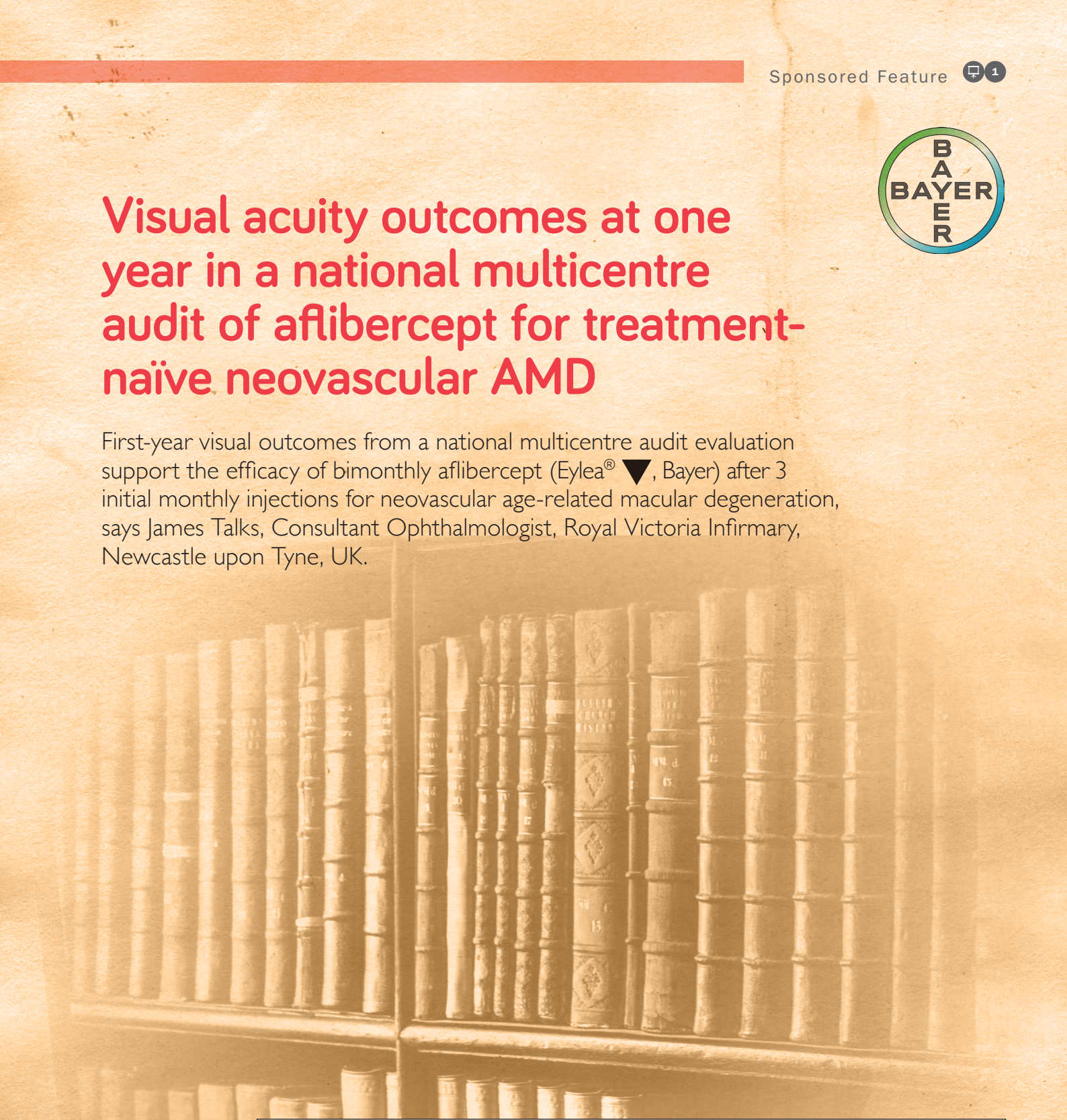
Visual acuity outcomes at one year in a national multicentre audit of aflibercept for treatment-naïve neovascular AMD

First-year visual outcomes from a national multicentre audit evaluation support the efficacy of bimonthly aflibercept (Eylea® ▼, Bayer) after 3 initial monthly injections for neovascular age-related macular degeneration, says James Talks, Consultant Ophthalmologist, Royal Victoria Infirmary, Newcastle upon Tyne, UK.



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Therapeutic strategies using intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy have advanced the standard of care for neovascular age-related macular degeneration (nAMD), preventing moderate visual acuity (VA) loss in most patients with nAMD. However, for optimal treatment outcomes, continuous or frequent injections and/or regular monitoring are required.

The greatest vision outcomes observed in clinical trials evaluating antiangiogenic agents ranibizumab and unlicensed bevacizumab for nAMD have been obtained with a 4-weekly dosing regimen (1–3). In the VIEW 1 and VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) studies, two similarly designed, phase 3 randomised controlled clinical trials, aflibercept dosed either monthly or given bimonthly after 3 monthly loading injections was non-inferior to monthly ranibizumab in maintaining vision (losing <15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters), and provided significant VA gains (≥15 letters vs. baseline VA) comparable to monthly ranibizumab at 52 weeks (4).*

Clinical trial treatment regimens for nAMD present challenges in real-world practice

Improvements in mean visual acuity observed in randomised clinical trials of anti-VEGF therapy for nAMD have not always been consistently replicated in everyday clinical practice (5–10).

Patient heterogeneity, measurement techniques, the quality of service delivery, treatment regimens, and adherence with recommended protocols differ substantially in clinical settings within and across national health systems. Delays in the initiation of treatment, as well as recurrence of neovascular activity and/or progressive morphological changes, may lead to visual acuity loss (10,11). Discontinuous or variable follow-up in routine clinical care may also underlie observations of reduced efficacy of anti-VEGF therapy compared with clinical trial results (5–10).

Service capacity and resource constraints pose challenges adopting and following the treatment regimens associated with optimal vision gains for patients with nAMD, with a continuous retreatment and monitoring burden impacting healthcare providers, patients, and national health systems. Various proactive and reactive anti-VEGF treatment regimens for nAMD have been progressively adopted in retinal practice in an effort to decrease injection and monitoring frequency. These include fixed-interval, pro re nata (PRN, treatment as needed), treat to target, and treat-and-extend protocols, as well as combination approaches.

In the first year of antiangiogenic therapy for nAMD, a fixed-interval dosing regimen may prove to be a more predictable treatment approach than as-needed treatment regimens, with less risk of visual compromise from active neovascular disease due to continuing VEGF inhibition. Less favourable clinical outcomes in nAMD are associated with decreased injection frequency and/or reduced monitoring visits with ranibizumab treatment (7). There was a mean loss of 0.2 letters by month 12 in the phase 3b PIER study (n=184), which involved an extension to quarterly injections of 0.5 mg ranibizumab following three consecutive monthly doses, suggesting that quarterly dosing is inferior to monthly retreatment (12).

Nonetheless, good visual outcomes have been reported using a treat-and-extend regimen in routine clinical practice (13,14). Treat-and-extend involves treating and then extending the interval until the next treatment, by 2-week intervals, to a maximum of 12 weeks, with the goal of maintaining visual and anatomical gains but with fewer injections. This approach with anti-VEGF therapy in nAMD is being used increasingly to improve resource use, reduce treatment burden and avoid unnecessary injections beyond the first year, for example in patients achieving stable vision and with inactive choroidal neovascularisation (15).

Mean baseline VA ETDRS letters (full eligible cohort, n=1,840 eyes)	*Mean VA ETDRS letter improvement in first-treated eyes (n=990)*	*Mean VA ETDRS letter improvement in all-comers (n=1,321)*	*Mean number of injections*	*Mean number of clinic visits*	*Proportion (%) with stable vision (losing <15 letters)*	*Proportion (%) with VA ≥70 ETDRS letters (vs. baseline)*
53.7	5.5	5.1	7.0	7.3	92.0	33.7 (16.4)

Table 1. National multicentre audit by the United Kingdom Aflibercept Users Group: outcomes at 1 year in treatment-naïve nAMD cohort treated with intravitreal aflibercept, March 2013-April 2014 (16). Abbreviations: nAMD, neovascular age-related macular degeneration; VA, visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

*The dosing regimen for ranibizumab used in the VIEW trial programme does not represent its current UK posology, which can be found in its Summary of Product Characteristics [Lucentis® Summary of Product Characteristics (SmPC): https://www.medicines.org.uk/emc/medicine/19409].

Real-life patient outcomes providing bimonthly aflibercept after initiation phase

To determine the first-year visual outcomes achieved in routine clinical practice providing aflibercept according to the licensed treatment posology (the VIEW study protocol for nAMD of bimonthly treatment for the first year after a loading phase of 3 consecutive monthly injections), the United Kingdom Aflibercept Users Group conducted a retrospective data analysis of anonymised electronic medical record (EMR) data from 16 National Health Service (NHS) centres for all treatment-naïve eyes initiated on intravitreal aflibercept treatment for nAMD between March 2013 and April 2014 (16). The audit involved 1,840 treatment-naïve eyes of 1,682 patients initiated on aflibercept therapy for nAMD at least 1 year before data extraction.

The overall aim of the audit was to assess whether the licensed treatment posology of aflibercept for nAMD in the first year could be realistically provided to newly-diagnosed nAMD patients and maintained in everyday clinical settings, and to evaluate the visual acuity outcomes achieved. An additional objective was to compare the recorded visual results at 1 year from treatment initiation with those observed in randomised clinical trials and real-world studies of anti-VEGF therapy for nAMD.

Analyses of this type are viewed as audit or service evaluations, therefore there was no requirement for ethics approval, and the study was conducted in accordance with the Declaration of Helsinki and the UK's Data Protection Act. Written approval for extraction of anonymised data was obtained from each centre's lead clinician and nominee responsible for data protection. The dataset mandated by the EMR system was defined prospectively prior to first data entry, hence the study methodology resembles an electronic case report form used in clinical trials rather than a conventional analysis of unstructured data in a retrospective chart review.

Clinical centres that confirmed they were providing aflibercept to treat nAMD according to the licensed treatment posology and that the same ophthalmology EMR system was being used to record all visual acuity and injection episodes throughout the AMD care pathway were selected to participate in the study. The minimum data set mandated by the EMR system included age, gender, visual acuity, injection episodes, and complications.

"…aflibercept administered according to the licensed treatment posology for nAMD is an effective strategy, yielding VA outcomes that approach those observed in pivotal clinical trials."

A diagnosis of nAMD was confirmed using optical coherence tomography (OCT) in all patients, augmented with fluorescein angiography assessment, including indocyanine green angiography, in most patients. Visual acuity, injection procedure, and follow-up data were entered live into the EMR system by staff members. Entry of operative and postoperative ocular and systemic complications data fields within the EMR system was mandatory at every clinic visit.

At each clinic visit at all centres, ETDRS visual acuity letter scores at 2 metres were recorded. The best-measured visual acuity value was used in the dataset analysis, with most visual acuities recorded using habitual correction. The value of 0 letters was used for values corresponding to counting fingers, hand movements, no light perception, and light perception. Investigators analysed visual acuity data in 4-week intervals, with any gaps in a patient's VA data imputed using the mean of the observation before and after the missing period. As loss to follow-up is common in clinical practice, no observations were carried forward beyond the last recorded VA score.

Top-line results confirm rapid and sustained vision improvement through 12 months

The one-year data analysis demonstrates that aflibercept administered according to the licensed treatment posology for nAMD is an effective strategy that can be implemented successfully by multiple treatment centres in the United Kingdom, yielding VA outcomes that approach those observed in pivotal clinical trials. First-year visual acuity outcomes show:

- The initial visual acuity improvement that followed an initial treatment loading phase of 3 monthly injections was maintained at the end of 1 year using a bimonthly fixed regimen.
- Overall, the mean VA improved to 58.8 ETDRS VA letters at 1-year follow-up (n=1,321 eyes), representing a mean VA letter gain of 5.1 from a mean baseline VA of 53.7 letters (n=1,840 eyes).
- First-treated eyes gained 5.5 letters to a mean VA of 58.2 letters at 1 year (n=990 eyes), from a mean starting VA of 52.7 letters (n=1,388 eyes).

	Integrated analysis of VIEW studies 2q8 arm Week 52 (4)*	*United Kingdom Aflibercept Users Group (all eyes, March 2013-April 2014) 1 Year (16)*	*Moorfields Eye Hospital Aflibercept Audit Weeks 8/16 (20)*	*Moorfields Eye Hospital Aflibercept Audit 1 Year (21)*
Number of patients/eyes	607	1,321	250	52
Mean baseline VA (letters)	53.6	53.7	55.6	56.0
Mean number of injections	7.5	7.0	Not reported	7.2
Mean VA change (letters)	+8.4	+5.1	8 weeks: +6.9 16 weeks: +6.7	+8.5
<15-letter loss (stable vision)	95.3%	92%	Not reported	96.2%
≥15 letters gained	30.9%	18%	Not reported	26.9%

Table 2. Outcomes in routine clinical practice providing aflibercept for treatment-naïve nAMD patients according to the VIEW study protocol (4,16,20,21). Abbreviations: VA, visual acuity. *2q8 regimen, bimonthly 2 mg aflibercept dosing after 3 initial monthly injections.

- For second-treated eyes, the mean VA improved from a baseline of 60.4 letters (n=245 eyes) to 63.7 letters at 1 year (+3.3 letter change, n=173 eyes).
- The proportion of eyes achieving a mean VA score of 70 letters or more increased two-fold, from 16.4 per cent at presentation to 33.7 per cent at 1 year.
- The proportion of eyes that maintained vision (losing <15 letters) at 1 year was 92 per cent.

The mean number of injections in all 1,840 eyes with potential for follow-up at 1 year was 7.0 (median, 8.0), and the mean number of clinic visits was 7.3 (median, 8.0).

Data covering 1,840 treatment-naïve eyes of 1,682 nAMD patients started on aflibercept treatment were included. The mean and median ages at baseline injection were 80.0 and 81.0 years (interquartile range, 50-102 years), respectively. A majority (63.4 per cent) were women. There was a total sample size of 1,321 eyes known to have been continually followed up at 1 year. Of these, the proportions losing 5, 10, or 15 ETDRS letters from baseline to 1 year were 22 per cent, 13 per cent, and 8 per cent, respectively, and the proportions that gained 5, 10, or 15 ETDRS letters or greater from baseline to 1 year were 48 per cent, 32 per cent, and 18 per cent, respectively.

The greatest visual improvements were observed in eyes that had the poorest vision at baseline. Visual acuity was <35 letters in 209 eyes at baseline: this cohort registered a mean VA improvement of 11.1 letters at 1 year. A mean decline of 2.0 letters at 1 year was observed in 210 study eyes that had a baseline VA of more than 70 letters. However, patients with good baseline vision (≥55 letters) maintained their visual function at 1 year. On average, second-treated eyes (n=245 patients) had a higher baseline vision and maintained a better visual acuity through 1 year of aflibercept treatment, but showed less vision improvement than first-treated eyes with poorer starting vision.

At 1 year, data were missing for 28 per cent of eyes. The median vision in these eyes when last seen was 55.0 letters (mean, 51.4 letters), with a wide standard deviation of 20.9, and one quarter had a mean VA of ≥69.0 letters.

Practice considerations

Pivotal clinical trial outcomes evaluating aflibercept for nAMD are slightly better than the visual outcomes observed in this audit of routine clinical practice and experience across multiple clinical centres in the United Kingdom providing aflibercept according to the licensed treatment posology. The mean vision improvement at 1 year from a mean untreated baseline of 53.7 letters was 5.1 ETDRS letters, compared with a mean increase in best-corrected VA of 8.4 letters at 52 weeks from a mean presentation baseline of 53.6 letters from the integrated analysis of the VIEW studies using the same treatment regimen (4,17).

The visual acuity outcomes recorded at 1 year following aflibercept treatment initiation appear better than those observed in previously published reports of real-world clinical practice evaluating other anti-VEGF therapies for nAMD. Moreover, early and rapid visual gains seen during the first 12 weeks of treatment with monthly aflibercept were successfully sustained through 12 months with proactive bimonthly dosing and with no monitoring required between treatment intervals. Principal VA outcomes are shown in Table 1 and Figure 1.

Compared with participants in randomised controlled clinical trials, patients in a real-world setting will present in clinic with variable morphological characteristics, have a broader range of lesion type and size, a wider range of starting vision, having more atrophy or fibrosis at baseline, more concurrent ocular comorbidities, such as epiretinal membrane or glaucoma, and a greater range of other health issues. There may also be early detection of fellow eye involvement. It is to be expected

therefore that visual acuity outcomes in real-life clinical practice may not necessarily mirror more robust efficacy results from rigorous randomised clinical trials that involve carefully selected and followed participants.

Elderly patients are known to achieve less vision improvement than younger patients (18), and the mean baseline age in this UK audit was higher than that in the integrated analysis of the VIEW studies (80.0 years vs. 75.8 years), with the age range at baseline rising to 102 years (interquartile range, 50-102 years) (16,17). This real-life clinical audit included second-treated eyes with better starting vision, which may have impacted the overall current findings as these eyes gained less vision than first-treated eyes over 1 year. Visual acuities were assessed using the patient's habitual correction, if any, in place, so there may have been instances of uncorrected or undercorrected refractive error (16,19). Also, provision of treatment within tight timelines is not always practical or achievable in busy hospital clinics.

The presenting VA at baseline is a major predictive factor in determining the magnitude of vision that is gained with intravitreal anti-VEGF therapy for nAMD. In the ANCHOR (Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration) study, there was a mean gain in visual acuity of 11.3 letters at year 1 using monthly ranibizumab treatment, although the mean baseline VA was only 47.1 letters (1). In the MARINA (The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration) study, the mean VA gain at year 1 from a baseline visual acuity of 53.7 letters was 7.2 letters (2). These vision improvement outcomes, expressed as gain from baseline in mean VA letter score, have rarely if ever been replicated in clinical practice.

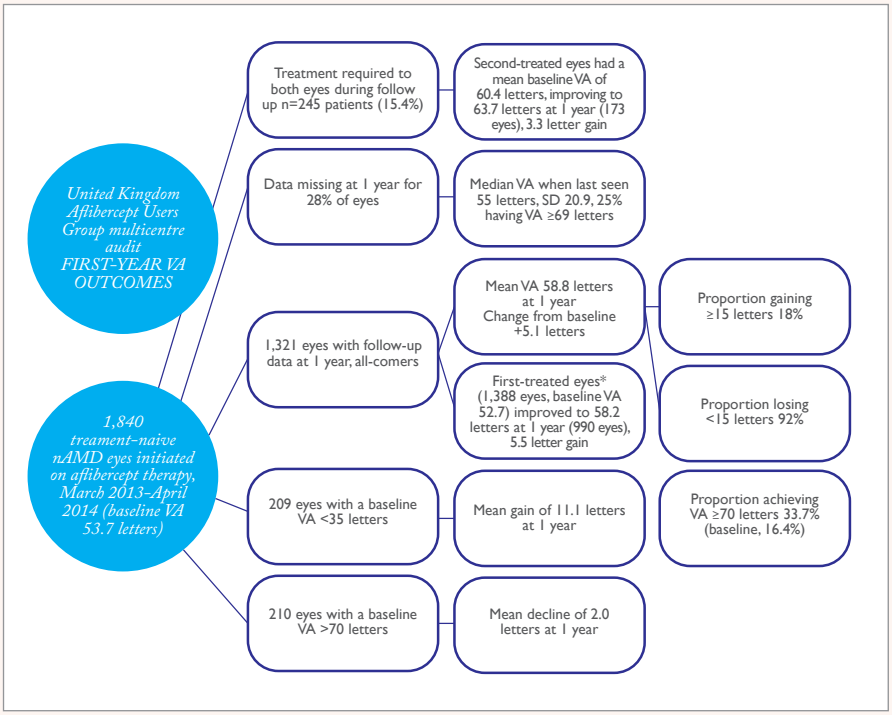

Figure 1. Flowchart describing audit population and clinical outcomes from the United Kingdom Aflibercept Users Group report of first-year outcomes providing aflibercept according to the licensed treatment posology for nAMD (16). Abbreviations: VA, visual acuity; nAMD, neovascular age-related macular degeneration; letters: Early Treatment Diabetic Retinopathy Study; SD, standard deviation. *Eyes were not classified as first- or second-treated eyes if treatment was initiated in both eyes on the same day (196 eyes of 98 patients), or if there was a different indication in each eye, such as vein occlusion (10 eyes), or a different drug (1 eye).

On balance, the United Kingdom Aflibercept Users Group believes that the visual outcomes observed in routine clinical practice in the UK compare well with results reported from pivotal aflibercept nAMD randomised clinical trials (Table 2) (4,16,20,21). A factor contributing to these positive outcomes is probably the fact that a bimonthly retreatment regimen was effectively delivered throughout the first year of treatment, with a median of 8 aflibercept injections given, the eighth injection administered at 12 months.

Treatment efficacy of a particular anti-VEGF administration regimen may also be assessed by the degree of long-term vision stabilisation after an initial maximum visual acuity gain. Reports of real-world ranibizumab data suggest a subsequent gradual decline in vision over time following an initial visual acuity gain after the initial treatment loading phase (6). In the current study, the initial visual acuity improvement following a 3 monthly treatment phase was maintained at the end of 1 year after an extension of the treatment interval to every 2 months.

The evaluation by the United Kingdom Aflibercept Users Group represents what is believed to be one of the largest efficacy audits of intravitreal aflibercept for nAMD in real-life multicentre clinical practice published to date. The outcome data confirm that implementing the licensed treatment posology can lead to fewer visits and less frequent monitoring in the first year of aflibercept treatment, and still generate positive and durable vision outcomes in nAMD patients. The visual acuity outcomes compare favourably with earlier audits of

Study	*Description*	*Mean number of visits (Year 1)*	*Mean number of injections (Year 1)*	*Number of patients enrolled*	*Mean VA change from baseline to Year 1 (ETDRS letters)*
ANCHOR (1)	Multicentre, 2 year, double-blind phase 3 study	12.0	12.0	423	+11.3
MARINA (2)	Multicentre, 2 year, double-blind phase 3 study	12.0	12.0	716	+7.2
AURA (7)	Retrospective, non-interventional, multi-country, global population	8.6	5.0	2,227	+2.4
UK AURA Cohort (23)	Retrospective, findings from the UK cohort of AURA	10.4	5.8	410	+6.0
LUMIERE (8)	Retrospective, descriptive, observational	8.6	5.1	551	+3.2
Zhu et al 2015 (9)	Retrospective case series	-	7.5	208	+1.9
UK nAMD EMR Users Group (22)	Multicentre, national database observational study	9.2	5.0	11,135	+2.0

Table 3. Real-life outcome data evaluating ranibizumab for nAMD do not match those from rigorous phase 3 randomised clinical trials (1,2,7–9,22,23). Abbreviations: nAMD, neovascular age-related macular degeneration; VA, visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

The ranibizumab studies discussed here may not represent the full range of current licensed posologies of ranibizumab. Please consult the ranibizumab SmPC.

intravitreal ranibizumab provided using an intended PRN regimen in clinical practice (5).

Real-world study outcomes evaluating anti-VEGF therapy for nAMD rarely match pivotal clinical trial results

The introduction of Intravitreal antiangiogenic therapy for macular degeneration has undoubtedly helped transform the visual outcomes achievable in patients with nAMD, the vast majority maintaining vision on continuous VEGF inhibition therapy. However, published real-world studies of ranibizumab treatment for nAMD show patient outcomes that are often far poorer than those reported in randomised controlled trials of both fixed and as-needed treatment regimens (Table 3) (1,2,7–9,22). Low dosing frequency and hence undertreatment appears to be commonplace in everyday practice. Effective service delivery and timely treatment provision for a broad heterogeneous population of patients requires sufficient capacity and funding, which can be challenging in an environment of finite resources and competing constraints.

An analysis of published real-world studies of ranibizumab treatment for nAMD found that, at 12 months, the mean change from baseline VA was between -2.0 letters and +5.5 letters, with a grand mean of +2.9±3.2 and weighted mean of +1.95 (5). The mean percentage of patients gaining 15 or more letters at 12 months was 19.0±7.5 per cent. A grand mean (±SD) of 5.5±0.8 ranibizumab injections were given over 12 months (range 4.2 to 7.5).

In a similar audit approach to that conducted by the United Kingdom Aflibercept Users Group, a large, multicentre nAMD EMR database study found that real-world outcomes achieved using ranibizumab to treat nAMD at a large number of centres across the UK do not match the results achieved in most randomised clinical trials (22). This study included 92,976 treatment episodes at 14 hospitals (n=12,951 eyes of 11,135 patients). Participating centres used a loading phase of 3 monthly ranibizumab injections and a PRN retreatment regimen. For eyes followed for at least 3 years, mean VA letter score (change from baseline) at 1, 2 and 3 years was 57.0 (+2.0), 56.0 (+1.0) and 53.0 (-2.0), respectively, from a baseline VA of 55.0 letters. The median number of treatments in years 1, 2 and 3 was 5, 4, and 4, respectively, reflecting substantially fewer injections than those given in pivotal randomised clinical trials.

An international multi-country evaluation of real-life experience of ranibizumab therapy for nAMD reported a mean change in visual acuity score from baseline to year 1 and year 2 of +2.4 and +0.6 letters, respectively, with an initial improvement in VA not maintained over time (6). The mean number of injections in the first and second year was 5 and 2.2 injections, respectively. Retreatment injection frequency varied between countries, and greater improvements in VA were seen with more frequent visits and injections, although even here vision declines over time (23).

Another observational database study

of two-year outcomes of treat-and-extend intravitreal anti-VEGF therapy, predominantly ranibizumab, for nAMD showed improved mean VA gains with more frequent retreatment injections (13). The mean change in VA at 24 months was +2.7 letters for eyes commencing treatment in 2007 after a mean of 9.7 injections over 2 years, compared with a mean change in VA of +7.6 letters for eyes starting therapy in 2012 and receiving a mean of 14.2 injections over 2 years. The latter injection frequency is similar to that associated with a bimonthly fixed regimen after an initial treatment loading phase.

Observational data from the Fight Retinal Blindness Study Group illustrate long-term outcomes of VEGF inhibition for nAMD in real-world practice. Seven years after initiating treatment, mean VA was 2.6 letters lower than baseline for the 131 eyes still being followed, and 40 per cent had a visual acuity ≥70 letters (20/40 Snellen equivalent) (14). More frequent ranibizumab injections were given to patients in this study than that reported in other earlier real-world studies of ranibizumab, with a median of 6 injections and 9 visits recorded over the first 12 months, and then 5 treatments and 7 to 9 visits per year thereafter through 7 years.

Reduced injection frequency and patient heterogeneity in real-life probably in part contribute to the reduced effectiveness of ranibizumab observed in clinical practice, but monitoring frequency and as-needed retreatment criteria may also account for limited efficacy. As-needed regimens entail treatment of symptomatic disease, and it is possible, with less intensive monitoring, that undetected leakage and recurring fluid (i.e., presence of active neovascularisation) may contribute to progressive damage and visual loss.

Benchmarks for good VA outcomes

The retrospective data analysis of a multicentre EMR database demonstrates that a bimonthly fixed regimen with aflibercept therapy produces meaningful visual improvements in treatment-naïve nAMD patients. Vision gains from baseline proved to be rapid, and were sustained through 12 months of continuous aflibercept dosing. The national multicentre audit also demonstrated that anti-VEGF therapy is effective in patients who have poor presenting visual acuity (<35 letters).

At 12 months, the overall mean vision gain from baseline was greater than 5 ETDRS letters, representing an additional one line on the ETDRS visual acuity chart. Moreover, 92 per cent of eyes maintained vision, and more than 30 per cent of eyes achieved functional vision of 70 letters or more. In the VIEW studies, 32.6 per cent of patients receiving bimonthly intravitreal aflibercept injection after 3 consecutive monthly doses had a VA of 70 letters or better (≥20/40) at 1-year follow-up (17). For the UK AMD EMR Users Group database study, the proportion of eyes with VA ≥70 letters increased from 16 per cent at baseline to 30 per cent at 1-year follow-up (22).

Multicentre audit evaluations allow comparisons of nAMD treatment outcomes achieved across different national sites. Benchmarking of outcomes obtained in clinical practice enables treatment centres to compare patient results, and to identify opportunities to improve standards of care and treatment protocols to ensure the best possible visual outcomes. This should allow clinicians, commissioners, and providers to better identify opportunities for continuing service improvements.

It is also important to consider useful visual outcome measures beyond change in mean visual acuity from baseline, in order to fully document and assess all facets of treatment and patient benefit, such as the proportion of eyes achieving functional vision of ≥70 letters. Early diagnosis, prompt treatment and good adherence to regular retreatment follow-up remain crucial in the effective ongoing management of nAMD, as those patients with better presenting vision are more likely to achieve good final VA outcomes and maintain useful functional vision.

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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 1 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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