Aflibercept in Europe: Setting New Standards in Retinal Disease Care

Strength and durability in the real world

Highlights from Bayer HealthCare's Satellite Symposium 'Aflibercept in Europe: Setting new standards in retinal disease care,' held on June 7, 2015, at the European Society of Ophthalmology Congress, Vienna, Austria

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Prescribing information can be found on the back cover

Real World Data in Wet AMD: The National Aflibercept Audit

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Since their introduction, anti-vascular endothelial growth factor (VEGF) drugs have transformed patients' visual outcomes in diseases like wet age-related macular degeneration (AMD), branch or central retinal vein occlusion (BRVO and CRVO), and diabetic macular edema (DME). They're also expensive, and that's why you want real-world data that shows that the drug you're using in your clinic works in your patients.

Several published real-world datasets exist, and all show that anti-VEGF therapy provides useful benefits, irrespective of the drug used. But real-world datasets have highlighted a disparity between the outcomes of clinical trials – where the best outcomes came from continuous treatment – and the real world. Many audits have shown that vision gains achieved in the clinic fail to live up to the trial results, as has shown to be the case with ranibizumab (1–3). Why? It seems clear to me that under-treatment is the main issue in real-world practice.

Across the UK (with some exceptions) we have largely followed a *pro re nata* (PRN) ranibizumab regimen (4). In Newcastle, we tried to review patients every four weeks, and treat them according to optical coherence tomography (OCT) findings. This is often a challenge, partly due to National Health Service (NHS) capacity issues, and the fact that many patients struggle to adhere to that schedule. So when the results from the aflibercept VIEW studies came out, which reported that you could get good visual outcomes when administering a 2 mg dose of aflibercept every eight weeks (2q8) – after three initial monthly injections (5,6) – several centers decided to implement this pathway. We hoped that such a regime would improve our outcomes, as we would be better able to provide the required, appointments at the correct time intervals, less monitoring would be required, and patients should find it easier to attend. We have audited our own results and have then rolled this audit out to 16 centers in the UK. The data has been extracted from an electronic medical record that all centers used. So far multi center data is available for patients with one-year follow up and some second year data from our center. Overall, the audit showed that treatment-naïve patients experienced a mean increase of 5.4 letters from baseline; the proportion of eyes with >70 letters rose from 17.2 percent at baseline, to 35.7 percent after one year (Figure 1), and patients received a mean of seven injections over that period. This is very similar to the Newcastle data, but here there were 4,355 eyes at baseline, and 790 eyes after a year. Therefore, the baselines and outcomes are similar even with this much larger patient population, reinforcing and confirming the real-world efficacy of aflibercept.

In reality, a five-letter improvement in a single patient isn't much of a gain and is within the margins of a test error, but for a large national audit group, it is more meaningful. You could argue that the primary aim of anti-VEGF treatment should therefore not be vision gain, but treating as many people as early as possible, to maintain their vision for as long as possible. As these data also show, regardless of the vision gain, on-label, bimonthly treatment does seem to maintain patients' vision in the first year and to a similar extent in the second year. In terms of improvement in patients' VA, about 50 percent gained ≥5

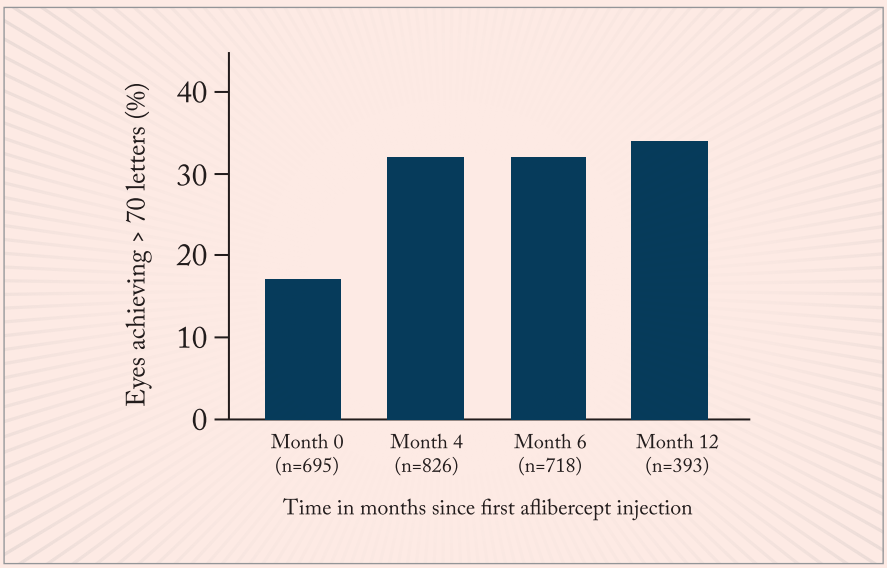

Figure 1. Percentage of eyes achieving over 70 letters in the UK National Aflibercept Audit.

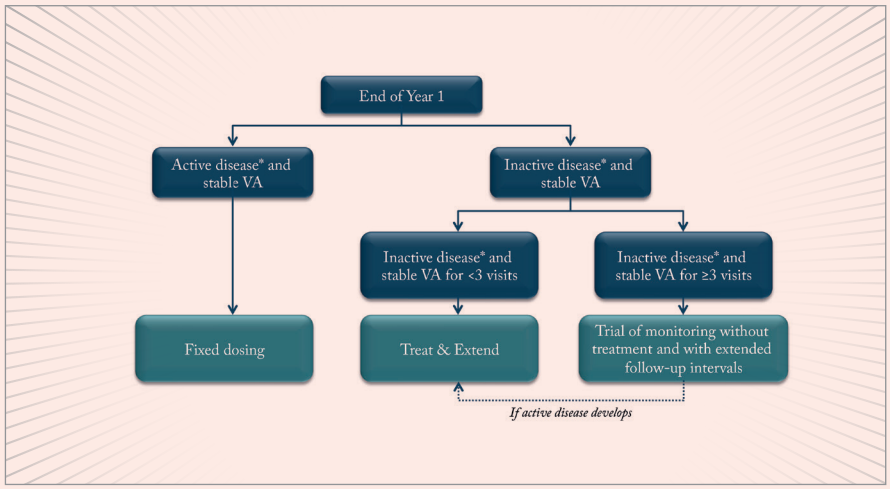

Figure 2. Algorithm for the treatment of wet AMD with aflibercept after Year 1 (7).
*In the opinion of the treating physician. VA, visual acuity.

letters from baseline, and about 35 percent gained >70 letters from baseline.

The multicenter dataset does contain some data on switch patients (3,181 eyes to begin with, and by 14 months, 1,021 eyes with a mean gain of 1.2 letters). These people had prior treatment for a number of years with different anti-VEGF drugs before changing to aflibercept therapy. The data show a slight VA decline in the year before switching and stabilization. It is not possible at this stage to say whether there is an improvement, but the data suggest that the decline is either slowed or arrested, consistent with most published reports on switching patients from other anti-VEGF agents to aflibercept (8–10).

So far we have looked at the first year of treatment, but what happens in the second year? Figure 2 is the proposed algorithm for the treatment of wet AMD with aflibercept after year one from the UK wAMD National Consensus Meeting.

This model recommends that in year two of treatment, patients can continue with aflibercept injections every two months, and our data show that this is effective. The model also suggests monitoring patients in the first year – but not at every visit – as it will provide information to help guide treatment in the second year. So, if patients still show signs of disease activity, you might consider continuing bimonthly injections, but if the retina is dry with infrequent activity, you might consider treat-and-extend. This helps address the issue of capacity, because it is difficult, if not impossible, to assess every patient at every visit. Ideally, at the end of the year we treat those with dry maculae, and extend their appointments by another couple of weeks, continuing this approach for as long as they remain dry. In some cases we stop treatment and observe if they have been stable and dry for some time.

In conclusion, the UK treatment registry data show that the on-label regimen: three monthly injections followed by bimonthly for a year produces useful VA improvements – and greater VA improvements than those achieved with other anti-VEGF agents in the real world (2,11). With switch patients, dramatic improvements are unlikely, but stabilization is certainly possible. Finally, I think this regimen allows us to at least make some effort toward managing capacity issues, which are a serious problem in many countries, not just in the UK.

Case Study: Royal Victoria Infirmary, Newcastle, UK

The Newcastle dataset contains one-year data on 200 eyes (188 patients) and two-year data on 76 patients receiving on-label aflibercept therapy.

Mean baseline visual acuity (VA) was 56.5 ETDRS letters (greater than the VIEW trials' baseline of 53.6 letters [5]).

Our mean vision gain was 5.5 from baseline, which was slightly lower than the VIEW studies' 8.4 [5], but of course, our baseline VA was higher.

In any event, the outcomes were identical by the end of the 12-month period, at 62.0 letters.

The percentage of patients with VA >70 letters was 41.5 percent (compared with 32.6 percent across the VIEW trials [5]), and the vast majority of patients maintained their VA, with 97.5 percent of Newcastle patients losing <15 letters from baseline, compared with 95.3 percent in the VIEW trials – very encouraging.

We maintained roughly the same visual improvement into the second year (mean VA at the end of year 2 was 61.8 letters), requiring a mean of 12 injections over the 2-year period, and the proportions of patients at the end of the second year of treatment with VA of ≥70, 55–69, 35–54, or <35 ETDRS letters were 38.3, 30.0, 26.7 and 5.0 percent, respectively.

Practical Benefits in Treatment Management

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As ophthalmologists, we are all aware of the challenges of managing our patients' anti-VEGF treatment regimens – irrespective of the approach we decide to use – in order to achieve the best possible patient outcomes. One thing is very clear to me: the advent of anti-VEGF drugs (aflibercept, ranibizumab and bevacizumab) has revolutionized the treatment of wet AMD, improving patient outcomes significantly.

Figure 3 charts data from a population-based, observational, Danish patient registry-based study that began in 2000 (12). The chart shows that there was a slow trend towards the reduction of the incidence of AMD-caused blindness between 2000 and 2006. This was then followed by a dramatic drop in incidence rates due to one thing: the introduction of anti-VEGF therapy. I have been fortunate enough to see 2014 data, which continues the downward trend.

When deciding between the various treatment regimens for AMD, we have several possibilities, including:

- a proactive, fixed dosing approach (monthly or bimonthly as per clinical trial data), and
- a reactive, flexible/PRN approach

Fixed proactive regimen

In my opinion, the VIEW studies (5) demonstrated that a fixed treatment regimen with bimonthly injections of aflibercept (after an initial period of three monthly injections) works well – patients experienced a significant visual gain in the first year of treatment. No other approach has shown better outcomes and this one is very straightforward, as monitoring may be necessary only every 3–6 months.

Fixed treatment does have disadvantages, as there is an increased risk of over- or under-treatment – an injection every three months may be too little, whereas monthly dosing might be too much and is also unpopular with both patients and doctors. Nevertheless, our own experience with monthly or bimonthly aflibercept dosing shows that it works; our clinic managed a treatment-naïve patient using this approach over a one-year period. From baseline to nine months, OCT imaging showed that the patient's retina changed from having significant subretinal fluid at baseline to a normal-looking retinal anatomy, and VA improved from 68 to 80 letters.

Flexible PRN

In the VIEW studies, (5,6,13) treatment was fixed for the first year before changing to a flexible PRN regimen (modified quarterly dosing) with aflibercept. The results demonstrate that VA was relatively stable in the first year, but over the next two years there was gradual loss of 3.5 letters (13). This loss could be relevant for some patients, but let's remember that they had fewer injections, so it's a trade-off.

So, PRN regimens are both flexible and individualized, and there's no likelihood of over-treating the disease. The main drawback is the significant risk of under-treatment, as demonstrated by the Bayer-sponsored AURA study (1) – a retrospective analysis of PRN treatments in Europe – which showed that most patients who lose their vision do so because of under-treatment. Another drawback is that the patient

Regimen Pros and Cons

Fixed Proactive Regimen Advantages
- Best outcome
- Straightforward logistics
- Minimum monitoring
- No need for a specialist to administer the injections or monitor the patient

Disadvantages
- Risk of over- or under-treatment

Flexible PRNAdvantages
- Individualized treatment regime
- No over-treatment

Disadvantages
- Lots of clinic visits needed
- Complicated logistics
- Every visit, expert opinion necessary
- Risk of under-treatment
- Variable outcome

Treat-and-extend Advantages
- Individualized treatment regime
- Certainty – treatment every visit
- Fewer clinic visits

Disadvantages
- Lack of data from large randomized controlled trials
- Risk of over-treatment

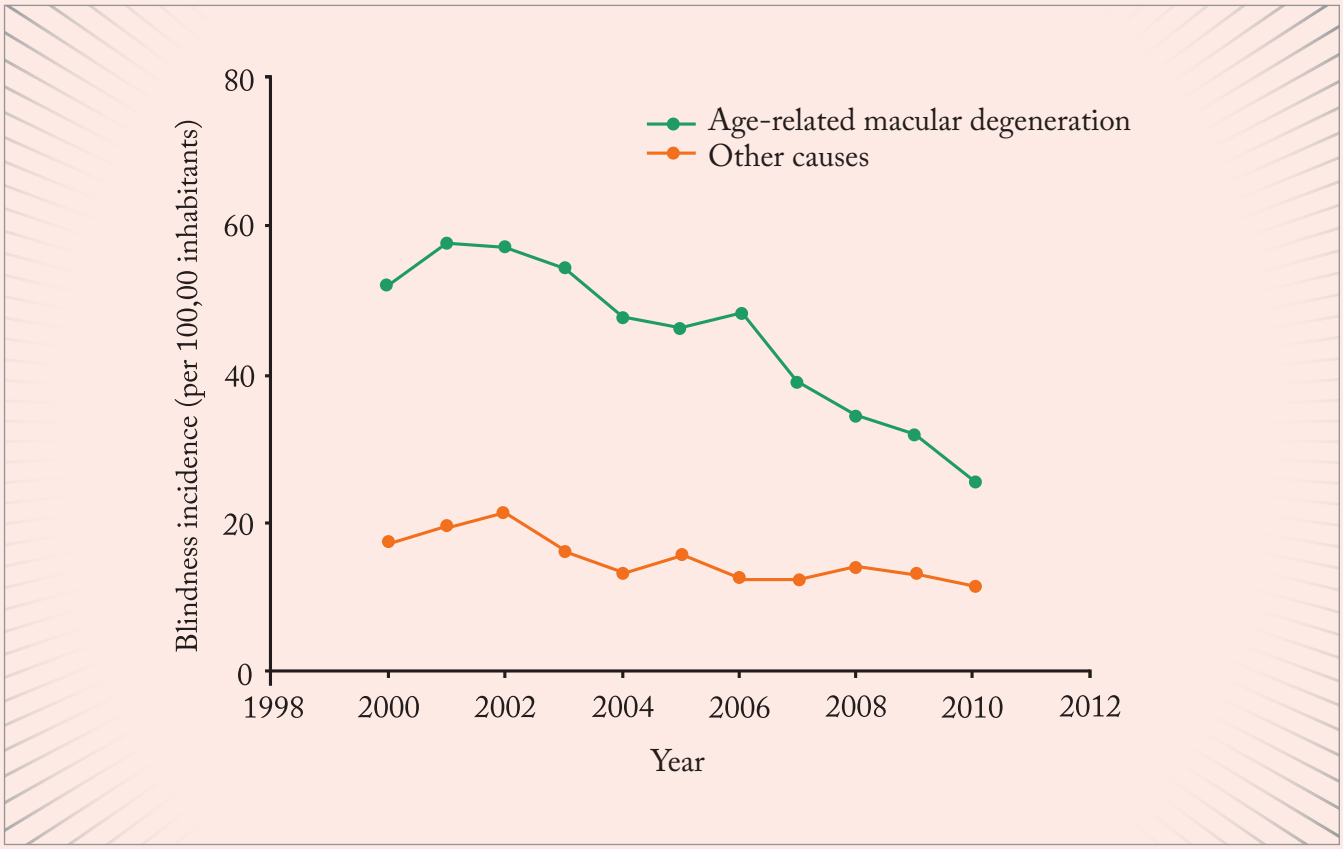

Figure 3. From 2000 to 2010, the incidence of legal blindness from AMD fell to half the baseline incidence. The largest reduction is after introducing intravitreally injected VEGF inhibitors in 2006. Adapted from (12).

must see the ophthalmologist every month for assessment to decide whether an injection is necessary, complicating matters for the patient and the clinic staff.

Treat-and-extend

Per aflibercept's approved posology (13), from the second year onwards, we can individualize treatment for patients according to their disease activity, and by doing so, we minimize the number of hospital visits required. This can mean a lot to patients and save their families and carers – many of whom transport patients to and from the clinic and care for them after the procedure – time, money, and schedule disruption.

In summary, I believe the main benefit of treat-and-extend for the retinal specialist after the appropriate fixed dosing period (4,13) gives us proactive control over the disease, instead of having to react to disease progression – and, at the same time, minimizes the chance of relapse. It also balances treatment, because there is a reduced risk of over-treatment – which is possible using a fixed regimen – and it reduces the risk of under-treatment inherent to reactive PRN regimens. I admit that we need to do more work, as we need more data from a large randomized control trial to provide a clearer view of its efficacy for a larger population. However, I feel that patient management and treatment regimens should always aim to maximize visual outcomes and reduce treatment burden to a manageable level. Therefore, treat-and-extend can help optimize the balance between achieving good vision outcomes and the burden of treatment on the patient.

"Patients experienced significant visual gains in the first year of treatment."

Treating Visual Impairment Due to DME and Macular Edema Secondary to BRVO with Aflibercept: The Highlights

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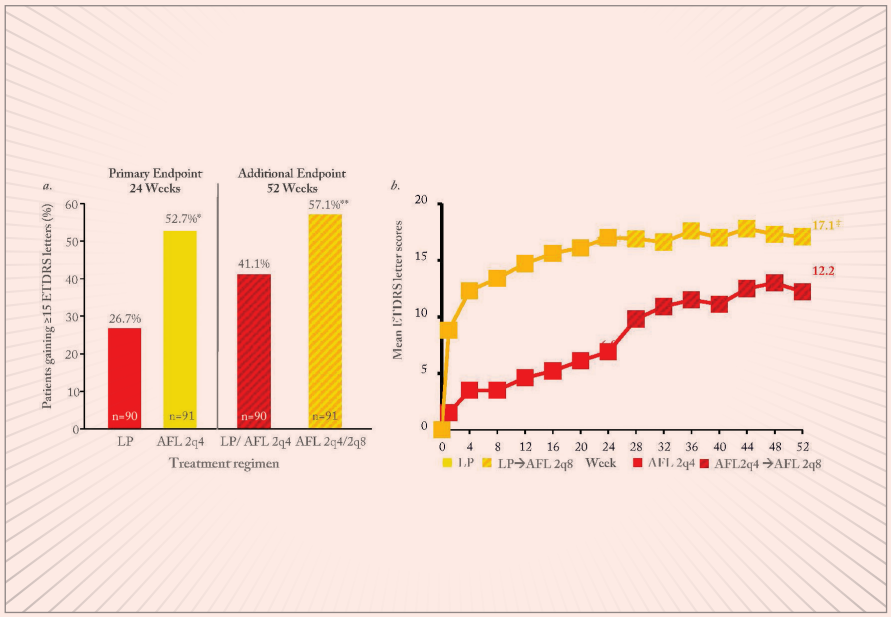

Figure 4. VIBRANT trial results (13,14). a. Proportion of patients gaining≥15 ETDRS letters at weeks 24 and 52 of laser photocoagulation and/or aflibercept treatment; b. Mean patient ETDRS letter score. AFL, aflibercept; LP, laser photocoagulation. *p=0.0003 *vs.* LP; **nominal p=0.0296 *vs.* LP. †p<0.0001 vs. laser. ‡nominal p=0.0035 vs. LP → AFL 2q8.

So far, you have read about the wonderful advances in treating wet AMD with aflibercept. But wet AMD is only one of aflibercept's many indications. I would like to review some of the more recent Phase III aflibercept clinical trial data, namely the VIBRANT, VISTA and VIVID studies, to show how it has benefited patients with other conditions too.

Branch retinal vein occlusion

VIBRANT (14), was a Phase III, randomized, multicenter, double-masked study that compared aflibercept with grid laser photocoagulation in 183 treatment-naïve patients with BRVO. The aflibercept group received a 2 mg dose every 4 weeks (2q4) for the first 20 weeks, followed by a 2 mg dose every 8 weeks (2q8) from weeks 24 to 52 (13,14). The second group received grid laser photocoagulation at baseline (and a single grid laser rescue treatment, if needed, from weeks 12 through 20); from weeks 24 to 52, these patients received an aflibercept 2q8 regimen. The primary outcome was the proportion of patients displaying an improvement in BCVA of ≥15 ETDRS letters from baseline. Other efficacy assessments included mean BCVA and mean reduction in central retinal thickness (CRT) from baseline levels. The primary and secondary analyses were performed at weeks 24 and 52, respectively, and the results are summarized in Figure 4.

At 24 weeks, aflibercept-treated patients fared better than their laser-treated counterparts: a significantly greater proportion of these patients gained ≥15 ETDRS letters from baseline (52.7 *vs.* 26.7 percent, p=0.0003; Figure 4a). Furthermore, mean BCVA was greater (17.0 *vs.* 6.9 letters, p=0.0001; Figure 4b), in the aflibercept group, relative to the laser treatment group. The second period of the trial (where all patients received a bimonthly aflibercept regimen) revealed that the initial visual gains and anatomical improvements achieved with the 2q4 aflibercept regimen were retained – and that patients switched to 2q8 aflibercept from laser therapy displayed dramatic improvements from baseline in BCVA and CRT, almost catching up with the patients originally randomized to receive aflibercept (Figures 4b and 4c).

Diabetic macular edema

Diabetes is the epidemic of the century, the complications from which include amputation, stroke, end stage kidney failure, and crucially, blindness. One form of diabetes-related blindness, DME, is particularly pernicious: unless detected by fundoscopy, patients are unaware of its presence until significant damage has occurred. It's a bilateral condition, growing in prevalence, and a leading cause of legal blindness. It affects many people of working age, meaning the societal impact of DME-related vision loss is profound.

DME is multifactorial in origin, but it's clear that a large part of the

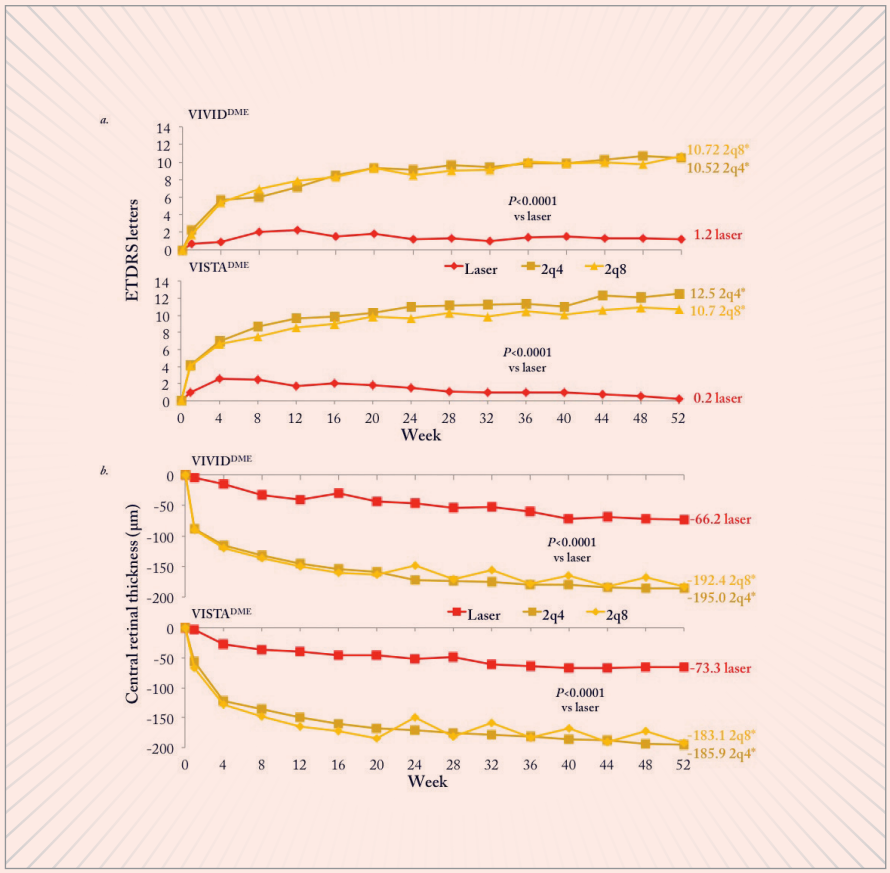

Figure 5. Efficacy results from the VIVID and VISTA trials. a. Mean change in BCVA (ETDRS letters) from baseline; b. Mean central retinal thickness. *Test for difference *vs.* laser (ANCOVA) P<0.0001. VIVID: Laser, n=132; 2q4, n=136; 2q8, n=135. VISTA: Laser, n=154; 2q4, n=154; 2q8, n=151.

problem is local hyperglycemia-related inflammation, which damages the retinal microvasculature, often leading to edema. DME can be challenging to treat – over the years, we have seen variable responses to mainstay therapy, where, according to the current literature, about 40 percent seem to be resistant to the drug. Aflibercept is the most recent anti-VEGF agent brought to the market in the EU, gaining approval for "the treatment of visual impairment due to DME" on the basis of results from the Phase III VISTA and VIVID trials (15). VIVID and VISTA enrolled 872 patients who had DME with central involvement, and randomized them to receive either a 2q4 aflibercept regimen for the 52-week duration of the trial, a 2q8 aflibercept regimen (after five initial consecutive 4-weekly 2 mg doses) or laser photocoagulation at baseline. The primary outcome was the mean change in BCVA (in ETDRS letters) from baseline to week 52 (Figure 5).

At week 52, both aflibercept regimens resulted in significant vision gains compared with laser therapy. In VISTA, mean BCVA gains in the 2q4 and 2q8 were +12.5 and +10.7 letters from baseline, compared with +0.2 letters with laser photocoagulation (p<0.0001); in VIVID, these gains were +10.5, +10.7 and +1.2 letters from baseline, respectively (p<0.0001; Figure 6a). Likewise, at week 52, both aflibercept regimens resulted in significantly greater reductions in mean CRT from baseline levels (Figure 6b). Of note, the benefits achieved with both aflibercept regimens in the first year were maintained out to 100 weeks (16).

"The benefits achieved with both aflibercept regimens in the first year were maintained out to 100 weeks."

These are impressive results. However, there is another factor worth noting: aflibercept's pharmacology (17-19). Designed as a cytokine trap, aflibercept is a soluble fusion protein that contains specific extracellular components of VEGF receptors 1 and 2, fused to the constant region of immunoglobulin G1. This results in a molecule with two identical arms, both capable of binding VEGF and, importantly, the pro-angiogenic cytokine placental growth factor (PlGF). Aflibercept, therefore, can uniquely bind both ends of activated, dimerized VEGF or PlGF between its arms, rendering them inert, and preventing it from binding to the native receptors or cross-linking – something that is possible with of monoclonal antibodies and antibody fragments. PlGF inhibition may have additional benefits beyond inhibiting angiogenesis; PlGF production has been associated with localized inflammation (20) – as is the case in patients with diabetes (21).

Aflibercept's unique pharmacology may help explain the favorable results seen in the aforementioned trials.

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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 of neovascular (wet) age-related macular degeneration (AMD), macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) and visual impairment due to diabetic macular oedema (DMO) in adults. **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. **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. **Contra-indications:** 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. **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. *Common*: retinal pigment epithelial tear, detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract (nuclear or subcapsular), corneal abrasion or erosion, corneal oedema, increased intraocular pressure, blurred vision, vitreous floaters, vitreous detachment, injection site pain, eye pain, foreign body sensation in eyes, increased lacrimation, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival or ocular hyperaemia. *Uncommon*: Injection site irritation, abnormal sensation in eye, eyelid irritation. *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: March 2015.**

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