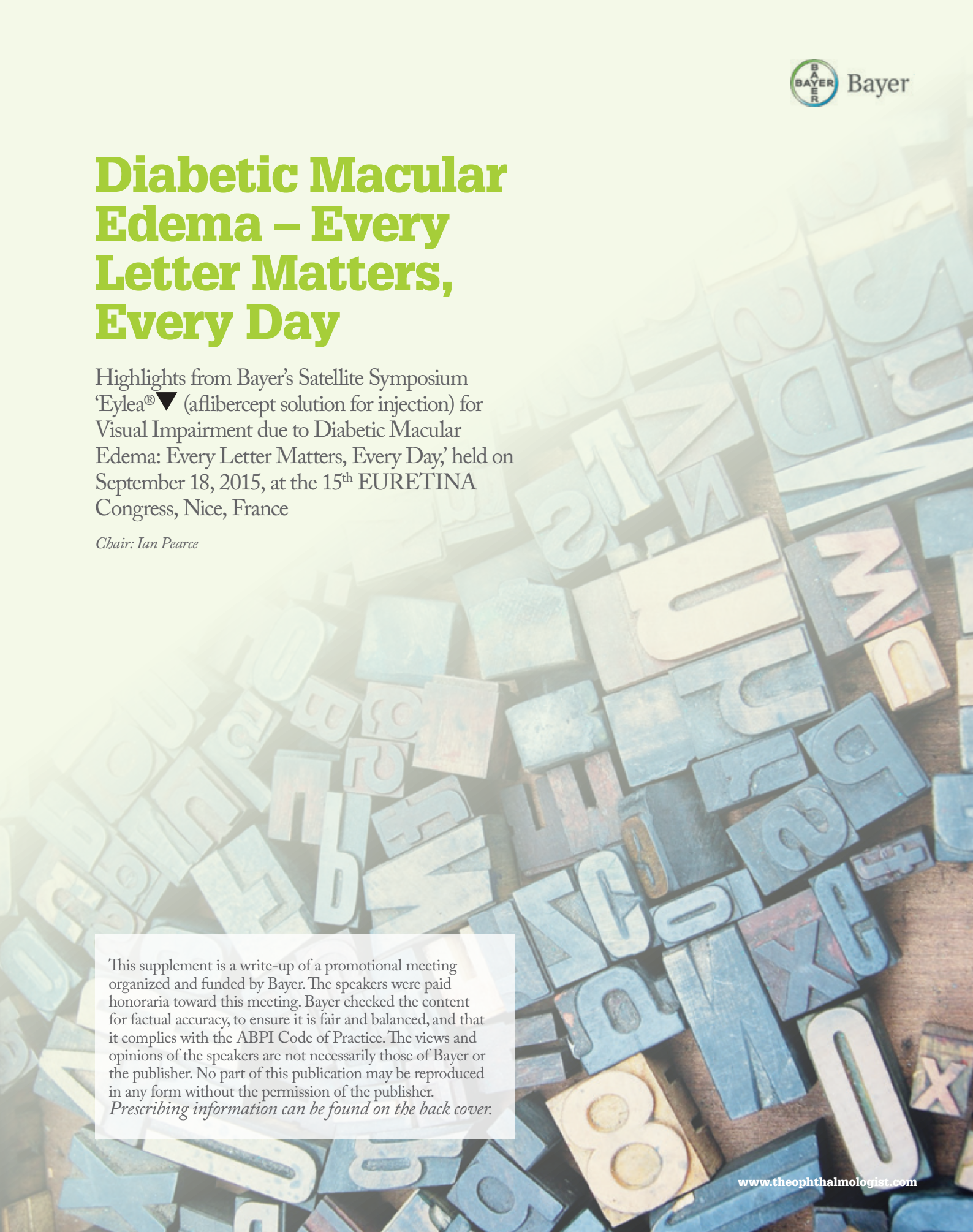
Diabetic Macular Edema – Every Letter Matters, Every Day

Highlights from Bayer's Satellite Symposium 'Eylea®▼ (aflibercept solution for injection) for Visual Impairment due to Diabetic Macular Edema: Every Letter Matters, Every Day,' held on September 18, 2015, at the 15th EURETINA Congress, Nice, France

Chair: Ian Pearce



The Current Treatment Landscape For Visual Impairment due to DME

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Diabetes is expected to affect almost 600 million people within the next quarter of a century (1, 2) and those with diabetes are at an increased risk of developing several chronic diseases that can cause considerable morbidity, including hypertension, acute coronary syndrome, nephropathy, neuropathy – and crucially, retinopathy (2-5). Globally, nearly 93 million people currently have diabetic retinopathy (DR); 17 million have proliferative DR, 21 million have diabetic macular edema (DME), and 28 million are living with a vision-threatening form of the disease (6).

The introduction of anti-vascular endothelial growth factor (anti-VEGF) drugs into ophthalmology represented a change in how patients with DME were treated, giving many patients considerably better visual outcomes than were achievable before with interventions like thermal laser photocoagulation and photodynamic therapy with verteporfin. Within the past few years, VEGF inhibitors, such as aflibercept (Eylea® [aflibercept solution for injection], Bayer) and ranibizumab (Lucentis®, Novartis), and intravitreal corticosteroid delivery systems like dexamethasone (Ozurdex®, Allergan) and fluocinolone acetonide (Iluvien®, Alimera) have come to market, expanding the therapeutic arsenal that ophthalmologists can use to treat visual impairment due to DME. But historically, no published prospective head-to-head comparisons between aflibercept and 0.5 mg ranibizumab, or between aflibercept and the corticosteroids exist, leaving many to wonder which treatment is actually superior.

Aflibercept posology when treating patients with visual impairment secondary to DME is one injection (2 mg aflibercept) per month for five consecutive doses, followed by one injection every two months: the 2q8 regimen in the first year (7). After this period, the treatment interval may be extended based on visual and/or anatomic outcomes, as determined by the treating physician. Within these pages, you will read more about the molecules (beyond VEGF) that drive DME, how aflibercept was designed to target more than just VEGF, its pharmacology, and recent data that compare aflibercept with other treatment options.

Aflibercept: Robust, Durable Efficacy in Visual Impairment due to Diabetic Macular Edema

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What we've learned over the past few years from our patients with DME is that the earlier we diagnose the disease and the earlier we treat it, the better our patients' outcomes. Our experience in the clinic has shown that the key to success when treating these patients is to be very aggressive with any VEGF inhibitor regimen in the first year, so we make sure that we treat the patient, according to the label. In the second year, we are able to move to a more flexible treatment regimen with fewer injections per annum.

The VEGF family consists of five members, VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF). Every anti-VEGF agent used in ophthalmology today inhibits the action of VEGF-A, the most potent inducer of angiogenesis and vascular permeability in the VEGF family. VEGF-A exerts its effects by binding and signaling through the VEGF receptors -1 (VEGFR-1) and -2 (VEGFR-2). But there's another VEGF family member that signals through

	Aflibercept	*Ranibizumab*	*VEGFR-1*	*VEGFR-2*
K_d (VEGF-A_{165})	0.49 pM	46 pM	9.33 pM	88.8 pM

Cell Line	VEGFR-1	VEGFR-1	VEGFR-2
Ligand	hVEGF-A_{165}*	hPlGF2†	hVEGF-A_{165}*
Aflibercept	16 pM	2.890 pM	26 pM
Ranibizumab	1,140 pM	No detectable blocking†	845 pM

Table 1. Aflibercept exhibits tighter VEGF-A binding and greater suppression of the biological activity of VEGF-A_{165} than ranibizumab in an *in vitro* study (9).
*IC_{50} at 20 pM; †IC_{50} at 40 pM. IC_{50}, 50% inhibitory concentration; K_d, equilibrium dissociation constant; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. Lower values equal stronger binding affinities.

VEGFR-1 to promote pathological angiogenesis and vascular permeability: PlGF. Unlike other, registered anti-VEGF agents available today, aflibercept also blocks PlGF (8).

How does it manage this? Aflibercept is a rationally designed recombinant fusion protein that combines the constant region of immunoglobulin G1 (IgG) and specific extracellular components of VEGFR-1 and VEGFR-2, resulting in a molecule with two arms that are both capable of binding both VEGF-A and PlGF with a higher affinity than their native receptors (Table 1). What this means is that aflibercept can bind both ends of activated dimers of either cytokine, trapping them, and preventing them from interacting with other molecules – in effect, rendering them (and the drug) inert after binding (9,10).

Another aspect worthy of consideration is the intravitreal half-lives of these drugs. Figure 1 shows a mathematical model of the duration of both drugs' biological activity, based on their intravitreal binding activities (10). We know the amount of time a drug remains in the eye is based on several factors, one of them being molecular weight – with larger molecules remaining for longer. However, as the concentration of the drug starts to diminish, the binding coefficient starts to become more important. If a drug has a high binding coefficient, it can still be bound preferentially over native ligands, even in low drug concentrations. One mathematical model estimated that intravitreally administered aflibercept persisted for 83 days in the eye, whereas ranibizumab persisted only for 30 days (10).

The key baseline characteristics were similar across all study parameters. In the U.S., over 40 percent of patients enrolled in VISTA (11) – a head-to-head comparison between VEGF inhibition with aflibercept 2 mg and macular laser grid photocoagulation for the treatment of visual impairment due to DME – had previously been treated with other anti-VEGF agents. This is notable, as in clinical practice, we've been using other anti-VEGF agents in most of our patient population. It is also relevant to note about 30–40 percent of patients in VISTA had poor glucose control, with hemoglobin A_{1c} greater than 8 percent,

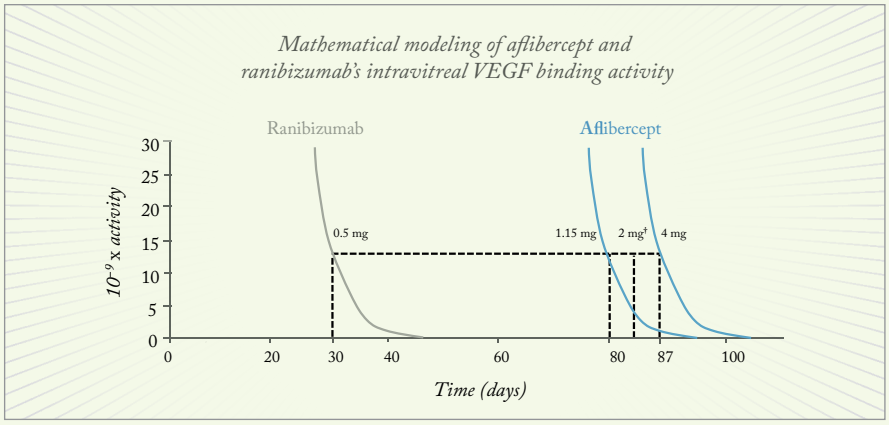

Figure 1. Mathematical modeling of aflibercept and ranibizumab's intravitreal VEGF binding activity. The extrapolated biological activity of aflibercept 2 mg at 83 days is comparable to that of ranibizumab 0.5 mg at 30 days (10).

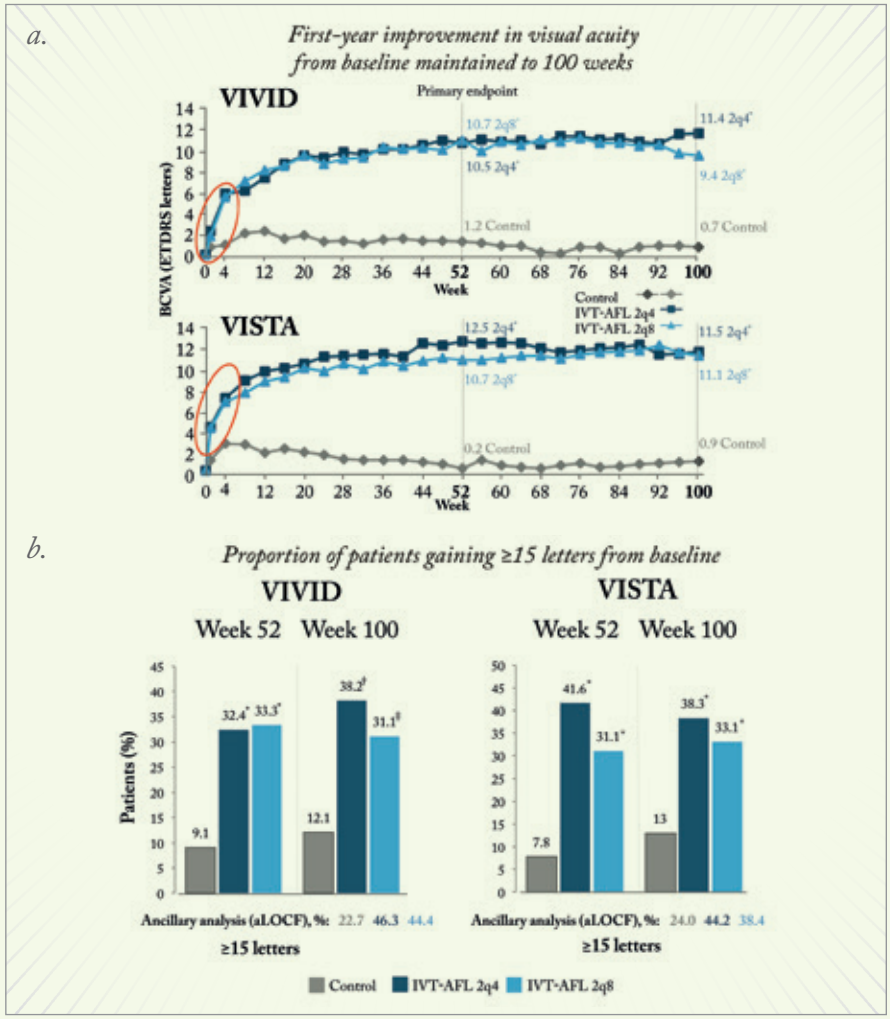

Figure 2. a. First-year improvement in visual acuity (from baseline) with aflibercept is maintained out to 100 weeks. Treatment with aflibercept 2 mg (both regimens) resulted in rapid BCVA gains from baseline levels, with a mean gain greater than 1 line of vision from baseline levels after the first injection (red ovals). b. Proportion of patients gaining ≥15 letters from baseline were stable over the first and second year of therapy; adapted from (11,12). *p<0.0001 vs. Control. †p≤0.0001 vs. Control; ‡p=0.0001 vs. Control. AFL, aflibercept; BCVA, best-corrected visual acuity; IVT, intravitreal; aLOCF, ancillary last observation carried forward.

and had been diagnosed with diabetes for about 10 years – these are challenging patients to manage.

VIVID and VISTA (11). were both designed to use last observation carried forward (LOCF) as the primary analysis; patients who received rescue therapy were excluded from the analysis and their vision at rescue is carried forward. However, analyzing patient data from those who received rescue therapy remains important, and "ancillary LOCF" (aLOCF) has been recently presented (11). In these studies "rescue treatment" was laser in the control group, and in the third year patients could receive aflibercept as rescue therapy if they were in the control group.

The primary outcome was improvement in best-corrected visual acuity (BCVA) at 52 weeks, and this occurred very rapidly and robustly in both aflibercept arms. In VIVID, there was an approximate gain of six Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline in the first month, and in VIVID, about an eight-letter ETDRS letter gain from baseline in the first month. This improvement continued throughout the first year, resulting in 10.5 and 10.7 ETDRS letter gains in VIVID and 10.7 and 12.5 letter gains in VISTA for the 2q4 and 2q8 arms from baseline, respectively. BCVA remained stable after the initial improvement out to 100 weeks (11–13). Figure 2a also shows that patients who received aflibercept 2q8 had about the same improvement from baseline as those receiving monthly injections (11,12). Those findings led to the EU approval of the 2q8 dosing regimen for patients with visual impairment secondary to DME (7).

For those who received rescue treatment in the control group (either active laser after week 12, or after week 24, aflibercept 2 mg every 4 weeks for 5 months and then 2q8), letter gains were substantial but did not reach the levels of visual acuity (VA) gains as those who had been given aflibercept initially (Figure 2b), but what this does show is that large vision gains are possible even after laser treatment. A post-hoc analysis of the number of patients who went on to develop proliferative disease was substantially higher in the control group (7.0 percent in the pooled data compared to 1.7 percent in the aflibercept arms; p=0.0002) (18).

The ocular safety and systemic safety outcomes were acceptable and maintained out to week 100. Anti-Platelet Trialists' Collaboration (APTC) events – nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death – were very similar between the control and aflibercept groups (12), and consistent with other anti-VEGF studies.

In conclusion, the rapid improvements seen in visual gains during the first year of VIVID and VISTA were maintained over time. The 2q8 dosing arm maintained vision gains as well as the monthly dosing group.

Beyond VEGF: The Role of PlGF in Diabetic Retinopathy

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I'd like to bring to life some of the research that has led us to understand the biology of PlGF in the context of diabetic retinopathy – and to do this, you need to understand the fundamentals of how the retinal microcirculation develops and how this process is regulated. It's this knowledge that gives us the critical tools to understand the pathologies involved in diabetic retinopathy, and the pharmacology of the therapeutics used to treat it.

Within the normal retina and choroid, there is a homeostasis of the microcirculation supplying the retinal tissues – a balance exists between positive and negative regulators of angiogenesis and permeability. There are some times where, physiologically, you require more vessels (such as in development or tissue repair following injury), but ultimately there are factors released that prune the vascular bed back to a physiological baseline – these are principles that apply to all vascularized tissue. In diabetes, these factors are dysregulated, preventing the pruning that would normally bring the microvasculature back to the physiological baseline.

I want to focus on what we know about the growth factors in diabetic retinopathy. Of the entire panoply of known angiogenic growth factors (Table 1), many are relevant to the eye, including VEGF-A – of which the VEGF-A_{165} splice variant has long been regarded as central to (and the most important inducer of) this process. But the fact that there are so many other pro-angiogenesis factors in the eye means that there are a number of other potential therapeutic targets, either untapped, or under-tapped, that merit an ongoing discussion about the disease state itself, its progression, its resistance to therapy, and the durability of current and proposed therapies going beyond those that target VEGF-A (Figure 3).

Let's examine the role of just one of these factors, PlGF, in diabetic retinopathy. PlGF was originally isolated from placenta in 1991 (14), but is actually expressed in (and has an impact on) many cell types – including endothelial cells and the retinal pigment epithelium (RPE). It has a strong effect on blood vessel growth and maturation, and a direct effect on angiogenesis. It acts by binding one of the angiogenic factor receptors, VEGFR-1, present on vascular endothelial cells, where it exerts a direct effect. But there is also cross-talk with another VEGF receptor present on endothelial cells, VEGF-2, where it serves to amplify the effect of VEGF (as it increases the probability of VEGF binding VEGF-1

if more VEGF-2 receptors are occupied). Further, PlGF also has an indirect effect by recruiting inflammatory cells (monocytes and macrophages) that amplify VEGF and cytokine release – which is another hallmark of diabetic retinopathies. Today, it's recognized that both PlGF and VEGF play a role in the pathogenesis of DME, and it's long been known that VEGF-A promotes vascular permeability and angiogenesis, and we now know that PlGF is involved in similar processes, in both the early and late stages of the course of the disease (19–23).

How do we actually make sense of this in terms of the disease itself? We know that cultured human RPE cells overexpress PlGF under hypoxic conditions; that PlGF is significantly elevated in the aqueous humor of patients with DME and proliferative diabetic retinopathy (PDR), and that PlGF levels are three times higher in patients with active PDR, compared with patients with quiescent PDR (Figure 4). Even VEGF expression levels are only 1.8 times higher in active, compared with quiescent, PDR (20,23–26). Clearly, PlGF expression correlates with both progression and activity of the disease.

Experiments performed in rats have shown that the intraocular delivery of PlGF can induce the same changes that are the hallmarks of DR, including subretinal fluid accumulation, formation of microaneurysms, vascular sprouting, and increased vascular permeability (25).

So what happens if you eliminate PlGF from the retina?

This can be studied rather elegantly in the laboratory using genetic knockout mice (27). There is an insulin-dependent mouse model of diabetes (the Akita mouse). These mice have a mutation in their *Insulin 2* gene *(Ins2)* that causes insulin to misfold. Homozygous Ins2 mice *($Ins2^{Akita/Akita}$)* rarely live beyond 12 weeks, but the heterozygotes *($Ins2^{Akita/+}$)* survive, breed, exhibit hyperglycemia from about 4.5 weeks of age, and go on to develop increased body weight, retinal cell death, capillary degeneration, pericyte loss, retinal vascular leak and blood-retina barrier dysfunction, as well as increased expression of HIF1α, VEGF and PlGF. The phenotype is therefore generally consistent both with clinical observations and other animal models of diabetes. So when these mice are crossed with PlGF genetic knockouts *($PlGF^{-/-}$)*, this results in the production of *$Ins2^{Akita/+}PlGF^{-/-}$* mice – diabetic mice with no PlGF. When comparing these diabetic, PlGF-free mice to wild-type and Akita "diabetic" mice, some very interesting findings emerge. The *$Ins2^{Akita/+}PlGF^{-/-}$* mice exhibit decreased retinal cell death – so knocking out PlGF leads to more retinal cells surviving, and these mice express greater levels of the survival factor p-Akt. When you look at retinal vascular leakage, the "diabetic" mice exhibit significantly more diabetic leakage than wild-type mice, but when PlGF is removed from the equation (in the *$Ins2^{Akita/+}PlGF^{-/-}$* mice), the retinal vascular leakage is reduced – albeit not quite to wild-type levels. There are other correlates in these *$Ins2^{Akita/+}PlGF^{-/-}$* mice – decreased retinal HIF1α and VEGF-A expression, and also increases in expression of junctional proteins like ZO-1 and VE-cadherin that help maintain the integrity of the blood-retinal barrier, and of the vessel maturation factor Ang-1. So in other words, when PlGF is knocked out in these mice, vascular degeneration, VEGF production, and retinal vascular leak are all reduced, while retinal survival is increased.

Outside the eye, PlGF also plays a role in the neovascularization of tumors. Preclinical data (28) have shown that blocking PlGF with a neutralizing monoclonal antibody (in mice) results in the inhibition of VEGF-resistant tumor growth, angiogenesis, inflammation, and metastasis. Notably, a Phase I clinical study of patients with advanced solid tumor cancers who were given a

Adrenomedullin	IL-3	PlGF
Angiogenin	IL-8	Progranulin
BMP-4	Leptin	Proliferin
CRH/CRF	Midkine	Secretoneurin
Cyr16	Neurokinin A	Substance P
Follistatin	Neuropeptide Y	TGF-α
G-CSF	NGF	TGF-β
HGF	PD-ECGF	TNF-α
IGF-1	PDGF	VEGF/VPF
FGF (1–7)	Pleiotrophin	VG5Q

Table 2. The panoply of known angiogenic growth factors, and those specific to the eye (green) (15–19).

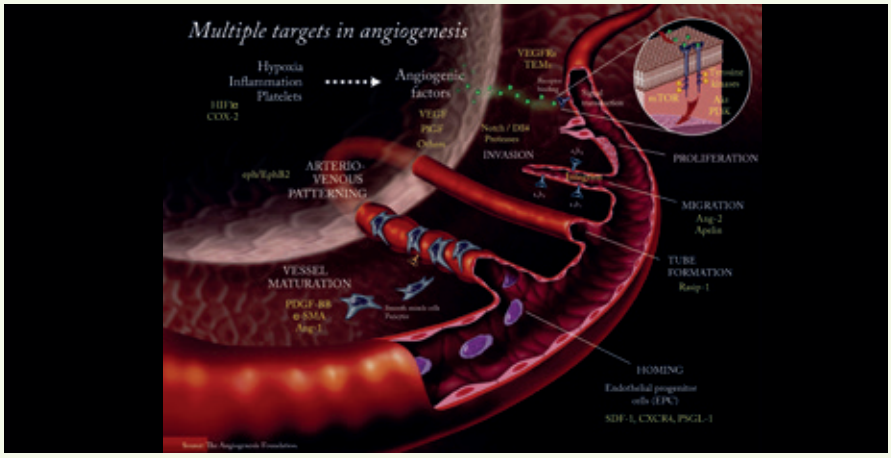

Figure 3. Potential targets for ocular angiogenesis inhibitors.

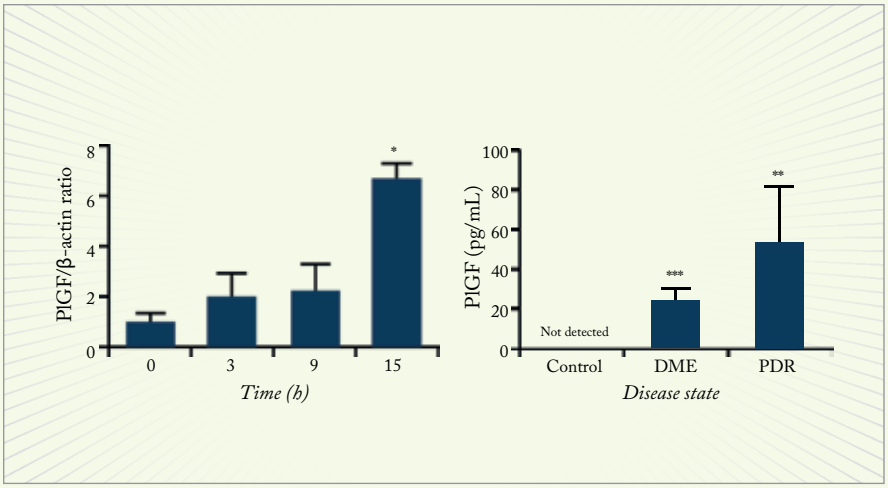

Figure 4. PlGF is elevated in diabetic retinopathy (relative to the constitutively-expressed β-actin acting as control); cultured RPE cells overexpress PlGF under hypoxic conditions in vitro, with elevated levels present in the aqueous humor of patients with DME and PDR. *p<0.05; **p<0.01; ***p<0.001 (25,28–30).

humanized anti-human PlGF antibody failed to show dose-limiting toxicity and, indeed, no maximum tolerated dose was determined in that study (29) – and no toleration ceiling for anti-human PlGF antibodies has been published to date.

Ultimately, the drivers of diabetic retinopathies are more complicated and numerous that we had previously thought. Although VEGF-A is relatively easily blocked with a Fab fragment (e.g. ranibizumab), that still leaves the rest of the VEGF family "sneaking through" that field, binding receptors, and causing angiogenesis and lymphangiogenesis. The anti-VEGF fusion protein, aflibercept, blocks not only VEGF-A, but also the other higher affinity VEGF receptor, VEGF-B, as well as PlGF.

PlGF may be "the new kid on the block", but we are just beginning to understand how prominent a role it plays in the VEGF cascade. As PlGF not only binds to VEGFR-1, but also amplifies VEGF effects through cross-talk between VEGFR-1 and VEGFR-2, recruits the inflammatory cells and induces the release of yet more inflammatory cytokines, from my perspective, it suggests PlGF should remain as much a target in treating DME as VEGF.

Assessing the Treatment Landscape in Diabetic Macular Edema: The Place of Aflibercept

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Clinical studies have continuously supported the hypothesis that anti-VEGF agents are more efficacious and have a comparable safety profile than laser in the treatment of visual impairment due to DME. Historically, because of the lack of head-to-head comparisons, meta-analyses have been our sole means of comparing outcomes of different anti-VEGF agents like ranibizumab and aflibercept (30–33).

However, these historical meta-analyses have been compromised by a number of factors, including the fact that ranibizumab was inconsistently dosed (some studies used monthly, others used *pro re nata* [PRN] regimens), only a limited number of outcomes were measured, and importantly, they disregarded differences in comparators (e.g., lasers vs. sham), which matters because if an outcome is mean change in VA versus the control arm, there is going to be a difference in the comparator arms if one is treated and another is not, leading to (at a minimum) a perceived bias in the results. Crucially, the previous studies primarily included the Phase II DA VINCI study for aflibercept, which used a different loading regimen of only three monthly treatments (34,35) to the Phase III trials and the subsequently approved posology in visual impairment due to DME (loading regimen of five monthly doses). All but one of these meta-analyses (33) did not consider the results from VIVID and VISTA (16) (understandably, as at the time, their results were not yet known), and finally, the results were typically reported in LogMAR instead of ETDRS letters.

Accordingly, a new meta-analysis (36) was undertaken using data from VIVID and VISTA (11), which is intended to provide an indication of comparative efficacy and safety between the anti-VEGF agents and other agents, including steroids, in the absence of randomized head-to-head data. The goal of the analysis was to systematically identify and review the effectiveness of aflibercept 2q8 (on-label) compared with ranibizumab 0.5 mg PRN (on-label), and aflibercept 2q8 compared with dexamethasone 0.7 mg implants (36). The authors took extreme care to control for baseline VA, as other analyses did not.

The meta-analysis inclusion/exclusion criteria included only patients with DME that had been treated with anti-VEGF or steroids using intravitreal injections in randomized clinical trials, and trials had to include mean change in vision and other VA outcomes (10- and 15-letter gains/losses). This is a large undertaking, as to

date, there have been 13,700 abstracts and papers evaluating the treatment of DME. In all, there were 11 studies included in this indirect meta-analysis. In order to maintain homogeneity, studies were only considered to be sufficiently similar and suitable for meta-analysis if laser was used in the control group. Finally, to be included, all studies had to have at least one-year outcomes available.

The treatment comparison in this meta-analysis, which is based on ETDRS letters, shows about a one-line difference in VA improvement from baseline when aflibercept was administered every eight weeks (2q8) compared with a PRN ranibizumab at the 12-month time point. In addition, when analyzing some of the other visual outcomes, the data also favored aflibercept, as a greater proportion of patients gained 10–15 ETDRS letters and fewer patients lost 10–15 letters from baseline, compared with ranibizumab.

The dosing regimen for ranibizumab used in clinical studies may not follow the current recommended treatment frequency, which varies according to response. Please consult the ranibizumab Summary of Product Characteristics.

Differences in how aflibercept and the 0.7 mg dexamethasone implant reported visual outcomes confounded any comparisons of VA other than 10-letter gains in VA. This was almost twice as likely to occur in patients receiving aflibercept compared to the dexamethasone implant at the one year time point (Table 4).

No significant differences in either ocular or systemic adverse events at 12 months between the aflibercept and ranibizumab regimens examined were found. Likewise, there was no significant difference in adverse event rates between aflibercept and the dexamethasone 0.7 mg implant at 12 months (although there was a trend toward fewer events with aflibercept). The lack of a significant difference in cataract formation rates between aflibercept and dexamethasone implant may be explained by the treated population's general age; many were elderly and may have been pseudophakic at baseline.

As with any meta-analysis, there are strengths and weaknesses inherent in the study. Among the strengths of this study is that it compared on-label doses and treatment regimens, it included a broader range of outcomes (including BCVA) than previous meta-analyses, and the mean change of BCVA was adjusted to baseline BCVA and reported in ETDRS, not LogMAR. The primary weakness remains that this was an indirect comparison. Despite that caveat, it appears as though aflibercept, administered every eight weeks, provides better visual outcomes than PRN ranibizumab or the 0.7 mg dexamethasone implant. The safety profiles of the drugs were similar, with no increased safety issues noted in this meta-analysis. Clearly, the gold-standard level of evidence would come from a head-to-head clinical trial comparing these drugs – but this systematic review and mixed treatment analysis contains the VIVID and VISTA trial data, and which importantly – and unlike previous indirect comparisons – controlled for differences in baseline VA, certainly brings a more up-to-date indirect comparison to the literature.

*Indirect comparisons of the effects of aflibercept 2q8 versus ranibizumab 0.5 mg PRN regimens on 12-month visual outcomes**

Aflibercept 2q8 vs. *ranibizumab 0.5 mg PRN*	*MTC (fixed effect)*	*MTC (fixed effect) adjusted for baseline BCVA*	*Bucher (fixed effect)*
Outcome	Effect size vs. ranibizumab [95% CI]	Effect size vs. ranibizumab [95% CI]	Effect size vs. ranibizumab [95% CI]
Mean change in BCVA	4.67 [2.45–6.87]†	4.12 [1.47–6.81]†	4.82 [2.52–7.11]¶
Gain of ≥10 ETDRS letters	1.32 [0.98–1.78]‡	1.36 [0.97–1.87]‡	0.993 [0.65–1.52]¶
Gain of ≥15 ETDRS letters	1.78 [0.96–3.29]‡	1.45 [0.82–2.50]‡	1.49 [0.78–2.85]¶
Loss of ≥10 ETDRS letters	0.27 [0.07–0.90]‡	0.11 [0.02–0.46]‡	0.31 [0.09–1.04]¶
Loss of ≥15 ETDRS letters	0.13 [0.004–1.35]‡	0.06 [0.00–0.79]‡	0.24 [0.03–1.90]¶

Table 3. Indirect comparisons of the effects of aflibercept 2q8 versus ranibizumab 0.5 mg PRN regimens on 12-month visual outcomes. *Indirect comparisons, as described in the table above, have a number of drawbacks (see text), but at least enable some form of comparison where no head-to-head clinical trial data exist. †10 studies (n=3,060): VIVID (11), VISTA (11), IBETA (37), RESTORE (38), REVEAL (39), RELATION (40,41), DRCR.net Protocol I (42), DRCR.net Protocol J (43), LUCIDATE (44), and reference (45). ‡6 studies (n=2,810): VIVID (11), VISTA (11), RESTORE (38), REVEAL (39), DRCR.net Protocol I (42), and DRCR.net Protocol J (43). ¶4 studies (n=1,611): VIVID (11), VISTA (11), RESTORE (38), and REVEAL (39). MTC, mixed treatment comparison; PRN, *pro re nata*.

*Meta-analysis: indirect comparison between aflibercept and dexamethasone 0.7 mg on 12-month visual outcomes**

Aflibercept 2q8 vs. *dexamethasone 0.7 mg implant*	*Bucher (fixed effect)*	*Bucher (random effect)*
Outcome	Relative risk [95% CI]	Relative risk [95% CI]
Gain of ≥10 ETDRS letters	2.10 [1.29–3.40]†	2.10 [1.21–3.66]†

Table 4. Meta-analysis: indirect comparison (Bucher analysis) between aflibercept and dexamethasone 0.7 mg on 12-month outcomes. *Indirect comparisons, as described in the table above, have a number of drawbacks (see text), but at least enable some form of comparison where no head-to-head clinical trial data exist. †3 studies (n=1,123): VIVID (11), VISTA (11), and PLACID (46).

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Prescribing information

Eylea® 40 mg/ml solution for injection in a vial (aflibercept)
Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 1 ml solution for injection contains 40 mg aflibercept. Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. **Indication(s):** Treatment in adults of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DMO) and visual impairment due to myopic choroidal neovascularisation (myopic CNV). **Posology & method of administration:** For intravitreal injection only. Must be administered according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. Each vial should only be used for the treatment of a single eye. The vial contains more than the recommended dose of 2 mg. The extractable volume of the vial (100 microlitres) is not to be used in total. The excess volume should be expelled before injecting. Refer to SmPC for full details. ***Adults:*** The recommended dose is 2 mg aflibercept, equivalent to 50 microlitres. For wAMD treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. No requirement for monitoring between injections. After the first 12 months of treatment, treatment interval may be extended based on visual and/or anatomic outcomes. In this case the schedule for monitoring may be more frequent than the schedule of injections. For RVO (branch RVO or central RVO), after the initial injection, treatment is given monthly at intervals not shorter than one month. Discontinue if visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment. Treat monthly until maximum visual acuity and/or no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. Shorten treatment intervals if visual and/or anatomic outcomes deteriorate. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response. For DMO, initiate treatment with one injection/month for 5 consecutive doses, followed by one injection every two months. No requirement for monitoring between injections. After the first 12 months of treatment, the treatment interval may be extended based on visual and/or anatomic outcomes. The schedule for monitoring should be determined by the treating physician. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, treatment should be discontinued. For myopic CNV, a single injection is to be administered. Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease. The schedule for monitoring should be determined by the treating physician. The interval between two doses should not be shorter than one month. ***Hepatic and/or renal impairment:*** No specific studies have been conducted. Available data do not suggest a need for a dose adjustment. ***Elderly population:*** No special considerations are needed. Limited experience in those with DMO over 75years old. ***Paediatric population:*** No data available. *Contraindications:* Hypersensitivity to active substance or any excipient; active or suspected ocular or periocular infection; active severe intraocular inflammation. **Warnings & precautions:** As with other intravitreal therapies endophthalmitis has been reported. Aseptic injection technique essential. Patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients must report any symptoms of endophthalmitis without delay. Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection; special precaution is needed in patients with poorly controlled glaucoma (do not inject while the intraocular pressure is ≥ 30 mmHg). Immediately after injection, monitor intraocular pressure and perfusion of optic nerve head and manage appropriately. There is a potential for immunogenicity as with other therapeutic proteins; patients should report any signs or symptoms of intraocular inflammation e.g pain, photophobia or redness, which may be a clinical sign of hypersensitivity. Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors. Safety and efficacy of concurrent use in both eyes have not been systemically studied. No data is available on concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular). Caution in patients with risk factors for development of retinal pigment epithelial tears including large and/or high pigment epithelial retinal detachment. Withhold treatment in patients with: rhegmatogenous retinal detachment or stage 3 or 4 macular holes; with retinal break and do not resume treatment until the break is adequately repaired. Withhold treatment and do not resume before next scheduled treatment if there is: decrease in best-corrected visual acuity of ≥30 letters compared with the last assessment; central foveal subretinal haemorrhage, or haemorrhage ≥50%, of total lesion area. Do not treat in the 28 days prior to or following performed or planned intraocular surgery. Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection. Populations with limited data: There is limited experience of treatment with Eylea in patients with ischaemic, chronic RVO. In patients presenting with clinical signs of irreversible ischaemic visual function loss, aflibercept treatment is not recommended. There is limited experience in DMO due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. Eylea has not been studied in patients with active systemic infections, concurrent eye conditions such as retinal detachment or macular hole, or in diabetic patients with uncontrolled hypertension. This lack of information should be considered when treating such patients. In myopic CNV there is no experience with Eylea in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions. **Interactions:** No available data. **Fertility, pregnancy & lactation:** Not recommended during pregnancy unless potential benefit outweighs potential risk to the foetus. No data available in pregnant women. Studies in animals have shown embryo-foetal toxicity. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last injection. Not recommended during breastfeeding. Excretion in human milk: unknown. Male and female fertility impairment seen in animal studies with high systemic exposure not expected after ocular administration with very low systemic exposure. **Effects on ability to drive and use machines:** Possible temporary visual disturbances. Patients should not drive or use machines if vision inadequate. **Undesirable effects:** *Very common:* conjunctival haemorrhage (phase III studies: increased incidence in patients receiving anti-thrombotic agents), visual acuity reduced, eye pain. *Common:* retinal pigment epithelial tear, detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract (nuclear or subcapsular), corneal abrasion or erosion, increased intraocular pressure, blurred vision, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, increased lacrimation, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival or ocular hyperaemia. *Serious: cf. CI/W&P – in addition:* blindness, endophthalmitis, cataract traumatic, transient increased intraocular pressure, vitreous detachment, retinal detachment or tear, hypersensitivity (incl. allergic reactions), vitreous haemorrhage, cortical cataract, lenticular opacities, corneal epithelium defect/erosion, vitritis, uveitis, iritis, iridocyclitis, anterior chamber flare. Consult the SmPC in relation to other side effects. **Overdose:** Monitor intraocular pressure and treat if required. **Incompatibilities:** Do not mix with other medicinal products. **Special Precautions for Storage:** Store in a refrigerator (2°C to 8°C). Do not freeze. Unopened vials may be kept at room temperature (below 25°C) for up to 24 hours before use. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** Single vial pack £816.00. **MA Number(s):** EU/1/12/797/002. **Further information available from:** Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, United Kingdom. Telephone: 01635 563000. Date of preparation: November 2015

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Bayer plc. Tel.: 01635 563500, Fax.: 01635 563703, Email: pvuk@bayer.com

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