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## FOREWORD

### Definitive diagnosis is a crucial first step in the management of common retinal diseases

Bożena Romanowska-Dixon, Jagiellonian University Medical College, Krakow, Poland

The Bayer satellite symposium at the 7th World Congress of Controversies in Ophthalmology explored, through expert debate and discussion, the latest thinking on different treatment protocols for neovascular age-related macular degeneration (AMD) and diabetic macular oedema (DMO).

A journey of a thousand miles begins with a first step, to quote Confucius, and this first step in neovascular age-related macular degeneration (nAMD) is of course a proper diagnosis, commented chair Prof. Bożena Romanowska-Dixon in opening remarks.

“Ocular symptoms and signs require careful assessment, as various pathologies involving the macula may mimic neovascular AMD,” Prof. Romanowska-Dixon added.<sup>1</sup> “A general ophthalmologic examination including colour fundus photography, together with additional diagnostic measures including fluorescein angiography (FA) and optical coherence tomography (OCT), help to establish a definitive diagnosis of choroidal neovascularisation (CNV) and also to identify subtype lesion classification and size.”

Fluorescein angiography allows visualisation of retinal vasculature and neovascular proliferations, the location and area of leakage, permits characterisation of CNV classification (eg, classic vs occult) and the detection of polypoidal choroidal vasculopathy. Both FA angio-

grams and OCT scans can help identify specific forms of AMD having a more aggressive natural history, such as retinal angiomatous proliferation, characterised clinically by focal haemorrhage, oedema, and lipid exudates within retinal layers.<sup>2</sup>

We are fortunate in having access to advanced OCT technologies (deep-range imaging OCT, spectral-domain OCT, swept-source OCT and emerging OCT angiography) to better detect, locate, and analyse neovascular lesions and CNV activity, as well as analyse morphologic changes in the retina, subretinal fluid, and retinal pigment epithelium.

For DMO, a major cause of visual morbidity associated with diabetic retinopathy, additional examinations beyond clinical evaluation for full assessment of macular changes need to be performed.<sup>3,4</sup> Different manifestations and clinical features such as diffuse macular thickening, cystoid macular oedema (CMO), CMO with serous retinal detachment, and vitreoretinal traction with and without CMO may be differentiated. Optical coherence tomography provides structural detail of the retina, and retinal imaging can help detect pathologies in the periphery of the retina, such as peripheral ischaemia.<sup>4</sup>

Accurate diagnosis depends on the underlying source of the ocular disorder, and definitive case assessment is crucial for prognostic assessment and for arriving at appropriate treatment decisions.

## DEBATE PRO:

### Treat early, make a difference

Giovanni Staurengi, Luigi Sacco Hospita, University of Milan, Italy

“There is no doubt that if you put together all of the visual acuity (VA) outcomes from pivotal nAMD clinical trials, the results consistently demonstrate the effectiveness of antiangiogenic therapy for nAMD,” Prof. Staurengi remarked. “Intravitreal inhibition of VEGF [vascular endothelial growth factor] can efficiently block the pathophysiological process of AMD, and maintain or increase visual function in most patients with nAMD. However, in longer-term efficacy and safety studies evaluating outcomes in patients who were followed after completion of landmark clinical trials of ranibizumab 0.5 mg, we find that VA gradually decreases with time.”

### *Vision gains gradually decline over time*

In the HORIZON study, a 24-month, open-label extension trial involving patients who had completed MARINA, ANCHOR, or FOCUS trials, there was an incremental decline of the VA gains achieved with monthly ranibizumab treatment.<sup>5</sup> (The ranibizumab posology discussed here may not represent the full range of current licensed posologies of ranibizumab. Please consult the ranibizumab Summary of Product Characteristics [SmPC].)

For patients treated with monthly ranibizumab for 2 years and then with access to ranibizumab administered at the investigator's discretion during the 2 years of HORIZON, the mean change in best-corrected visual acuity (BCVA) from initial study baseline was a gain of 2.0 ETDRS [Early Treatment Diabetic Retinopathy Study] letters at 4 years' follow-up. Pooled results show a mean decline of 11.8 letters from original baseline for patients

either crossed over to ranibizumab treatment on entry to HORIZON or who were ranibizumab untreated. These results reinforce the benefit of early diagnosis and treatment of nAMD.

Patients with neovascular AMD remain at risk for substantial visual decline. Seven-year outcomes from a multicentre cohort study (n=65) show that approximately 7 years (mean, 7.3 years; range, 6.3–8.5 years) after commencing ranibizumab therapy in the phase 3 ANCHOR or MARINA trials, one third of study eyes (34%) experienced a decline of 15 letters or more compared with baseline, while 43% of eyes had a stable or improved letter score ( $\geq 0$ -letter gain from baseline).<sup>6</sup> Study eyes received a mean of 6.8 anti-VEGF injections during the mean 3.4-year interval following exit from the HORIZON study. Active neovascular disease was detected in 68% of study eyes, suggesting a long-term persistence of disease activity in the majority of patients.

## Treatment practice and outcomes differ between countries

“Further evaluations of real-life experience of anti-VEGF therapy for neovascular AMD indicate that visual acuity outcomes differ substantially between countries, with poorer than expected visual results overall,” added Prof. Staurengi.

A 2-year retrospective, observational study (AURA) conducted in Canada, France, Germany, Ireland, Italy, the Netherlands, UK, and Venezuela assessed ranibizumab use and treatment outcomes in a real-life setting, evaluating patients with nAMD who started anti-VEGF therapy during the first 8 months of 2009.<sup>7</sup> (The ranibizumab posology discussed here may not represent the full range of current licensed posologies of ranibizumab. Please consult the ranibizumab Summary of Product Characteristics [SmPC].) Major differences in visual outcomes and injection frequency between countries were evident [Table]:

- Overall, for the global study population (n=2227, effectiveness analysis set), mean change in VA score from baseline VA of 55.4 letters to years 1 and 2 was +2.4 and +0.6 letters, respectively, with a mean of 7.2 ranibizumab injections given during the 2 years.
- Better VA outcomes were observed in the UK cohort (n=410), with a mean (SD) change in VA from baseline of +6.0 (15.4) letters at year 1 and +4.1 (16.9) at year 2. Over 2 years, the mean (SD) number of clinic visits and injections was 18.4 (5.0) and 9.0 (4.7), respectively; a majority of patients received a loading phase of 3 ranibizumab injections within 90 days.<sup>8</sup>
- By contrast, there was a decline in mean VA from baseline to year 2 in patients in Germany, France, and Italy. For the Italy cohort (n=365), the mean number of visits and injections for the full 2 years was 12.7 and 5.2, respectively, and the change in VA score from baseline to year 2 was -2.9 letters (from a baseline VA of 65.5 letters).<sup>7</sup>

Prof. Staurengi explained that patients in the Italy cohort had a higher baseline VA score than the UK group, with a lower comparative gain in VA seen during the treatment loading phase due possibly to a ceiling effect.

“Similar to longer-term findings from HORIZON and SEVEN-UP, investigators in the AURA study pointed out that the good initial improvement in visual acuity following ranibizumab treatment was not maintained over time,” Prof. Staurengi commented.

**Table. Summary findings from AURA\* evaluating resource use and changes from baseline in visual acuity (study countries enrolling >300 patients)**

Country	Baseline VA score (letters)	Overall visits in full 2 years (mean)	Injections in full 2 years (mean)	Change in VA score at year 1 (letters)	Change in VA score at year 2 (letters)
Germany	52.9	10.8	5.6	1.1	-0.8
France	56.0	13.4	6.3	0.8	-1.1
UK	55.0	18.4	9.0	6.0	4.1
Italy	65.5	12.7	5.2	0.0	-2.9
Netherlands	50.1	12.7	8.7	3.8	2.6

VA, visual acuity.

\*Adapted from Holz FG, et al.<sup>7</sup>

Visual acuity outcomes measured as change from baseline in ETDRS letter score may be related partly to differences in baseline vision and partly due to inconsistent monitoring and treatment practices. In general, fewer injections are administered in routine clinical practice than in landmark clinical trials, suggesting that more frequent monitoring and retreatments may be needed to secure the best outcome with ranibizumab.

### Early treatment may help preserve vision at higher ETDRS letter scores

“When considering outcome data from audits of nAMD clinical practice, it is important that baseline visual acuity and final mean visual acuity at follow-up are compared and assessed,” argued Prof. Staurengi. “Patients with a lower baseline visual acuity score have more to gain. In the UK cohort of AURA for example, mean improvement in visual acuity through 2 years was higher in patients with baseline vision <35 letters (+15.1 and +11.6 letters at year 1 and at year 2, respectively).”<sup>8</sup>

The message from this is that if you detect and treat nAMD early, when there is less marked severity based on baseline letter count, greater mean VA scores overall are more likely to be maintained, yet improvements of VA may be modest compared with the vision gains observed in phase 3 registration trials.

## DEBATE CON: Treat early, make a difference

Anat Loewenstein, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

“I’ve always advocated early intervention and treatment for retinal disorders when

indicated, especially so in cases of active progressive disease,” countered Prof. Anat Loewenstein. “But treating early does not always make a significant difference to the final outcome in all cases.”

Let’s first consider an example outside ophthalmology where early treatment may cause more harm than benefit. Among men with localised, low-risk prostate cancer, more than 90% are treated with radical prostatectomy, external beam radiation, or brachytherapy, but as many as 60% may not have required therapy in their lives.<sup>9</sup> Observation may be more effective and costs less than initial treatment in low-risk populations. A study by Wilt and colleagues reported that, for men with localised prostate cancer, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation, through at least 12 years’ follow-up.<sup>10</sup>

Prof. Loewenstein described several case presentations of DMO, with mild thickening of the retina or uncontrolled diabetes, where patients improved under watchful waiting and successful diabetic control during follow-up. A substantial number of eyes with central-involved DMO may retain good vision with no serious advancement of their disease for many years.

Clinical trials have demonstrated the efficacy of intravitreal anti-VEGF therapy for central-involved DMO in eyes with poor VA (78 letters or worse, approximately 20/32 or worse), and that it is more effective than laser alone in increasing vision gain and decreasing vision loss. It is not known definitively whether eyes with central-involved DME and good vision do better with anti-VEGF therapy initially, or laser treatment or observation

initially followed by anti-VEGF therapy only if vision deteriorates.

To identify the best strategy and possible treatment approaches in clinical practice, the Diabetic Retinopathy Clinical Research Network ([www.DRCR.net](http://www.DRCR.net)) has initiated a randomised, multicentre clinical trial to evaluate treatment benefit for central-involved DMO in eyes with very good VA of 20/25

or better (BCVA letter score  $\geq 79$  letters).<sup>11</sup> Enrolled subjects will be assigned randomly on a 1:1:1 basis to receive prompt focal/grid photocoagulation plus deferred intravitreal anti-VEGF therapy (2 mg aflibercept [Eylea<sup>®</sup>, Bayer]), observation plus deferred anti-VEGF therapy, or prompt anti-VEGF treatment. In the deferred intravitreal anti-VEGF groups (laser or observation), treatment will be provided if VA worsens by at least 10 letters from baseline VA at 1 study visit or 5 to 9 letters from the baseline VA at 2 consecutive study visits, with vision loss presumed to be due to DMO. The primary outcome measure is the proportion of eyes losing  $\geq 15$  letters of VA at 2 years.

“Even in cases of AMD, observation via watchful waiting may be a better approach than initial treatment, for instance, in early suspected occult CNV, or asymptomatic CNV with 20/20 vision and no classic component, no subretinal fluid, or cystoid macular oedema,” commented Prof. Loewenstein. “Observation for a certain period may be considered in patients with cystoid abnormalities but with no evidence of neovascularisation on fluorescein angiography examination. However, if persistent disease activity is overlooked and there is substantial fibrosis between visits, visual acuity may not necessarily recover. That said, early treatment may not necessarily influence the final outcome.”

“Early initial treatment is effective and warranted in most cases of active central-involved DMO with visual impairment and for CNV secondary to AMD,” acknowledged Prof. Loewenstein in a closing rebuttal. “However, there will be instances where observation rather than intervention may be appropriate and recommended, at least for a certain period of time, thus avoiding the risks and costs of repeated intravitreal injections to both patients and the healthcare system. In some cases of non-central oedema in DMO or occult nonprogressive CNV, observation via surveillance or watchful waiting may be the better initial approach.”

## Counterpoint Rebuttal

Giovanni Staurenghi

Clinical examination and the diagnosis are crucial in determining treatment strategy, emphasised Prof. Staurenghi in a counterpoint rebuttal: “If you have a definitive diagnosis of neovascular AMD, then treating early is advisable for the best visual results. For DMO, clinicians do not need to treat so intensively, although prompt initial treatment and with less frequent dosing can yield good visual outcomes long term and also improve the underlying diabetic retinopathy.”

## DEBATE PRO: Retreatment: We can now balance simplicity, practicality, and effectiveness

Sobha Sivaprasad, Moorfields Eye Hospital and King's College Hospital, London, UK

“Today we now have a choice of 3 regimens for delivering intravitreal anti-VEGF treatment services, offering the opportunity for a better balance of practicality and effectiveness when selecting the most appropriate retreatment strategy,” stated Prof. Sobha Sivaprasad.

The first approach is fixed-interval dosing, where intravitreal injections are given proactively in a predetermined fashion at regular intervals. Second is as-needed or PRN treatment, involving close individualised monitoring and reactive retreatment on signs of disease activity. Third is treat and extend, where appointments may be extended or vary but patients receive an injection on each clinic visit.

### Greater simplicity and practicality

Prof. Sivaprasad argued that having this choice of treatment approach has led to greater simplicity in the provision of anti-VEGF treatment services: “In a real-life clinic setting, if you think of patients going through the security channel at Heathrow airport, the first place everyone has to pass through is a fixed-interval treatment loading phase. After that, some patients will be asked to sideline to a PRN pathway, while most patients will pass through to treat and extend. I believe this is a simple strategy to implement in real-life clinic settings. In terms of practicality, dedicated injection clinics allow for effective management with regular fixed-interval dosing, ensuring that patients can attend and receive treatment on

a regular basis, while treat and extend allows de-escalation of the injection schedule with fewer clinic visits.”

### Clinical effectiveness

Fixed-interval anti-VEGF dosing is clinically effective for the first year of treatment across all indications. For example, the United Kingdom Aflibercept Users Group reported first-year VA outcomes providing aflibercept every 2 months following 3 initial monthly doses for treatment-naïve nAMD patients that are comparable to randomised trial results and better than many previous real-world data collections.<sup>12</sup> At 12 months, mean change in VA from baseline was +5.5 letters in first-treated eyes, compared with a mean change in BCVA from baseline to week 52 of +8.4 letters in an integrated analysis of the phase 3 VIEW studies.<sup>12,13</sup>

There is a risk of undertreatment when delivering anti-VEGF treatment as needed, cautioned Prof. Sivaprasad. In a large, multicentre, national nAMD database study involving 12,951 eyes of 11,135 patients, there was a decline from baseline VA of 2 letters at 3 years' follow-up in treatment-naïve nAMD eyes treated with as-needed ranibizumab after a treatment initiation phase of consecutive monthly injections.<sup>14</sup> (The ranibizumab posology discussed here may not represent the full range of current licensed posologies of ranibizumab. Please consult the ranibizumab Summary of Product Characteristics [SmPC].) However, for DMO, patients may be effectively managed using an as-needed anti-VEGF retreatment regimen after an initial loading phase of monthly injections, with the number of required retreatments declining substantially in subsequent years.

Prof. Sivaprasad noted that each regimen had advantages. Fixed-interval dosing is simplest, involving minimum monitoring and regular appointments and injection at each clinic visit. A PRN strategy averts overtreatment issues and provides a cost-effective approach based on individualised treatment. Treat and extend entails fewer overall clinic visits, individualised management, and permits effective use of finite clinic time and resources.

“Using treat and extend, physicians first treat and then extend the interval until the next treatment by 2-week intervals, to a maximum of 12 weeks, provided the disease remains inactive,” explained Prof. Sivaprasad. “If there is new evidence of disease activity, treatment is administered and the interval to the next treatment shortened.”

## Switch to treat-and-extend regimen may improve outcomes

For ranibizumab, the recommended treatment posology is monthly injections until maximum VA is achieved and/or there are no signs of disease activity. Thereafter, monitoring and treatment intervals can be extended (by no more than 2 weeks) until signs of disease activity or visual impairment recur. In nAMD, the recommended treatment posology for aflibercept is initiation of treatment with 1 injection per month for 3 consecutive doses, followed thereafter by 1 injection every 2 months. After the first 12 months of treatment,

the treatment interval may be extended on the basis of visual and/or anatomical outcomes.

Hatz and Prünke conducted a retrospective, consecutive, comparative case series evaluation of treatment-naïve nAMD patients initially treated with 0.5 mg ranibizumab according to a PRN schedule and subsequently switched to a treat-and-extend regimen (n=146 eyes).<sup>15</sup> The study analysed changes in BCVA and anatomical parameters during 12-months' follow-up in routine clinical practice.

After the switch to treat and extend, BCVA improved from 0.49±0.22 during the PRN maintenance phase to 0.56±0.24 (P<0.001),

and mean central retinal thickness decreased from 355±112 µm to 320±103 µm, at 12 months' follow-up. The mean number of visits per month was lower during treat and extend than PRN treatment phases (0.73±0.18 vs 1.05±0.13, respectively; P<0.001). Investigators concluded that a treat-and-extend regimen can improve and stabilise outcomes compared with as-needed treatment.

Another 12-month comparative case series study by the same authors compared outcomes associated with treat-and-extend versus PRN anti-VEGF regimens in nAMD patients naïve to treatment.<sup>16</sup> Better visual outcomes with fewer

## CHALLENGE THE EXPERTS

### Your Questions Answered

**PANELISTS:** Bożena Romanowska-Dixon, Neil Bressler (Professor of Ophthalmology, Johns Hopkins Wilmer Eye Institute, Baltimore, Maryland, United States), Giovanni Staurenghi, Anat Loewenstein, Sobha Sivaprasad, Michael Larsen.

Presentation debates were reviewed during an interactive panel discussion, focusing largely on controversies and comments on making a difference by treating early. Spotlight insights and panelist contributions are summarised below.

We should invest resources into those areas where we get most value for money. Time definitely matters when you have newly diagnosed active CNV with definite visual field loss. We undertook a retrospective study examining visual outcomes in relation to time to treatment from diagnosis in neovascular AMD. Early diagnosis and treatment of nAMD was shown to be of value for functional outcomes, with a shift to same-day injection on diagnosis associated with a 5-letter gain in mean VA at 3 months after presentation.<sup>20</sup> Visual acuity on treatment improved by changing clinical practice to reduce the median time to treatment from 16 days to 1 day, and observed an improved prognosis with a gain in visual acuity as a result.

—Michael Larsen

Guidance from The National Institute for Health and Care Excellence (NICE) recommends treatment with ranibizumab or aflibercept for subfoveal CNV, and includes detailed criteria for initiating, continuing, or discontinuing intravitreal anti-VEGF treatment.<sup>21,22</sup> Criteria for treatment include a best-corrected VA between 6/12 and 6/96, which means that we cannot treat nAMD patients with presenting vision better than 6/12 (≥73 letters). Clinicians can challenge these treatment thresholds under exceptional circumstances, for example, if there is good vision but marked vision distortion or evidence of recent fluid leakage.

—Sobha Sivaprasad

In general I support early treatment of eye disease. In DMO, the crucial issue to evaluate is whether there is deterioration, or whether the VA is not controlled—in such cases, clinicians may not want to wait and withhold treatment. In AMD, even with an accurate diagnosis, we tend to wait until occult CNV progresses

before initiating treatment. Early treatment for second eye or only eye? I would be less happy to observe in such cases and would likely decide to be more proactive in these cases.

—Anat Loewenstein

Deterioration with recurrent exudation in AMD is quite different to deterioration in diabetes. Again, I believe that high-resolution spectral-domain OCT imaging is the key factor, both for imaging of fluid and also of the anatomy, to determine the need for early aggressive intervention. In diabetes, changes at the level of the retina may be observed, and if there are signs of degenerative change, then I will treat. Also, in diabetes the general health condition of the patient needs to be carefully considered in guiding treatment decisions.

—Giovanni Staurenghi

While in favour of early treatment, we should have regard to both cost and benefit when considering optimal treatment approaches. For elderly individuals, for example, we should personalise the treatment approach to take account of the specific needs of patients. It is important that each case is properly evaluated and patient needs assessed in deciding how aggressive the treatment approach should be.

—Bożena Romanowska-Dixon

Even for cases of age-related macular degeneration, physicians should discuss treatment regimen or options (treatment vs observation) with individual patients. A slam-dunk case warranting treatment would be presenting vision of 20/50 with fluid leakage on fluorescein angiography.

—Neil Bressler

clinic visits were seen with ranibizumab given using a treat-and-extend regimen: mean change in BCVA from baseline to month 12 was  $+0.18 \pm 0.17$  for patients in the treat-and-extend group ( $n=70$ ) compared with  $+0.07 \pm 0.20$  in the PRN group ( $n=70$ ), with a substantially higher number of follow-up visits attended in the PRN group with monthly OCT evaluation ( $11.9 \pm 1.1$  vs  $8.6 \pm 1.9$ , respectively).

"Having alternative treatment regimens available allows clinicians to switch to another retreatment schedule if a particular regimen is not effective or proves insufficient on continued treatment," added Prof. Sivaprasad. "All clinical factors and patient preferences need to be considered before initiating a change in treatment regimen. But with multiple regimens and different licensed anti-VEGF agents to choose from, clinicians can balance simplicity, practicality, and effectiveness when considering the most appropriate retreatment strategy."

## DEBATE CON:

### Retreatment: We can now balance simplicity, practicality, and effectiveness

Michael Larsen, University of Copenhagen and the Glostrup Hospital, Copenhagen, Denmark

"There are multiple barriers to balancing simplicity, practicality, and effectiveness," argued Prof. Michael Larsen in a rebuttal presentation. "These include limited healthcare resources, poor coordination, lack of adherence to guidelines, lack of quality control, poor patient awareness, and conflicts of interest between individualised care versus population-based management pathways. So we have to consider what we can do as ophthalmologists to improve service provision and clinical efficacy outcomes in nAMD and DMO."

### Real-life experience suggests patient management could be improved

Current clinical practice neither reflects pivotal trial regimens nor approved labels, Prof. Larsen added, who observed that injection frequencies for nAMD are typically much lower than they should be in real-world clinical practice and the outcomes on follow-up oftentimes fail to match randomised clinical trial results.<sup>7,17</sup>

Does this reflect a shortage of resources or suggest limited patient adherence? Visual acuity outcomes were poorer than expected

and also varied substantially between countries in AURA, an international, retrospective, observational study of real-life use and effectiveness of ranibizumab in nAMD patients treated between August 2009 and August 2011.<sup>7</sup>

For the global AURA population, the initial good response in VA declined over time: there was a mean VA gain of +4.1 letters at day 120 after treatment initiation, with a mean change in VA score from baseline of +2.4 letters at year 1 and +0.6 letters at year 2. However, evidence from the UK cohort of AURA, where monitoring including OCT and retreatment rates were higher than in the global population, show that translation of clinical study outcomes in real-life settings is achievable, albeit with some decline over time.<sup>8</sup> Here, the mean change in VA from baseline was +6.0 letters at year 1 and +4.1 letters at year 2, with a mean of 18.4 clinic visits and 9.0 injections over 2 years.

Efficacy outcomes comparable to those observed in randomised clinical trials can be secured when clinicians stay close to the regulatory label, said Prof. Larsen. Results evaluating aflibercept administered according to the VIEW study protocol for nAMD show that early VA gains can be maintained through the first year with fixed bimonthly dosing after initiation with 3 consecutive monthly doses, with visual outcomes that are better than many previous real-world data collections examining anti-VEGF treatment benefits.<sup>12</sup> With a mean of 7 injections given during the first year, the proportion of eyes with vision  $\geq 70$  letters increased to 33.7% at 1 year compared with 16.4% at baseline.

Prof. Larsen commented: "Positive initial responses to anti-VEGF therapy can be maintained without a decline over time when clinicians adhere to randomised trial protocols and the regulatory licensed posology. This helps also to keep matters simple and clear for patients and physicians. But that is not what we in the ophthalmology community in general are doing: relatively low injection frequency together with inferior efficacy outcomes indicate that patient management could be improved."<sup>18</sup>

### Simpler and more systematic approaches to retreatment may lessen the burden of care

"We can clearly do much better," explained Prof. Larsen. "The burden of care may per-

haps be lessened by adopting simpler, more systematic anti-VEGF treatment regimens. Increasing the frequency of monitoring (with OCT evaluation) and higher retreatment rates may improve the outcomes attained in real-world practice."

Findings from the AURA study suggest that the observed decline of treatment benefits with ranibizumab therapy may be associated with number of injections and a failure to visit clinicians and receive OCT evaluation as required.<sup>19</sup> Significant ( $P < 0.05$ ) prognostic factors for vision maintenance (loss  $< 15$  letters from baseline) or vision gain ( $\geq 15$  letters) in AURA were baseline age, number of clinical examinations and OCT evaluations (combined), and number of injections given (ranibizumab).

"If there are golden rules for the management of DMO and nAMD using intravitreal anti-VEGF therapy, then it must be those set by the respective regulatory drug authority," commented Prof. Larsen in concluding arguments. "If clinicians choose to deviate from these golden rules, then they should prepare themselves to be scrutinised in the future by payers, healthcare authorities, and informed patients."

Big Data analysis and an explosion of available information are coming to ophthalmology. Clinicians need to make sure that they conduct regular self-audits and prepare for the new world of total transparency.

## Counterpoint Rebuttal

Sobha Sivaprasad

"This debate essentially centres on the simplicity of treatment regimen and retreatment schedule using intravitreal antiangiogenic therapy," commented Prof. Sivaprasad in a brief counterpoint presentation. "In the UK experience, where treatment practice was dominated by just one approach for several years, vision gains from baseline measured by change from baseline in ETDRS BCVA letter score have been lower than those reported in pivotal randomised clinical trials. Nevertheless, we have seen improvements in clinical outcomes with the availability and adoption of alternative anti-VEGF retreatment schedules. So I believe that the current approach is characterised by greater simplicity."

## RAPID FIRE Q&A

In a concluding rapid-fire session, Dr. Neil Bressler briefly addressed several questions from symposium delegates.

**Q:** *Is geographic atrophy an issue when you are treating neovascular AMD and is there an increased risk with a fixed-interval anti-VEGF dosing regimen?*

**A:** It is most likely that the atrophy that is seen is not geographic that you see with drusen. Rather, the actual appearance of a lesion treated with anti-VEGF therapy is that the retina becomes atrophic—it is not that the drug necessarily is causing more atrophy.

**Q:** *How frequently is aflibercept administered in the treatment of DMO?*

**A:** In VISTA and VIVID, for the intravitreal aflibercept 2q8 arm, treatment was given monthly for 5 initial doses and then every other month through the next several years. And that led to excellent improvements in visual and anatomic outcomes. From baseline to week 100, study eyes in the aflibercept 2q8 group received a mean of between 13.5 and 13.6 injections, and approximately 8 injections during

the first year of treatment.<sup>23</sup> For both phase 3 studies, a significantly greater proportion of eyes treated with aflibercept experienced an improvement.

**Q:** *What is your preferred treatment regimen for nAMD?*

**A:** Administering ranibizumab monthly maximises a nAMD patient's chance of retaining their vision. The CATT and IVAN trials showed that good outcomes are achievable with strict monthly monitoring and treatment given as needed.<sup>24,25</sup>

In DMO, we have registration trials involving monthly treatment for 5 months followed by treatment every other month demonstrating significant superiority over laser, with similar efficacy in the aflibercept monthly and aflibercept bimonthly groups despite the extended dosing interval in the 2q8 group.<sup>26</sup> And we have “well-conducted,” randomised clinical trials showing that using as-needed anti-VEGF treatment for DMO can generate excellent results too. It is AMD that presents the challenge with regard to selection of treatment regimen.

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## Eylea® ▼ 40 mg/ml solution for injection in a vial (afibercept)

**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).

### POSOLGY & 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 75 years 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  $\geq 30$  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  $\geq 30$  letters compared with the last assessment; central foveal subretinal haemorrhage, or haemorrhage  $\geq 50\%$ , 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](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to Bayer plc. Tel: 01635 563500, Fax: 01635 563703, Email: [pvuk@bayer.com](mailto:pvuk@bayer.com)