The 3rd annual meeting of the Global Retinal Network Program, an educational initiative developed by Bayer to foster scientific exchange and dialogue, attracted more than 350 delegates from 31 countries. A faculty of international retina specialists reviewed and debated current knowledge, shared clinical experience and considered practical approaches for achieving and maintaining optimal outcomes in the management of patients with retinal disease.

This supplement has been produced on behalf of Bayer and reports the Bayer-funded and organised 3rd Global Retinal Network Program Annual Meeting, May 20–21, 2017, Lisbon, Portugal. Attributed comment and opinion reflect the views of faculty speakers and participants and do not necessarily reflect those of Bayer. Prescribing information can be found on the last page.

Program proceedings

Plenary session I: The nature of retinal diseases

- The underlying mechanisms of retinal diseases
  Mr Richard Gale, The York Hospital, York, UK
- A focus on nAMD: early diagnosis and prompt proactive treatment in year 1
  Mr Ian Pearce, Royal Liverpool University Hospital, Liverpool, UK
- A focus on DME: early diagnosis and intensive treatment in year 1
  Dr Figen Şermet, Ankara University School of Medicine, Ankara, Turkey
- Management of DME and nAMD in year 1 and beyond
  Dr Susan B Bressler; The Julia G. Levy, PhD Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine & Hospital, Baltimore, MD, USA
- Impact of retinal disorders: a patient perspective
  Professor Bora Eldem, Hacettepe University, Ankara, Turkey

Plenary session II: Insights in retinal disease management

- Maximizing the use of OCT
  Mr Richard Gale
- Aflibercept across the retinal disease spectrum
  Dr Susan B Bressler
- Real-world evidence of anti-VEGF treatment outcomes
  Mr Ian Pearce
- Treatment options in DME: the role of anti-VEGF agents, laser and steroids
  Dr Neil Bressler; Wilmer Eye Institute, Johns Hopkins University School of Medicine & Hospital, Baltimore, MD, USA

Plenary session III: Management of DME in clinical practice

- Clinician debate on the role of laser in DME
  Proponent: Dr Hazem El-Sabagh, Magrabi Eye Center, Dammam, Saudi Arabia
  Opponent: Mr Igor Kozak, Moorfields Eye Hospital Center, Abu Dhabi, United Arab Emirates
- Clinician debate on the role of steroids in DME
  Proponent: Professor Ângela Carneiro, Faculty of Medicine of University of Porto, Centro Hospitalar São João, Porto, Portugal
  Opponent: Mr Ian Pearce
- Guideline recommendations from EURETINA

Learnings: clinical insights from plenary presentations and discussions

- Reflection on take-home clinical learnings
- Dr Susan B Bressler

DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor.
The underlying mechanisms of retinal diseases and mode of action of intravitreal antiangiogenic therapies were reviewed by Mr Richard Gale, The York Hospital, York, UK. These considerations are believed to be especially helpful when comparing across anti-vascular endothelial growth factor (anti-VEGF) therapies and consider how these agents are best administered, remarked Mr Gale.

Hypoxia in the retina leads to the upregulation of cytokines, inflammatory mediators and growth factors such as VEGF, placental growth factor (PGF) and interferon-γ (IFN-γ). The presence of diabetic macular edema (DME) and retinal vein occlusion (RVO) is associated with increased levels of VEGF, PGF and inflammatory factors (2–4). Intravitreal VEGF and PGF levels increase with severity of RVO and diabetic retinopathy (DR), and are elevated in ischemic retinal vascular diseases (2–4). Aflibercept (Eylea®, Bayer) provides rapid and sustained gains in visual acuity (VA) in both ischemic and non-ischemic RVO and significantly reduces the severity of DR compared with sham intravitreal injections in clinical trials (5,6).

In vitro assessments show that intravitreal aflibercept blocks VEGF-induced activation of receptor tyrosine kinases (RTKs) while abluminal aflibercept also inhibits the activity of PGF. Inhibiting VEGF and PGF is believed to be more effective than inhibiting VEGF alone (3).

Mr Gale considered translation of these findings to clinical evidence and practice settings. The pivotal randomized, active-controlled phase III VIEW studies show that aflibercept given every 8 weeks after three initial monthly injections (2q8) and ranibizumab every 4 weeks were equally effective over 52 weeks in age-related macular degeneration (R AMD). Patients treated with aflibercept in the VIEW 2 study were maintained on their initial treatment throughout the year. After a switch to a capped pro re nata (PRN, as-needed) regimen, the proportion of patients remaining VA ≥ 20/40 at the end of year 1 (unassisted nAMD) was 79% (99). This demonstrates the importance of anti-VEGF loading doses in clinical practice: The AURA Study. AURA collected data from 100,000 patients on treatment-naïve nAMD (9)*. Through year 2, after a loading phase of 3 monthly anti-VEGF injections, follow-up dosing regimens may be fixed, proactive or reactive. Mr Pearce described studies of clinical effectiveness in clinical practice showing that good real-world outcomes can be achieved using the licensed aflibercept posology of fixed repeat dosing for nAMD in the first year of treatment (18, 19).

The global prevalence of diabetes has increased every 8 weeks, following 5 initial monthly doses; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward (PROP) on an as-treated basis. VEGF, vascular endothelial growth factor. Adapted from FG Holz et al., Br J Ophthalmol, 98, 1470–1476 (2014).

Twelve-month results of PERSEUS, a prospective, observational study involving 66 centers in Germany, show rapid and sustained visual gains with aflibercept for nAMD, with better visual outcomes in patients who received an early diagnosis and treatment of diabetic retinopathy (DME) and other related complications (23). Global survey results from the DR Barometer Study show that more than a quarter of patients have never discussed eye complications with their doctor or did so only after symptoms arose and two-thirds of specialists reported that most of their diabetic patients only attend screening after vision problems arise (23).

There is a need to raise awareness of diabetic eye disease among general physicians and patients to promote early diagnosis and treatment, said Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," Dr Şermet explained (23,24). Additionally, a multidisciplinary team approach is encouraged to ensure broad communication between healthcare professionals involved in the management of people with diabetes (24).

Irreversible vision loss from diabetic eye disease may occur if treatment is delayed, stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet.

As shown by the phase III RISE and RIDE trials of ranibizumab in DME, chronic retinal edema may result in the potential vision gain being irreversibly lost if left untreated (27). In the phase III VIVID-DME and VISTA-DME studies, which compared aflibercept with macular laser photocoagulation for macular edema, patients treated with laser control who then received aflibercept after week 12 achieved only modest vision gains (see Figure 2) (25).

DME requires an intensive series of therapeutic monthly doses on initiation of anti-VEGF therapy and continued regular treatment in the first year, stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet. "Irreversible vision loss from diabetic eye disease may occur if treatment is delayed," stressed Prof Dr Şermet.
Diabetic Retinopathy Clinical Research
deterioration in VA when visit frequency is reduced despite capped PRN regimen at 8–12 weeks. ETDRS, Early participants (56 percent of VIEW participants at the participating sites that were alive). The results suggest subtle Figure 3. Results from the VIEW 1 extension study (33). Results are for 323/1217 (26.5 percent) of VIEW 1 optical coherence tomography (OCT) retinal
VEGF injections and a continuing benefit seen over time in eyes with DME involving the central macula (30). Dr Bressler said there may be relaxed over time when VA and anatomic outcomes stabilize.” The Protocol I study from the Diabetic Retinopathy Clinical Research (DRCR.net) demonstrated that improvements in VA and retinal thickness obtained with anti-VEGF treatment, with immediate or deferred laser, are sustained over time in eyes with DME involving the central macula (30). Dr Bressler said there is a rapid ascent in VA letter score from baseline after the first series of monthly anti-VEGF injections and a continuing benefit seen between months 6 and 12. Considering both optical coherence tomography (OCT) retinal thickness and VA improvement (a2020 VA), initial responder rates increase with each successive injection during commencement of initial monthly dosing. This shows that the commitment to at least 5 monthly loading injections on treatment start is beneficial, observed Dr Bressler. Vision and anatomic outcomes may be maintained through 5 years, with a strict loading phase of five or more injections and a structured retreatment retreatment protocol thereafter (30). The injection burden decreases after year 1 and even more so in years 4 and 5, without jeopardizing outcomes.

In contrast to DME, nAMD most often is an unremitting, lifelong disease, added Dr Bressler. A continuing proactive treatment approach with monthly dosing is needed for nAMD in year 1, for example using a fixed dosing regimen, and throughout the patient’s therapeutic course. She recounted evidence from multiple long-term studies that diligent clinic follow-up and higher retreatment frequency are associated with better VA outcomes than often seen with variable as-needed dosing regimens (31, 32).

Seven-year outcomes in ranibizumab-treated patients (n=165) from the SEVEN-UP multicenter cohort study showed that at this late stage in the therapeutic course, exudative AMD patients remain at risk for substantial visual decline (31). At 5 years in the CATT Research Group Follow-Up Study, there was a mean change in VA from baseline of -3 letters, with the mean VA gain of 11 letters at 2 years being lost following a switch to retreatment based on best medical judgement (32).

Recent published data from the VIEW 1 Extension Study demonstrated a reliable maintenance of VA gains through 4 years of continued aflibercept retreatment, with a final mean VA improvement from baseline of 71 letters compared with a 10.2-letter gain at week 96 in the aflibercept 2q8 group (33). “Frequent clinic attendance for regular assessment and monitoring of exudative processes is essential to maintain the very best level of VA for AMD patients,” explained Dr Bressler. “Continuous long-term retreatment generally maintains the vision achieved in the first year with anti-VEGF treatment.”

Impact of retinal disorders: a patient perspective Impairment of vision has a significant impact on quality of life of patients, affecting both physical and mental health, observed Professor Bora Eldem, Hacettepe University, Ankara, Turkey (34, 35). Patients are burdened by the impact of vision loss on their daily life and the resources needed for eye clinic visits. Quality-of-life loss associated with AMD can be devastating. Very severe AMD (VA ≤20/200) caused a 60 percent decrease in the average AMD patient’s quality of life, similar to that encountered with end-stage prostate cancer or a catastrophic stroke (35). Wet AMD, defined as VA of 20/200 to 20/400 in the better-seeing eye, is associated with a greater quality-of-life decrement than that encountered with cancer; mild stroke, impotence or gout.

Patients reported an average time per clinic visit of almost 12 hours, in a prospective, observational study of disease burden in the treatment of DME (36). Prof Eldem cited findings illustrating that 5-letter gains of VA in both DME and nAMD patients provide relevant improvements in visual functioning performance.

Visual improvement of 5 letters or more in best corrected visual acuity (BCVA) was associated with important and measurable benefits for patients with DME, from an analysis of patient data up to week 52 from the VIVID and VISTA studies (37). Those patients who gained ≥10 letters were more likely to be able to read, drive at night and drive in difficult conditions (37). Clinically meaningful improvements in visual function outcomes, measured using the National Eye Institute Visual Functioning Questionnaire (NEI VFQ), were more effective in improving outcomes in patients who gained only in those nAMD patients who gained 5 ETDRS letters or more over 52 weeks with aflibercept 2q8 or monthly 0.5 mg ranibizumab in the VIEW studies (38). Plenary session II: Insights in retinal disease management Maximizing the use of OCT Advances in OCT technology have provided a better understanding of retinal disease activity (39). OCT, with its finite, more circumscribed life cycle. But in contrast to DME, nAMD may have a more aggressive activity phase. OCT is effective in monitoring anatomic outcomes stabilize.”

In VIVID and VISTA, aflibercept every 4 weeks (2q4) and aflibercept 2q8 resulted in better vision and anatomic outcomes than laser treatment in patients with visual impairment from central-involved DME at 1 year (6). Visual improvements observed with both aflibercept regimens over laser control at weeks 52 and 100 were maintained at week 148 (23). Mean BCVA gain from baseline to week 148 with aflibercept 2q4, aflibercept 2q8, and laser control was 10.3, 11.7 and 1.6 letters (P < 0.001) in VIVID and 5.8, 10.5 and 1.4 letters (P<0.0001) in VISTA, respectively (23). From week 100, laser control patients who had not required rescue treatment received aflibercept as needed per retreatment criteria, but visual gains through the following 48 weeks were limited (25).
anti-VEGF agents for nAMD.

Mr Pearce reviewed real-world evidence standardized care protocol. In a shift of focus well-defined patient populations using a treatment outcomes Real-world evidence of anti-VEGF Figure 4. VA gains in aflibercept-treated patients. The majority of aflibercept-treated patients had significant VA gains (≥15 letters), which were maintained up to 100 weeks. *AFL 3x2q4 then 2q8 if rescue criteria are met. **AFL, aflibercept; PRN, pro re nata; VA, visual acuity. treatment efficacy with the use of

Results of COPERNICUS, GALILEO VIBRANT studies evaluating

• COPERNICUS, GALILEO and VIBRANT studies evaluating aflibercept in RVO

Results of COPERNICUS, GALILEO and VIBRANT clinical trials show that the majority of aflibercept-treated RVO patients had significant VA gains from baseline (≥15 letters) that were maintained up to 100 weeks (≤4, ≤5 or sham treatment) (Figure 4) (49, 51). Between 52 and 60 percent of RVO patients gained 3 or more lines of vision after 24 weeks of aflibercept treatment, which was sustained at 52 weeks and beyond. The percentage of perfused (fewer than 10 disc areas of non-perfusion) patients increased with aflibercept treatment in both aflibercept-treated patients in VIBRANT, the percentage of perfused patients in the laser arm remained relatively stable and increased after aflibercept macular treatment became available from week 24 (51).

Real-world evidence of anti-VEGF treatment outcomes

Randomized clinical trials often lack generalizability as they are conducted in well-defined patient populations using a standardized care protocol. In a shift of focus from clinical trial data to clinical practice, Mr Pearce reviewed real-world evidence of treatment effectiveness with the use of anti-VEGF agents.

Prospective and retrospective studies demonstrate that nAMD patients treated less frequently tend to lose initial vision gains achieved with fixed and typically more frequent dosing, noted Mr Pearce. Results from the UK nAMD Database Study of real-life outcomes of PRN ranibizumab (following loading with 3 monthly injections) in treatment-naïve nAMD show worse visual outcomes than those obtained in the registration randomized controlled clinical trials (52). Mean VA (letters) change from baseline at years 1, 2 and 3 was +2, +1 and +2, respectively. The median number of treatments for eyes followed for at least 3 years in years 1, 2 and 3 was 5, 4, and 4, respectively, a substantially lower dosing frequency than the monthly dosing regimen followed in the pivotal ranibizumab randomized clinical trials.

Poor VA outcomes in clinical practice seem to relate largely to undertreatment with anti-VEGF therapy, observed Mr Pearce, who acknowledged there are limitations to how often patients can be monitored in eye clinics. Maintaining a sufficient frequency of anti-VEGF injections is nevertheless important for achieving optimal gains in VA over time (16). The ALLURE multicountry observational study reported greater improvements in VA in those countries delivering a higher frequency of both anti-VEGF treatments and clinic visits over 2 years (16, 51). Good outcomes may be achieved and maintained when following the licensed treatment posology for aflibercept in the first year, illustrated by growing evidence from multiple countries and across diverse patient populations, Mr Pearce observed (Figure 5).

A large multicenter, national Electronic Medical Record (EMR) study compared the effectiveness of predominantly PRN ranibizumab versus continuous (fixed or treat-and-extend) aflibercept therapy in UK clinical practice, involving, 1,884 eyes across 21 UK hospitals (54). At one year, patients treated with PRN ranibizumab (average of 5.7±2.0 injections) gained a mean of 11 letters compared with a mean improvement of 6.1 letters for patients receiving fixed or treat-and-extend aflibercept (10 injections). The adjusted difference in change of vision at 1 year was +1.4 letters (P=0.001) in favor of continuous aflibercept (figure 6).

Data from RAINBOW, an ongoing retrospective and prospective 4-year observational study in France evaluating real-life outcomes in treatment-naïve nAMD patients treated with aflibercept, illustrate the importance of the loading phase. For patients treated with a loading phase of 3 injections within 90 days (29.84 mean baseline BCVA ±9.27±17.8), mean change in BCVA from baseline to month 12 was +6.8±1.45 letters, with a mean of 6.6±1.8 injections, compared with a mean change of 5.3±1.0 letters and a mean of 6.0±2.1 injections for all patients (n=353), mean baseline BCVA 57.7±17.8 in the full analysis cohort (17).

After year 1, initial VA gains may be maintained using a treat-and-extend dosing regimen, added Mr Pearce. Epstein and Amrom reported maintenance of the 12-month VA improvement of 72 letters at the 18-month visit following a switch from fixed to treat-and-extend dosing in 85 nAMD patients (55). Approximately two initial monthly injections were given during the first 6 months. Mr Pearce concluded: “Collecting real-world evidence of effectiveness helps benchmark performance to improve standards of care and treatment patterns in clinical practice. In real life, a proactive treatment regimen for nAMD appears to be the most successful approach to vision improvement and preservation of VA gains.

After year 1, treatment intervals with aflibercept may be extended in some patients using treat and extend dosing, stabilizing VA gains long-term while decreasing treatment frequency and clinic visits” (57).

Treatment options in DME: the role of anti-VEGF agents, laser and steroids

Dr Neil Bressler, Wilmer Eye Institute, Johns Hopkins University School of Medicine and Howard Hughes Medical Institute, Baltimore, MD, USA, explored treatment options for DME, emphasizing that anti-VEGF therapy for the initial management of center-involved DME with vision loss. Results from DRCR.net Protocol I show that ranibizumab with prompt or deferred laser was more effective than laser for center-involved DME (58). Overall, improvement in VA at 1 year with ranibizumab was maintained at 5 years alongside a diminishing need for retreatment over time (30). Longer-term assessment also confirmed that combining laser initiation of ranibizumab treatment was no better than delaying laser for at least by 24 weeks (30). The observed difference in VA in favor of deferred laser may be related to the greater number of ranibizumab injections during follow-up or the potentially destructive effect of prompt laser.

For a DME patient with diminished VA of 20/462, Mr Bressler recommended commencement of anti-VEGF treatment with 5 to 6 initial monthly doses, securing continuing improvements in anatomic and visual response with each consecutive injection. For a patient with persistent DME after this induction phase and beyond, clinicians may consider adding focal/grid laser and resume anti-VEGF treatment only if outcomes worsen.

Dr Bressler said there is some evidence of harm following cataract surgery in eyes with central-involved DME and persistent edema and argued that corticosteroids should be avoided in phakic patients as they will cause statural progression. DRCR.net Protocol I found that 40 percent of eyes with DME undergoing cataract surgery had no meaningful improvement or had worsening of VA and 53 percent of eyes had a VA of ≤20/40 at the 16-week postoperative visit (59). Even in pseudophakic eyes there is no rationale to start anti-VEGF treatment for central-involved DME with corticosteroids rather than anti-VEGF therapy, argued Dr Bressler.

The role of switching to corticosteroids in pseudophakic patients with persistent edema despite initial anti-VEGF therapy is not yet known. DRCR.net Protocol II found no short-term efficacy outcomes at 24 weeks of combination corticosteroid (dexamethasone implant [Ozurdex®, Allergan]) and anti-VEGF treatment (ranibizumab) in comparison with continued anti-VEGF monotherapy in eyes with persistent center-involved DME and VA impairment despite previous anti-VEGF therapy, in both pseudophakic and phakic patients.

Clinician debate on the role of laser in DME: Dr Haim El-Sabagh, Magrabi Eye Center, Dammam, Saudi Arabia, said laser may be an effective primary treatment option for some patients with DME (60). Considerations include: need to control retinal exudation (e.g., pregnancy), cost or exhaustion of health budget and morphological signs of recalcitrant or chronic persistent edema. Furthermore, laser treatment can induce regression and reduce retinal thickness in some patients with non-center-involved DME and achieves similar outcomes to steroid treatment in DME but with fewer side effects (60–62).

DME patients should be treated first-line with anti-VEGF agents to ensure maximal initial treatment outcomes, argued Mr Igor Kozak, Moorfields Eye Hospital Center, Abu Dhabi, United Arab Emirates, in a counterpart presentation (25, 63). He cited head-to-head comparative effectiveness studies showing that laser treatment is less efficacious than anti-VEGF therapy in improving vision in DME patients (25, 63). Ranibizumab 0.5 mg treatment for 12 months either as monotherapy or as an adjunct to laser therapy produced
significantly greater improvements in BCVA and QoL than laser treatment alone in the randomized, laser-controlled RESTORE study (63). The DRCR.net Protocol I study showed that patients treated with laser at baseline achieved poorer visual outcomes than those treated with deferred laser (Figure 7) (30). In VIVID and VISTA, visual and anatomic improvements as well as improvements in Diabetic Retinopathy Severity Scale (DRSS) score with macular laser photoacgotagulation were inferior to those with aflibercept (25, 64). Over 80% of patients with the laser control groups required additional treatment with aflibercept (25).

Scaring remains a side effect of laser treatment despite technology advances, added Mr Kozak. The underlying mechanism of action of laser treatment in DME is unknown and, despite several decades of use, the optimal protocol for subthreshold laser photocoagulation is unclear. For these reasons, laser should not be used first-line for the treatment of DME.

Clinician debate on the role of steroids in DME – the speakers’ opinions

Corrösténsors may agree that DME that is unresponsive to alternative treatments and there may well be opportunities to use steroids as first-line therapy for DME, commented Professor Ángela Carneiro, Faculty of Medicine of University of Porto, Centro Hospitalar São João, Porto, Portugal. Intravitreal steroid treatment is a feasible first-line option for central-involved DME in patients who are pseudophakic, who are unable to adhere to a more intensive treatment regimen, have experienced prior or recent arterial thromboembolic events and in patients for whom anti-VEGF treatment is not reimbursed (65–67).

Aflibercept monotherapy may be considered for initial therapy early on to prevent scarring, cautioned Dr Susan B Bressler. She explained there is no evidence from controlled studies showing that switching to alternative steroid treatment will alter outcomes beyond that of the initial intervention.

Clinical insights from plenary presentations and discussions

Dr Susan B Bressler reflected on the main clinical insights from plenary presentations and faculty discussions and presented take-home learning points:

- Cytokines other than VEGF-A may play a contributory role in the pathogenesis of common retinal diseases. Aflibercept has a higher binding affinity, longer duration of VEGF suppression and broader mechanism of action than other ophthalmic anti-VEGF therapies. It is the only intravitreal antiangiogenic agent at clinicians’ disposal that inhibits both VEGF-A and PIGF. These distinguishing molecular features may partly account for the observed differences in clinical effectiveness from prospective and retrospective studies of different anti-VEGF agents in routine clinical practice.
- VA at baseline is an important predictor of later visual outcomes with continuing anti-VEGF therapy, underscoring the importance of early detection. When edema starts to encroach on the macular center, clinicians are encouraged not to delay proceeding to anti-VEGF therapy, as patients receiving deferred antiangiogenic therapy do not achieve the magnitude of vision improvement attained by prompt early treatment.
- The standard of care for the primary treatment of central-involved DME with aflibercept is three injections of the agent at clinicians’ disposal that inhibits both VEGF-A and PIGF. Responder rates continue to increase with each successive dose through at least 5 monthly injections, so it is important not to underdose during the mandated induction phase. While DME requires intensive initial treatment, it is possible for a decreased visit and treatment frequency in subsequent years.
- nAMD is a chronic condition requiring aggressive initial treatment early on and diligent proactive follow-up and retreatment for preservation of visual outcomes long term. Treatment initiation with an adequate loading phase of initial monthly injections and continuing proactive treatment within the first year and beyond ensures maximal visual benefit longer term.
- Vision functioning outcomes reflect the beneficial effects of treatment from the patient’s perspective. There is evidence of a correlation between level of EDRS letter score improvement and percent treated to continue to perform everyday vision-related tasks.
- Advances in OCT imaging technology have provided greater insights into disease pathogenesis and OCT provides the ability to monitor key morphological features for assessment of chronic change in response to treatment. Emerging and evolving technologies likely to impact clinical practice include OCT-A, ultra-widefield imaging and automated retinal image assessment for detection of referable retinopathy.
- Aflibercept monotherapy may be a cost-effective alternative for the initial management of PCV without having to resort to adjunctive PDT in the vast majority of cases.

Treatment outcomes of aflibercept in nAMD from clinical practice evaluations across multiple countries and disease centers compare favorably to the visual and anatomic results observed in the pivotal phase III VIVID and VISTA studies.

Anti-VEGF therapy is superior to laser therapy or corticosteroids as initial treatment for center-involved DME with vision loss and has emerged as the preferred first-line treatment option.

For center-involved DME without vision loss and for diffuse DME, without central involvement, more evidence comparing careful observation with alternative treatment interventions is needed.

References


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**Presentation:** 1 ml solution for injection contains 40 mg aflibercept. Each vial contains 100 microtitre, equivalent to 4 mg aflibercept. **Indication(s):** Treatment of neovascular (wet) age-related macular degeneration (AMD), macular oedema secondary to retinal vein occlusion (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 microtitre) 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 microtitre. 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, and based on visual and/or anatomic outcomes, the treatment interval may be extended such as with a treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes; however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The schedule for monitoring should therefore be determined by treating physician and 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, and based on visual and/or anatomic outcomes, the treatment interval may be extended such as with a treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes; however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The schedule for monitoring should therefore be determined by the treating physician and may be more frequent than the schedule of injections. 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 75 years old. **Pediatric 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, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract have 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 or any of the above mentioned events without delay. Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection; special precautions is needed in patients with uncontrolled 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 haemorrhage and other thromboembolic events have been reported following intravitreal injection of VEGF inhibitors. Safety and efficacy of concurrent use in both eyes have not been systematically 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 pigmented 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 ≥20 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. In patients presenting with clinical signs of irreversible ischaemic visual function loss, aflibercept treatment is not recommended. Population with limited data. There is limited experience in DMO due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. Eylea has not been studied in patients with active systemic infections, concurrent eye conditions such as retinal detachment or macular hole, or in diabetic patients with uncontrolled hypertension. This lack of information should be considered when treating such patients. In myopic CNV there is no experience with Eylea in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions. **Interactions:** No available data. Fertility, pregnancy & lactation: Not recommended during pregnancy unless potential benefit outweighs potential risk to the foetus. No data available in pregnant women. Studies in animals have shown embryofetal 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: Visual acuity reduced, conjunctival haemorrhage (wet AMD phase III studies: increased incidence in patients receiving anti-thrombotic agents), eye pain. Common: retinal pigment epithelial tear (known to be associated with wet AMD; observed in wet AMD studies only), 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 hypertension. Serious: cf. CI/W&P - in addition: blindness, culture positive and culture negative endophthalmitis, cataract traumatic, transient increased intraocular pressure, vitreous detachment, retinal detachment or tear, hypersensitivity (during the post-marketing period, reports of hypersensitivity included rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions), vitreous haemorrhage, cortical cataract, lenticular opacities, corneal epithelium defect/erosion, vitritis, uveitis, iritis, iridocyclitis, anterior chamber flare, arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. As with all therapeutic proteins, there is a potential for immunogenicity. 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 stored 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, 400 South Oak Way, Reading RG2 6AD, United Kingdom. Telephone: 0118 206 3000. Date of preparation: November 2017.