Aflibercept – Setting its Sights on Diabetic Macular Oedema

Proceedings of a Symposium Presented at
European Association for Vision and Eye Research (EVER) 2014 Congress, Nice, 3 October 2014

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Abstract

A satellite symposium entitled 'Aflibercept* – Setting Its Sights On Diabetic Macular Oedema (DMO)' was chaired by Jean-François Korobelnik and was convened at the 2014 European Association for Vision and Eye Research (EVER) Congress. The symposium discussed the science behind DMO, in particular, the role of vascular endothelial growth factor (VEGF) and associated inflammatory mechanisms that alter fluid transport from capillaries into retinal tissues leading to focal leakage, fluid accumulation, macular damage and eventual blindness. This discussion of the pathophysiology emphasised the importance of VEGF as a target for DMO treatments. Management of diabetes and prevention of progression of diabetic retinopathy leading to DMO requires strict control of glycated haemoglobin (HbA_{1c}), blood pressure and lipid levels. Once DMO has developed and vision is impaired, the anti-VEGF agents have emerged as vital components of disease management and are becoming the first-line standard of care. Aflibercept (EYLEA® ▼) and ranibizumab (Lucentis®) are approved agents for DMO and have shown significant efficacy in clinical trials in terms of visual acuity gains, decreased retinal thickness and have good safety profiles. The symposium finally focused on the use of aflibercept in DMO. In large-scale trials (VIVID and VISTA), this treatment has been compared head-to-head with laser treatment and during 1 year of treatment, showed substantial efficacy benefits, no new safety signals and the potential for lower frequency intravitreal dosing at 8- rather than 4-week intervals for monitoring and *pro re nata* dosing.

Keywords

Diabetic macular oedema, VEGF, anti-VEGF agents, aflibercept

Disclosure: Jean-François Korobelnik is a consulant for Alcon, Alimera, Allergan, Bayer, Horus, Novartis, Roche, Théa and Zeiss. Ian Pearce has engaged in consultancies, advisory boards, speaking engagements, conducted clinical research or owns shares in Alcon, Alimera, Allergan, Bayer and Novartis. Reinier Schlingemann is a consultant, has engaged in advisory boards and received speaker fees from Astellas, Bayer and Novartis.

Acknowledgements: Editorial assistance was provided by James Gilbart at Touch Medical Media, London, UK.

Received: 22 October 2014 **Accepted**: 14 November 2014 **Citation**: *European Ophthalmic Review*, 2014;8(2):152–8 *DOI: 10.17925/EOR.2014.08.02.152*

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Support: The publication of this article was supported by Bayer Healthcare. The views and opinions expressed are those of the authors and not necessarily those of Bayer Healthcare.

Diabetic macular oedema (DMO) is an increasingly common vision-threatening disease that results from retinal vascular dysfunction and low-grade inflammation, developing into diabetic retinopathy (DR) and then to DMO over 10 or more years following the onset of diabetes.[1] Areas of retinal tissue lose capillary vasculature and become ischaemic, stimulating secretion of vascular endothelial growth factor (VEGF) and other cytokines.[2–4] Changes in paracellular and transcellular transport across the capillary endothelium and altered hydrostatic and osmotic pressure gradients result in fluid movement into retinal tissues, leading to consequent oedema and retinal damage.

Effective prevention and management of DR and DMO require intensive treatment of diabetes in terms of controlling glycaemia, blood pressure and lipid levels.[5] Hyperglycaemia drives vascular dysfunction and DR, and it is important that patients understand the critical importance of controlling blood glucose levels. Treatment of DMO during the past decades has been almost entirely limited to laser photocoagulation but, recently, anti-VEGF agents have emerged as first-line agents in a subset of patients.[6] Among these, two medications have been approved for this indication: aflibercept (EYLEA® ▼) and ranibizumab, (Lucentis®) and in large clinical trials, these have shown greater efficacy in central DMO than laser treatment or placebo, respectively.[7–9]

This article reports the proceedings of a symposium that reviewed the pathophysiology of DMO and the possible approaches to its management, particularly laser, anti-VEGF agents and corticosteroids. It also discussed the results of two large ongoing phase III clinical trials that are evaluating treatment of a large population of DMO patients with the anti-VEGF agent, aflibercept. These novel trials involve two regimens of aflibercept, in a head-to-head comparison with laser therapy. They are providing much-needed data on the comparative efficacy of these treatments in DMO in terms of visual acuity (VA) and retinal pathology and are also providing useful data on their relative safety and tolerability.

*EYLEA® ▼ (aflibercept solution for injection). Prescribing information can be found on page 158.

The Science Behind the Disease

Professor Reinier Schlingemann

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DMO is an increasing threat to vision worldwide and is the leading cause of blindness in young adults in developed countries.[10] This rising prevalence is driven by the burgeoning numbers of people with type I and especially, type II diabetes. In Europe in 2013 it was estimated that 56 million people had diabetes, and this is expected to rise to 69 million by 2035 (22 % increase).[11] Globally, 382 million people were estimated to have diabetes in 2013 with a projected rise to 592 million by 2035 (55 % increase).[11] Among people with diabetes, approximately one-third have DR and approximately one-third of those have DMO. Therefore, 6.2 million people (11 % of people with diabetes) in Europe currently have DMO and 0.6–1.7 million have clinically significant MO.[11,12] Given this burden, effective treatments for DMO are a critical need worldwide.

Main risk factors for the development of DR and DMO include: poorly controlled diabetes, chronic hyperglycaemia, dyslipidaemia, hypertension, high body mass index, low levels of physical activity and insulin resistance.[13,14] Less strongly associated potential risk factors include: sleep apnoea; non-alcoholic fatty liver disease; levels of serum prolactin, serum adiponectin and serum homocysteine; age; renal disease; and pregnancy.[13,15]

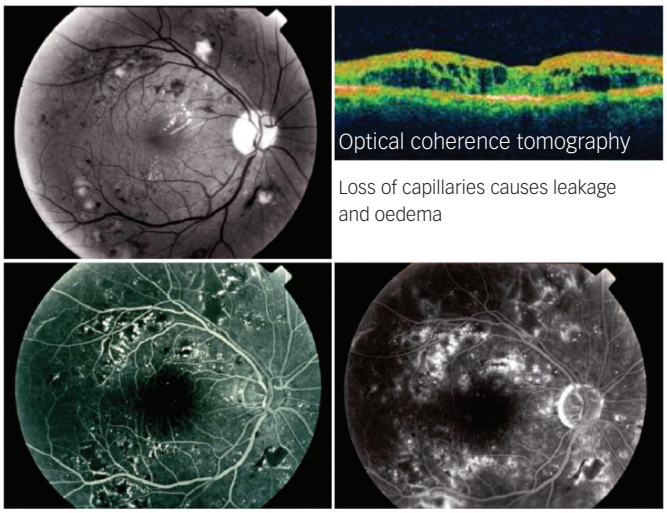
The effects of diabetes on the retina are slow to manifest: signs of DR take approximately 10 years to appear after disease onset. The criteria for clinically significant DMO that will benefit from laser therapy were defined by the Early Treatment Diabetic Retinopathy Study Group during the 1980s.[16] These include thickening of the retina (≤500 µm of the foveal centre), possibly with hard exudates and changes in the vasculature. Early damage is seen to both vascular and neural cells. Within retinal capillaries, pericytes and endothelial cells are lost leading to the appearance of 'ghost' capillaries. The relationship between neuropathy and vasculopathy in DMO, however, is unclear.

In DMO, there appear to be two pathological processes: a primary one causing vascular loss in small areas and a secondary one causing these areas to enlarge. The areas of vascular loss become ischaemic, stimulating growth factor secretion, which attracts inflammatory cells, and microaneurysms may occur. This creates a vicious circle of increasing vascular activation and inflammation in which areas of capillary non-perfusion tend to enlarge to sight-threatening DR (*see Figure 1*).[2–4]

Possibly the most important factor stimulated in DMO is vascular endothelial growth factor-A (VEGF-A). VEGF is secreted by all hypoxic cells and has vital roles in maintaining normal tissue function and in disease. These functions include: cell survival, permeability, angiogenesis, inflammation, mitogenicity, chemotaxis and neuroprotection.[17,18] VEGF causes blood vessels to grow but also to leak and is consequently a target for several treatments of DMO.

Evidence that VEGF is involved is DMO first came from a South American study in which 88 patients with the disease were given intravitreal treatment with at least one injection of the anti-VEGF agent, bevacizumab (1.25 mg or 2.5 mg).[19] In just 1 month, both VA in terms of best corrected VA (BCVA) and retinal thickness were significantly improved and this was sustained during 6 months of follow-up (p<0.0001 for both parameters).

Figure 1: Focal and Widespread Vasoregression, Retinal Ischaemia and Vascular Leakage of the of Retina and a Macular Cyst in Patients with Diabetic Macular Oedema



Anti-VEGF agents are now widely used to successfully treat DMO in the clinic as discussed in the next section.[20]

Further evidence of the role of inflammation in DMO has come from analysis of vitreous fluids from patients with DMO. Two studies conducted in Japan (n=92 and n=53) revealed significantly raised inflammatory cytokines in patients with DMO versus patients without diabetes (p<0.05 for all).[21,22] In particular, levels of interleukin-6 (IL-6) IL-8, monocyte chemoattractant protein-1 (MCP-1) and intracellular adhesion molecule (ICAM-1) were elevated indicating an inflammatory state. In addition, corticosteroids such as triamcinolone acetonide have demonstrated efficacy in the treatment of DMO, reducing retinal thickness and improving VA.[23,24] Corticosteroids have multifactorial actions against various inflammatory cytokines but they also have a direct effect in restoring the blood–retina barrier (BRB) in retinal endothelium, independently of inflammation. Their efficacy in DMO therefore not necessarily supports inflammation as a driver of DMO, a notion widely advocated.

The accumulation of fluids in retinal tissues in DMO follows the well-established principles of the Starling equation.[25,26] This states that the flow of liquids between capillaries and surrounding tissues is the result of both hydrostatic pressure and osmotic pressure gradients resulting from vascular and tissue solute concentrations. In normal tissue, these forces are balanced and there is no net change in fluid volume but in DMO, they become unbalanced leading to disrupted fluid transport in and out of the tissue and fluid accumulation. The changes in hydrostatic and osmotic pressure and inflammation in DMO are mediated by multiple cellular and protein factors leading to localised breakdown of the BRB and consequent leakage into retinal tissues.[27] The passage of plasma solutes out of retinal capillaries occurs through either a paracellular pathway via tight junctions between epithelial cells or via a transcellular

pathway through the cells involving caveolae. Studies on rat retinal cells exposed to VEGF showed a transient down-regulation of some proteins such as occludin and claudin-5 that control tight junctions.[28] In addition, long-term upregulation of the vesicular transport-related genes encoding caveolin-1 and plasmalemma vesicle protein-1 (PV-1) was observed. This indicates that in DMO there is a transient induction of paracellular transport but a more important sustained activation of transcellular transport that results in BRB breakdown. These findings were supported by a study of monkey eyes in which exposure to VEGF resulted in intense retinal microvascular leakage.[29] Electron microscopy of leaky blood vessels in these tissues showed significantly increased pinocytotic vesicles (caveolae) that had moved to a luminal position indicating greatly increased transcellular transport. This increased transcellular transport of fluid in DMO is likely to decrease osmotic pressure in tissues, and as vascular hydrostatic pressure is also increased in DR, these forces result in net fluid movement to the tissues and consequent oedema. □

Key points:

The pathophysiology of DMO results from:

- Retinal vascular disease
  - Vasoregression and retinal ischaemia
- VEGF and inflammatory factors induced by ischaemia and tissue damage
- Loss of the BRB
  - Paracellular transport – small molecules
  - Transcellular transport – large molecules
  - Starling equation: hydrostatic versus osmotic pressures affect oedema
  - Role of abnormal vascular structures
  - Chronic DMO may be a separate condition

Managing the Patient with Diabetic Macular Oedema

Mr Ian Pearce

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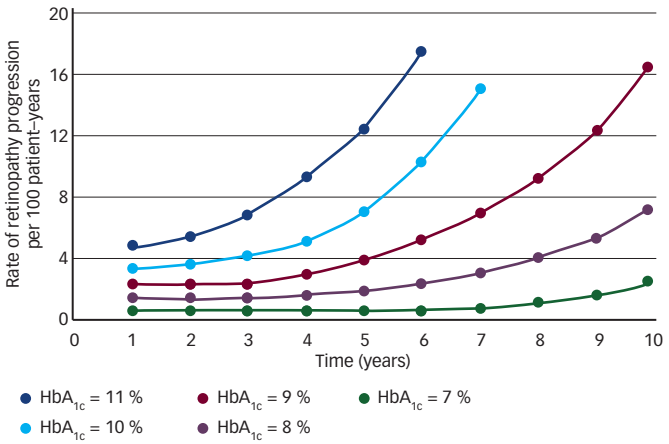
The primary objective of diabetes management is to regain control of blood glucose levels and to optimise blood pressure and blood lipid levels.[5] Despite these interventions, over time patients develop multiple diabetes-related complications, of which they are often unaware of until they have progressed significantly.[11] Patients with diabetes are 25x more likely to be blind than patients without diabetes[30] and many patients fear blindness more than premature death. Ophthalmologists therefore have an important role in educating patients in the need to control hyperglycaemia, the major driver of retinopathy. Ophthalmologists are also likely to be the first healthcare professionals to observe end-organ damage in these patients and are responsible for reporting it to their treating physicians.

If diabetes is well managed, the risk of macro- and micro-vascular complications can be reduced.[5,31] This has been demonstrated in several large-scale clinical studies including the Diabetes Control and Complications Trial (DCCT),[32] the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[33] and the UK Prospective Diabetes Study (UKPDS).[34] The DCCT showed that rates of DR rise steeply in patients whose glycated haemoglobin (HbA_{1c}) levels are not maintained at approximately 7 % (*see Figure 2*).[32] For every 1 % reduction in HbA_{1c} there is a 30 % reduction in the progression of DR. However, too rapid a reduction in HbA_{1c} can also result in DR and so no more than a 1 % reduction in 6 months is advised.

Clinical studies also show that controlling blood pressure in patients with diabetes is vital. The UKPDS showed that treating to target a blood pressure of <150/85 mmHg (preferably 140/80) substantially reduces the risk of death and complications due to diabetes.[34] In another large study, DMO was reduced over a 4-year period when patients with diabetes received blood pressure-lowering treatment.[35] Lipidaemia is also influential in DR but not as important as glycaemia and blood pressure. An analysis of data from the DCCT showed that higher serum lipids (total lipids, low-density lipoprotein [LDL] and high-density lipoprotein [LDL] cholesterol, total-to-HDL cholesterol ratio and triglycerides) are associated with an increased risk of clinically significant MO (CSMO) and retinal hard exudate.[36] In addition, other clinical studies have shown reductions in the progression of retinopathy following treatment with atorvostatin[37] or fibrates.[38]

Figure 2: Time versus Rate of Retinopathy Progression in Patients with Diabetes with Glycated Haemoglobin Levels between 7 % and 11 %



HbA_{1c} = glycated haemoglobin. Adapted from: DCCT Research Group, 1995.[32]

The successful management of diabetes and avoidance of DR requires a systematic approach in which all of the risk parameters are adequately controlled. An analysis of data from the National Health and Nutrition Examination Surveys (NHANES) in the US found that only 19 % of patients with diabetes met all their targets for HbA_{1c}, blood pressure and LDL cholesterol, indicating a substantial need for improvement.[39] To counter this problem, multifactorial treatments are needed to provide intensive control of all risk factors. This approach was evaluated in a Danish study (Steno-2) in which patients with diabetes received tight glucose regulation, renin-angiotensin system blockers, aspirin and lipid-lowering agents.[40] This intense treatment regimen produced a risk

reduction of 43 % for the progression of DR compared with controls given standard treatment (p=0.01).[40]

Until recently, laser photocoagulation was the 'gold standard' therapy in DMO and had been for 3 decades. Focal laser photocoagulation targets specific areas whereas macular grid photocoagulation applies a localised pattern to treat areas of diffuse leakage. Despite the emergence of medications, laser therapy still has a role in the treatment of DMO. The classic Early Treatment in Diabetic Retinophy Study (ETDRS) that commenced during the 1980s demonstrated that macular (focal/macular grid) laser photocoagulation was more effective when administered early rather than deferred.[41] In this study, laser treatment reduced the risk of moderate vision loss by approximately 50 %, and was effective at preserving vision/preventing further vision loss. [41]

More recently, intravitreal corticosteroid and anti-VEGF agents have become available for the treatment of DMO and these can be used as alternatives to or in combination with laser therapy.[6,42,43] Extended-release implants of dexamethasone or fluocinolone acetonide are effective and more convenient than injections.[44,45] In some countries such as the UK, however, their use is currently restricted to pseudophakic patients who are unresponsive to anti-VEGF agents due to their side effects.[46]

Since VEGF is a major factor in the inflammation that drives DMO, several anti-VEGF medications have been used effectively to treat DMO.[20] These are used alone or in combination with or before laser therapy or with other treatments. Ranibizumab (Lucentis®) is a humanised fragment, a mouse monoclonal antibody and also binds VEGF-A.[47] Aflibercept (Eylea®) is a fully human, recombinant fusion protein that tightly and stably binds VEGF-A and also binds placenta growth factor (PlGF).[48] Bevacizumab (Avastin®) is a humanised, recombinant monoclonal antibody with high affinity for VEGF-A. It is widely approved for systemic treatments of various cancers but is also used extensively off-label for ocular diseases including DMO.[49,50] Pegatanib (Macugen®) is a 28-base RNA aptamer covalently linked to two branched 20 kDa polyethylene glycol moieties that binds potently to VEGF. It is approved for the treatment of wet AMD but is also used for off-label treatment of DMO.[51]

Both aflibercept and ranibizumab have shown significant efficacy against DMO in clinical trials. The efficacy of aflibercept is discussed in the next section. In the ranibizumab for macular oedema (RIDE and RISE) phase III studies, patients with DMO were randomized to ranibizumab 0.3 mg/day, 0.5 mg/day or sham treatment.[7] In both studies there was a gradual improvement in VA in terms of BCVA scores in both ranibizumab-treated groups. At 24 months there was a substantially greater improvement in VA for the ranibizumab-treated groups compared with the controls (RIDE: 12.0, 10.9 and 2.3 letters; RISE: 12.5, 11.9 and 2.6 letters). At this stage, patients receiving sham injections were switched to ranibizumab 0.5 mg/day. Over the following 12 months, however, these patients showed slight gains but did not achieve the improvements in VA as those who had been treated with ranibizumab from the outset. This suggests that patients with DMO should be treated early to avoid vision losses. □

Key points:

- Systematic management is central to limiting progression of DR
- Anti-VEGF agents have demonstrated the most-significant improvements in VA:
  - Improvements in VA are greater than with steroids
  - Considered by some guidelines to be the current 'gold standard' treatment for DMO in the presence of reduced visual function
- Challenges:
  - Injection frequency and interval between visit frequency
  - A longer-acting agent may address both these concerns

VIVID and VISTA – Clinical Trial Results and Implications

Professor Jean-François Korobelnik

University Hospital, Bordeaux, France

The VIVID and VISTA trials are two similarly designed phase III head-to-head comparisons of the efficacy and safety of intravitreal aflibercept and laser therapy. These are double-masked, randomized, active-controlled trials conducted at multiple centres in Europe, Asia, Australia, (VIVID) and the US (VISTA).[8] A total of 872 patients with type 1 or 2 diabetes who presented with DMO with central involvement and ETDRS BCVA 20/40 to 20/320 were recruited. Patients were then randomised to receive either intravitreal aflibercept injection, 2 mg every 4 weeks (2q4), 2 mg every 8 weeks after five initial monthly doses (2q8), or macular laser photocoagulation.

Baseline characteristics were similar between groups within each study; central retinal thickness (CRT) was slightly greater in VIVID but the proportion who had received prior anti-VEGF therapy was markedly greater in VISTA (in the US) as was the duration of disease (*see Table 1*). The primary endpoint results show that VA rapidly improved during the first 4 weeks of treatment with aflibercept and then improved more steadily up to 52 weeks in both the VIVID and VISTA trials and this was substantially greater than improvements seen with laser treatment. BCVA letter improvement for aflibercept 2q8, 2q4 and laser treatment were 10.7, 10.5 and 1.2, respectively (p<0.0001), in the VIVID trial and 10.7, 12.5 and 0.2 (p<0.0001) in the VISTA trial (*see Figure 3*).[8] This shows that less-frequent dosing of aflibercept at 8-week intervals rather than 4-week intervals has little effect on visual outcomes and both are markedly more effective than laser treatment. Early reports of data from extended follow-up in these trials indicate that the benefits in VA in aflibercept-treated groups subsequently stabilised and the similarities between dosing regimens and improvements over laser treatment were maintained to 100 weeks.[9]

For secondary endpoints, the aflibercept treatment regimens showed greater improvements in retinal pathology compared with laser treatment. Mean reductions in CRT at 52 weeks, as determined by optical coherence tomography (OCT), for aflibercept 2q8, 2q4 versus laser were: 192.4, 195.0 and 66.2 µm, respectively, (p<0.0001) in the VIVID study and 183.1, 185.9 and 73.3 µm, respectively, (p<0.0001) in the VISTA study (*see Figure 4*).

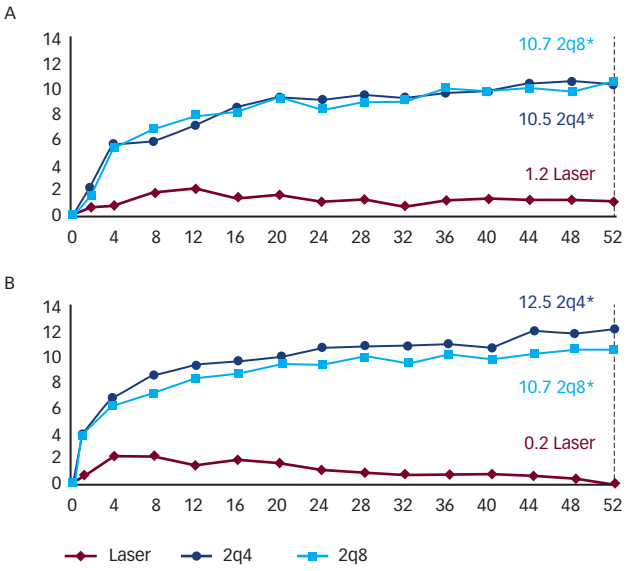
*EYLEA® (aflibercept solution for injection). Prescribing information can be found on page 158.

Table 1: Major Baseline Characteristics of Patients with Diabetic Macular Oedema Recruited to the VIVID and VISTA Clinical Trials

	VIVID			VISTA		
	Laser	IAI 2q4	IAI 2q8	Laser	IAI 2q4	IAI 2q8
Patients, n	132	136	135	154	154	151
Mean age, years (SD)	63.9 (8.6)	62.6 (8.6)	64.2 (7.8)	61.7 (8.7)	62.0 (11.2)	63.1 (9.4)
Mean BCVA, letters (SD)	60.8 (10.6)	60.8 (10.7)	58.8 (11.2)	59.7 (10.9)	58.9 (10.8)	59.4 (10.9)
Mean CRT, µm (SD)	540 (152)	502 (144)	518 (147)	483 (153)	485 (157)	479 (154)
Prior anti-VEGF treatment, n (%)	13 (9.8)	8 (5.9)	15 (11.1)	63 (40.9)	66 (42.9)	68 (45.0)
Mean HbA_{1c}, % (SD)	7.7 (1.3)	7.8 (1.5)	7.7 (1.4)	7.6 (1.7)	7.9 (1.6)	7.9 (1.6)
HbA_{1c} >8% n (%)	42 (31.8)	55 (40.4)	44 (32.6)	45 (29.2)	57 (37.0)	57 (37.7)
Mean duration of diabetes (years)	14.5 (9.8)	14.3 (9.2)	14.1 (8.9)	17.2 (9.5)	16.5 (9.9)	17.6 (11.5)

BCVA = best corrected visual acuity; CRT = central retinal thickness; HbA_{1c} = glycated haemoglobin; IAI = intravitreal aflibercept injection; SD = standard deviation; VEGF = vascular endothelial growth factor.

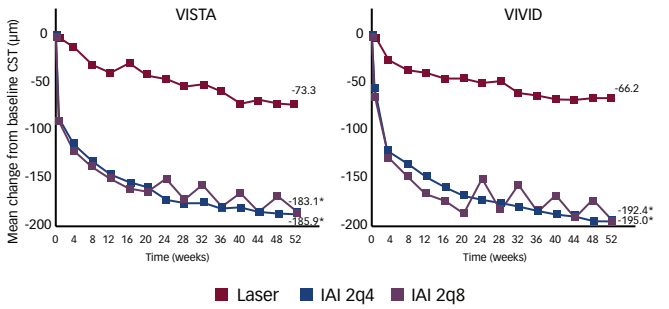
Figure 3: Primary Endpoints from the (A) VIVID and (B) VISTA Clinical Trials – Gains in Visual Acuity in Patients with Diabetic Macular Oedema Over 52 Weeks of Treatment with Aflibercept (2 mg every 4 or 8 weeks) or Laser Photocoagulation



**p<0.0001 versus laser. Source: Adapted from Korobelnik et al. 2014.[8]*

The aflibercept treatments were well tolerated and there were no new safety signals compared with laser treatment. The frequency of ocular and non-ocular adverse events were similar in the three treatment groups in both studies. Treatment emergent, Anti-Platelet Trialists' Collaboration-defined arterial thromboembolic events occurred at similar frequencies in the aflibercept 2q8, 2q4 and laser groups (3.5 %, 3.1 % and 2.8 %). These events were non-fatal myocardial infarction, non-fatal stroke and vascular death. Serious adverse events (SAEs) occurred in 1.7 % of aflibercept 2q8-treated patients, 1.7 % of aflibercept 2q4-treated patients and 4.2 % of laser-treated patients. SAEs included mainly cataract, DR and vitreous haemorrhage.[8] Early reports indicate that no new safety concerns were identified in the additional period to week 100.[9]

Figure 4: Change in Central Subfield Thickness in the VISTA and VIVID Clinical Trials



*Mean change from baseline in central subfield thickness (CST) at study visits up to week 52. *p<0.0001.*

Key points:

- In DMO clinical trials to date, proactive treatment regimens resulted in higher VA gains than reactive *pro re nata* treatment
- In the VIVID (Europe, Asia, Australia) and VISTA (US) trials, in a large patient population, aflibercept demonstrated a greater ability than laser to improve vision and CRT in DMO
- Aflibercept administered 2 mg every 8 weeks performed similarly to the 2 mg every 4 weeks
- Proactive aflibercept 2 mg every 8 weeks provides excellent efficacy, and safety with low patient and clinic burden

Conclusion

In DMO, hyperglycaemia drives vascular dysfunction and low-grade inflammation that is mediated by numerous cytokines among which VEGF is central. These processes result in disrupted fluid transport, a breakdown in the BRB and leakage into retinal tissues causing fluid accumulation and macular cysts. Inhibition of VEGF action therefore is a key approach to managing DMO and preventing retinal damage and eyesight loss.

In patients with diabetes, prevention of DR progression to DMO requires a systematic approach. Management should involve good glycaemic control as well as control of blood pressure and lipid levels (especially LDL-cholesterol). Maintaining these parameters below set limits markedly reduces the risk of DR and DMO progression but this requires intensive monitoring and treatment. Such individual attention

*EYLEA® (aflibercept solution for injection). Prescribing information can be found on page 158.

may not be available to all patients for durations of approximately 10 years that DMO takes to develop after diabetes onset.

For patients who have developed DMO, until recently, laser photocoagulation was the only treatment available.[52] However, anti-VEGF agents, especially aflibercept and ranibizumab, are now becoming established as the 'standard of care' as first-line treatments for a subset of patients with DMO. In the RIDE and RISE trials, ranibizumab showed significant improvements in VA and retinal thickness versus sham treatment and was well tolerated in such patients. This efficacy was markedly better than can be achieved with corticosteroid treatments. The VIVID and VISTA trials, in which aflibercept was directly compared with laser-only treatment, showed significant improvements in efficacy over laser treatment. It is notable that the lower frequency (2q8) regimen provided similar efficacy to the higher frequency (2q4) and there were no safety differences between these two regimens. Aflibercept was very well tolerated and no retinal atrophy was seen in either of the VIVID or VISTA trials. In cases in which DMO occurs in both eyes of a patient, at some clinics, intravitreal treatment of the second eye is not given at the same time but may be delayed by hours or days. This ensures that there are no adverse events following the first injection; there is little evidence that consecutive injections of an anti-VEGF agent into each eye could cause clinically relevant blood levels of the medication. Use of the 2q8 regimen may be more suitable in cases of bilateral administration. It should be emphasised that anti-VEGF medications have not replaced laser therapy but can be used prior to, or in combination with, laser treatment especially in cases of focal leakage.

The disease stage at which different intravitreal medications should be used and how long they should be administered in DMO is not universally agreed. In the past, it was normal practice to wait until HbA_{1c} levels and blood pressure were under control before initiating treatment. This strategy, however, costs time and may lead to retinal damage so now treatments increasingly commence earlier before these targets are reached. Anti-VEGF agents are indicated for first-line use in DMO when the fovea is involved and when vision is impaired. Corticosteroid injections and implants are mainly used second-line and are restricted to patients who fail to respond to anti-VEGF agents. Patients with a CRT of approximately 420 µm should be given anti-VEGF agents but those with a CRT of 370 µm may be given laser, corticosteroid or bevacizumab treatment. Treatment decisions are, however, challenging in DMO and therapy is often stopped too early. A 6-month course of anti-VEGF treatment is the absolute minimum but further treatment should be based on individual requirements.[53,54] It is important when treating DMO that the clinician takes an interest in the patients' diabetes history and adjusts the treatment strategy appropriately.

Aflibercept and ranibizumab are both approved for use in DMO. They have proved effective in clinical trials and as experience of their regular clinical use increases it is likely that they will be used in a wider population of patients as a first-line treatment. Such strategies are likely to help control this increasingly prevalent threat to vision worldwide. □

This article has been produced on behalf of Bayer Healthcare and reports on a Bayer funded and organised symposium.

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