt and Aiello, 1996].

Conclusion

The previous standard of care for patients with DME has focused on the prevention of further deterioration in vision using macular laser once some degree of loss has already occurred, with very few patients experiencing any subsequent gains in vision. Studies of the pathophysiology of DME demonstrate a crucial role for VEGF in disease development and this has led to successful clinical trials of VEGF inhibitors. Data from several large, prospective randomized clinical trials indicate that, on average, intraocular inhibition of VEGF is associated with rapid resolution of DME (as indicated by reduction of the thickness of the retina) and significant VA gains, better than those achieved with focal/grid laser photocoagulation, demonstrating that the focus of treatment should be on improvements in vision and not the prevention of further worsening. Prior studies showed the importance of early diagnosis and treatment of clinically significant edema with laser and this remains the case with the new treatments that are being developed. Therefore, to ensure that patients who have vision loss as a result of diabetes have the best possible VA outcomes, it is important that they are promptly referred to an ophthalmologist (preferably a retina specialist) for diagnosis and appropriate treatment. In an era when new treatments are available for DME, it is crucial for all patients with diabetes mellitus to be appropriately screened for DR in order to prevent vision loss and to identify those at risk of losing vision.

Conflict of interest statement

David S. Boyer: consultant (Alcon, Allegro, Allergan, Eyetech, Genentech, Inc., Novartis/QLT, Neurotech, Ohr, Pfizer, Regeneron), speakers bureau (Alcon, Allergan, Genentech, Inc., Pfizer), clinical research projects (Alcon, Allergan, Genentech, Inc., Pfizer, Regeneron); J. Jill Hopkins, Jonathan Sorof, and Jason S. Ehrlich are employees of Genentech, Inc., a member of the Roche Group, and hold equity and/or options in Roche.

References

Adamis, A., Miller, J., Bernal, M., D'Amico, D., Folkman, J., Yeo, T. *et al.* (1994) Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol* 118: 445–450.

Adamis, A., Shima, D., Tolentino, M., Gragoudas, E., Ferrara, N., Folkman, J. *et al.* (1996) Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. *Arch Ophthalmol* 114: 66–71.

Adamis, A., Shima, D., Yeo, K., Yeo, T., Brown, L., Berse, B. *et al.* (1993) Synthesis and secretion of vascular permeability factor/vascular endothelial growth factor by human retinal pigment epithelial cells. *Biochem Biophys Res Commun* 193: 631–638.

Afzal, A., Shaw, L., Ljubimov, A., Boulton, M., Segal, M. and Grant, M. (2007) Retinal and choroidal microangiopathies: therapeutic opportunities. *Microvasc Res* 74: 131–144.

Alimera Sciences (2013) Alimera Sciences announces ILUVIEN® now available in U.K. Available at: http://investor.alimerasciences.com/releasedetail.cfm?ReleaseID=759915 (accessed 12 September 2013).

American Academy of Ophthalmology (2008) Preferred practice pattern® guidelines. Available at: http://www.aao.org/ppp (accessed 30 October 2013).

American Diabetes Association (2012) Standards of medical care in diabetes – 2012. *Diabetes Care* 35(Suppl. 1): S11–S63.

American Diabetes Association (2013) Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 36: 1033–1046.

Baffert, F., Le, T., Sennino, B., Thurston, G., Kuo, C., Hu-Lowe, D. *et al.* (2006) Cellular changes in normal blood capillaries undergoing regression after inhibition of VEGF signaling. *Am J Physiol Heart Circ Physiol* 290: H547–H559.

Bloomgarden, Z. (2007) Screening for and managing diabetic retinopathy: current approaches. *Am J Health Syst Pharm* 64(17, Suppl. 12): S8–S14.

Bragge, P., Gruen, R., Chau, M., Forbes, A. and Taylor, H. (2011) Screening for presence or absence of diabetic retinopathy: a meta-analysis. *Arch Ophthalmol* 129: 435–444.

Brown, D., Nguyen, Q., Marcus, D., Boyer, D., Patel, S., Feiner, L. *et al.* (2013) Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* 120: 2013-2022.

Burditt, A., Caird, F. and Draper, G. (1968) The natural history of diabetic retinopathy. *Q J Med* 37: 303–317.

Bursell, S., Brazionis, L. and Jenkins, A. (2012) Telemedicine and ocular health in diabetes mellitus. *Clin Exp Optom* 95: 311–327.

Callanan, D., Gupta, S., Boyer, D., Ciulla, T., Singer, M., Kuppermann, B. *et al.* (2013) Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema. *Ophthalmology* 120: 1843–1851.

Campochiaro, P., Brown, D., Pearson, A., Chen, S., Boyer, D., Ruiz-Moreno, J. *et al.* (2012) Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology* 119: 2125–2132.

Campochiaro, P., Brown, D., Pearson, A., Ciulla, T., Boyer, D., Holz, F. *et al.* (2011) Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology* 118: 626–635 e2.

Centers for Disease Control and Prevention (2011) National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf (accessed 15 October 2012).

Chakravarthy, U., Harding, S., Rogers, C., Downes, S., Lotery, A., Wordsworth, S. *et al.* (2012) Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology* 119: 1399–1411.

Chen, H. and Cleck, J. (2009) Adverse effects of anticancer agents that target the VEGF pathway. *Nat Rev Clin Oncol* 6: 465–477.

Crosby, M. and Shuman, V. (2011) Physicians' role in eye care of patients with diabetes mellitus – are we doing what we need to? *J Am Osteopath Assoc* 111: 97–101.

Cunningham, E., Jr, Adamis, A., Altaweel, M., Aiello, L., Bressler, N., D'Amico, D. *et al.* (2005) A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology* 112: 1747–1757.

Curtis, L., Hammill, B., Qualls, L., DiMartino, L., Wang, F., Schulman, K. *et al.* (2012) Treatment patterns for neovascular age-related macular degeneration: analysis of 284 380 Medicare beneficiaries. *Am J Ophthalmol* 153: 1116–1124.

Diabetes Control and Complications Trial Research Group (1995) The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 44: 968–983.

Diabetes Prevention Program Research Group (2007) The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. *Diabet Med* 24: 137–144.

Diabetic Retinopathy Clinical Research Network (2008) A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 115: 1447–1459.

Diabetic Retinopathy Study Research Group (1987) Indications for photocoagulation treatment of diabetic retinopathy: Diabetic Retinopathy Study Report no. 14. *Int Ophthalmol Clin* 27: 239–253.

Diabetic Retinopathy Vitrectomy Study Research Group (1985) Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Two-year results of a randomized trial. Diabetic Retinopathy Vitrectomy Study Report 2. *Arch Ophthalmol* 103: 1644–1652.

Diabetic Retinopathy Vitrectomy Study Research Group (1988) Early vitrectomy for severe proliferative diabetic retinopathy in eyes with useful vision. Results of a randomized trial – Diabetic Retinopathy Vitrectomy Study Report 3. *Ophthalmology* 95: 1307–1320.

Do, D., Nguyen, Q., Boyer, D., Schmidt-Erfurth, U., Brown, D.,Vitti, R. *et al.* (2012) One-year outcomes of the DA VINCI Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology* 119: 1658–1665.

Do, D., Nguyen, Q., Khwaja, A., Channa, R., Sepah, Y., Sophie, R. *et al.* (2013) Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment. *JAMA Ophthalmol* 131: 139–145.

Do, D., Nguyen, Q., Shah, S., Browning, D., Haller, J., Chu, K. *et al.* (2009) An exploratory study of the safety, tolerability and bioactivity of a single

intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema. *Br J Ophthalmol* 93: 144–149.

Do, D., Schmidt-Erfurth, U., Gonzalez, V., Gordon, C., Tolentino, M., Berliner, A. *et al.* (2011) The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology* 118: 1819–1826.

Early Treatment Diabetic Retinopathy Study Research Group (1985) Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 103: 1796–1806.

Early Treatment Diabetic Retinopathy Study Research Group (1991) Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology* 98(Suppl. 5): 766–785.

Elman, M., Aiello, L., Beck, R., Bressler, N., Bressler, S., Edwards, A. *et al.* (2010) Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 117: 1064–1077.

Elman, M., Bressler, N., Qin, H., Beck, R., Ferris, F., III, Friedman, S. *et al.* (2011) Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 118: 609–614.

Elman, M., Qin, H., Aiello, L., Beck, R., Bressler, N., Ferris, F., III *et al.* (2012) Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology* 119: 2312–2318.

Eremina, V., Sood, M., Haigh, J., Nagy, A., Lajoie, G., Ferrara, N. *et al.* (2003) Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. *J Clin Invest* 111: 707–716.

European Medicines Agency (2013) Lucentis: EPAR – all authorized presentations EMEA/H/C/000715 -IAIN/0039. Available at: http://www.ema.europa. eu/docs/en_GB/document_library/EPAR_-_Product_ Information/human/000715/WC500043546.pdf (accessed 31 July 2013).

Ferrara, N., Gerber, H. and LeCouter, J. (2003) The biology of VEGF and its receptors. *Nat Med* 9: 669–676.

Ferrara, N., Damico, L., Shams, N., Lowman, H. and Kim, R. (2006) Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina* 26: 859–870.

Fong, D., Aiello, L., Ferris, F., III and Klein, R. (2004) Diabetic retinopathy. *Diabetes Care* 27: 2540–2553.

Frank, R. (2004) Diabetic retinopathy. *N Engl J Med* 350: 48–58.

Funatsu, H., Yamashita, H., Noma, H., Mimura, T., Yamashita, T. and Hori, S. (2002) Increased levels of vascular endothelial growth factor and interleukin-6 in the aqueous humor of diabetics with macular edema. *Am J Ophthalmol* 133: 70–77.

Gaede, P., Vedel, P., Larsen, N., Jensen, G., Parving, H. and Pedersen, O. (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 348: 383–393.

Gower, E., Cassard, S., Chu, L., Varma, R. and Klein, R. (2011) Adverse event rates following intravitreal injection of avastin or lucentis for treating age-related macular degeneration [Abstr 6644], 2011 ARVO Annual Meeting, Fort Lauderdale, FL, USA.

Gragoudas, E., Adamis, A., Cunningham, E., Jr, Feinsod, M. and Guyer, D. (2004) Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 351: 2805–2816.

Haas, L., Maryniuk, M., Beck, J., Cox, C., Duker, P., Edwards, L. *et al.* (2012) National standards for diabetes self-management education and support. *Diabetes Educ* 38: 619–629.

He, H., Venema, V., Gu, X., Venema, R., Marrero, M. and Caldwell, R. (1999) Vascular endothelial growth factor signals endothelial cell production of nitric oxide and prostacyclin through flk-1/KDR activation of c-Src. *J Biol Chem* 274: 25130–25135.

Hirai, F., Knudtson, M., Klein, B. and Klein, R. (2008) Clinically significant macular edema and survival in type 1 and type 2 diabetes. *Am J Ophthalmol* 145: 700–706.

Holash, J., Davis, S., Papadopoulos, N., Croll, S., Ho, L., Russell, M. *et al.* (2002) VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci U S A* 99: 11393–11398.

International Diabetes Federation (2011) *IDF Diabetes Atlas*, 5th edition. Available at: http://www. idf.org/diabetesatlas (accessed 11 October 2012).

Ip, M., Domalpally, A., Hopkins, J., Wong, P. and Ehrlich, J. (2012) Long-term effects of ranibizumab on diabetic retinopathy severity and progression. *Arch Ophthalmol* 130: 1145–1152.

Javitt, J. and Aiello, L. (1996) Cost-effectiveness of detecting and treating diabetic retinopathy. *Ann Intern Med* 124: 164–169.

Johnson, M. (2009) Etiology and treatment of macular edema. *Am J Ophthalmol* 147: 11–21.

Kempen, J., O'Colmain, B., Leske, M., Haffner, S., Klein, R., Moss, S. *et al.* (2004) The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol* 122: 552–563.

Kim, I., Ryan, A., Rohan, R., Amano, S., Agular, S., Miller, J. *et al.* (1999) Constitutive expression of VEGF, VEGFR-1, and VEGFR-2 in normal eyes. *Invest Ophthalmol Vis Sci* 40: 2115–2121.

Klein, R., Klein, B., Moss, S. and Cruickshanks, K. (1995) The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology* 102: 7–16.

Klein, R., Klein, B., Moss, S., Davis, M. and DeMets, D. (1984) The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmology* 91: 1464–1474.

Kohner, E. (1972) The natural history of diabetic retinopathy. *J R Coll Physicians Lond* 6: 259–270.

Kohner, E. (1991) The natural history of proliferative diabetic retinopathy. *Eye (Lond)* 5: 222–225.

Krebs, I., Schmetterer, L., Boltz, A., Told, R., Vécsei-Marlovits, V., Egger, S. *et al.* (2013) A randomised double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration. *Br J Ophthalmol* 97: 266–271.

Krzystolik, M., Afshari, M., Adamis, A., Gaudreault, J., Gragoudas, E., Michaud, N. *et al.* (2002) Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. *Arch Ophthalmol* 120: 338–346.

Martin, D., Maguire, M., Fine, S., Ying, G., Jaffe, G., Grunwald, J. *et al.* (2012) Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 119: 1388–1398.

Martin, D., Maguire, M., Ying, G., Grunwald, J., Fine, S. and Jaffe, G. (2011) Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 364: 1897–1908.

Massin, P., Bandello, F., Garweg, J., Hansen, L., Harding, S., Larsen, M. *et al.* (2010) Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. *Diabetes Care* 33: 2399–2405.

Michaelides, M., Kaines, A., Hamilton, R., Fraser-Bell, S., Rajendram, R., Quhill, F. *et al.* (2010) A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology* 117: 1078–1086.

Miller, J., Adamis, A., Shima, D., D'Amore, P., Moulton, R., O'Reilly, M. *et al.* (1994) Vascular endothelial growth factor/vascular permeability factor is temporally and spatially correlated with ocular angiogenesis in a primate model. *Am J Pathol* 145: 574–584.

Miller, J., Le Couter, J., Strauss, E. and Ferrara, N. (2012) Vascular endothelial growth factor A in intraocular vascular disease. *Ophthalmology* 120: 106–114.

Mitchell, P., Bandello, F., Schmidt-Erfurth, U., Lang, G., Massin, P., Schlingemann, R. *et al.* (2011) The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 118: 615–625.

Morello, C. (2007) Etiology and natural history of diabetic retinopathy: an overview. *Am J Health Syst Pharm* 64(17 Suppl. 12): S3–S7.

Moss, A. (2013) The angiopoietin: Tie 2 interaction: a potential target for future therapies in human vascular disease. *Cytokine Growth Factor Rev* [ePub ahead of print].

Murphy, S., Xu, J., Kochanek, K. and Division of Vital Statistics (2012) Deaths: preliminary data for 2010. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_04.pdf (accessed 30 October 2013).

Nguyen, Q., Brown, D., Marcus, D., Boyer, D., Patel, S., Feiner, L. *et al.* (2012a) Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 119: 789–801.

Nguyen, Q., Schachar, R., Nduaka, C., Sperling, M., Basile, A., Klamerus, K. *et al.* (2012b) Dose-ranging evaluation of intravitreal siRNA PF-04523655 for diabetic macular edema (the DEGAS study). *Invest Ophthalmol Vis Sci* 53: 7666–7674.

Nguyen, Q., Shah, S., Heier, J., Do, D., Lim, J., Boyer, D. *et al.* (2009) Primary end point (six months) results of the ranibizumab for edema of the macula in diabetes (READ-2) study. *Ophthalmology* 116: 2175–2181.

Nguyen, Q., Shah, S., Khwaja, A., Channa, R., Hatef, E., Do, D. *et al.* (2010) Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. *Ophthalmology* 117: 2146–2151.

Nissen, N., Polverini, P., Koch, A., Volin, M., Gamelli, R. and DiPietro, L. (1998) Vascular endothelial growth factor mediates angiogenic activity during the proliferative phase of wound healing. *Am J Pathol* 152: 1445–1452.

Papadopoulos, N., Martin, J., Ruan, Q., Rafique, A., Rosconi, M., Shi, E. *et al.* (2012) Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis* 15: 171–185.

Rajendram, R., Fraser-Bell, S., Kaines, A., Michaelides, M., Hamilton, R., Esposti, S. *et al.*

(2012) A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Arch Ophthalmol* 130: 972–979.

Regeneron (2013) Regeneron and Bayer report positive one-year results from two phase 3 trials of EYLEA® (aflibercept) injection for the treatment of diabetic macular edema. Available at: http://investor.regeneron.com/releasedetail.cfm?ReleaseID=782911 (accessed 12 September 2013).

Ryan, G. (2007) New pharmacologic approaches to treating diabetic retinopathy. *Am J Health Syst Pharm* 64(17, Suppl. 12): S15–S21.

Santulli, R., Kinney, W., Ghosh, S., Decorte, B., Liu, L., Tuman, R. *et al.* (2008) Studies with an orally bioavailable alpha V integrin antagonist in animal models of ocular vasculopathy: retinal neovascularization in mice and retinal vascular permeability in diabetic rats. *J Pharmacol Exp Ther* 324: 894–901.

Shima, D., Adamis, A., Ferrara, N., Yeo, K., Yeo, T., Allende, R. *et al.* (1995) Hypoxic induction of endothelial cell growth factors in retinal cells: identification and characterization of vascular endothelial growth factor (VEGF) as the mitogen. *Mol Med* 1: 182–193.

Soliman, A., Silva, P., Diala, P., Noble, J., Cavallerano, J., Tolson, A. *et al.* (2011) Awareness of retinopathy and timeliness of follow-up among patients presenting to a diabetes teleophthalmology program, ARVO Annual Meeting, 1–5 May 2011, Fort Lauderdale, FL, USA (abstract 1287/A37).

Stefánsson, E. (2001) The therapeutic effects of retinal laser treatment and vitrectomy. A theory based on oxygen and vascular physiology. *Acta Ophthalmol Scand* 79: 435–440.

Steinkuller, P. (2010) Legal vision requirements for drivers in the United States. *Virtual Mentor* 12: 938–940.

Stewart, M. (2012) Anti-vascular endothelial growth factor drug treatment of diabetic macular edema: the evolution continues. *Curr Diabetes Rev* 8: 237–246.

Stratton, I., Aldington, S., Taylor, D., Adler, A. and Scanlon, P. (2012) A simple risk stratification for time to development of sight-threatening diabetic retinopathy. *Diabetes Care* 36: 580–585.

Sultan, M., Zhou, D., Loftus, J., Dombi, T. and Ice, K. (2011) A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. *Ophthalmology* 118: 1107–1118.

Suñer, I., Kokame, G., Yu, E., Ward, J., Dolan, C. and Bressler, N. (2009) Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. *Invest Ophthalmol Vis Sci* 50: 3629–3635.

Thomas, G., Rael, L., Bar-Or, R., Mains, C., Slone, D., Boyd, S. *et al.* (2012) Biphasic effect of danazol on human vascular endothelial cell permeability and f-actin cytoskeleton dynamics. *Biochem Biophys Res Commun* 421: 707–712.

Tolentino, M., Miller, J., Gragoudas, E., Chatzistefanou, K., Ferrara, N. and Adamis, A. (1996) Vascular endothelial growth factor is sufficient to produce iris neovascularization and neovascular glaucoma in a nonhuman primate. *Arch Ophthalmol* 114: 964–970.

UK Prospective Diabetes Study (UKPDS) Group (1998a) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352: 837–853.

UK Prospective Diabetes Study Group (1998b) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 317: 703–713.

Ulbig, M. and Hamilton, A. (1993) Factors influencing the natural history of diabetic retinopathy. *Eye (Lond)* 7 (Pt 2): 242–249.

White, N., Sun, W., Cleary, P., Danis, R., Davis, M., Hainsworth, D. *et al.* (2008) Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the Diabetes Control and Complications Trial. *Arch Ophthalmol* 126: 1707–1715.

World Health Organization (2010) Priority eye diseases. Available at: http://www.who.int/blindness/causes/priority/en/index.html (accessed 11 October 2012).

Yu, L., Liang, X. and Ferrara, N. (2011) Comparing protein VEGF inhibitors: in vitro biological studies. *Biochem Biophys Res Commun* 408: 276–281.

Yuen, H. (2012) Factors associated with preventive care practice among adults with diabetes. *Prim Care Diabetes* 6: 75–78.

Zhang, P., Zhang, X., Brown, J., Vistisen, D., Sicree, R., Shaw, J. *et al.* (2010a) Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 87: 293–301.

Zhang, X., Saaddine, J., Chou, C., Cotch, M., Cheng, Y., Geiss, L. *et al.* (2010b) Prevalence of diabetic retinopathy in the United States, 2005–2008. *JAMA* 304: 649–656.