Aflibercept and the Evolution of CRVO Management

Tackling visual impairment early, effectively and flexibly

Highlights from Bayer HealthCare's Satellite Symposium 'Aflibercept and the evolution of CRVO management,' held on September 12, 2014, at the 14th EURETINA Congress, London, UK

Prescribing information can be found on the back cover

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A brief history of CRVO and the treatment options

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Central retinal vein occlusion (CRVO) is a global health concern. It's estimated to affect 2.5 million people worldwide; its age- and sex-standardized prevalence is 0.8 per 1,000 people (1). Prevalence is not thought to be affected by gender or ethnic background, but it's known to increase significantly with advancing age – as do many of the systemic and ocular risk factors for CRVO, like systemic hypertension, diabetes mellitus and glaucoma. The consequences of vision loss or impairment are stark. In the US alone, $8 billion is lost in productivity each year as a result of visual impairment and blindness (2), a figure to which CRVO contributes. This figure doesn't even begin to account for the devastating impact CRVO-induced vision loss has on patients' quality of life, every day for the rest of their lives (3). Clearly, halting disease progression as early, and for as long, as possible is our objective when treating macular edema (ME) in patients with CRVO.

In order to understand current treatment approaches, we need first to map the natural history of CRVO, which typically follows this course: thromboembolism in the central retinal vein impairs retinal blood flow, resulting in increased intraluminal pressure, forcing both fluid and blood products through the blood-retinal barrier (4-6). Fluid accumulates in the retina (edema), and this reduces capillary perfusion, resulting in hypoxia and a rise in levels of vascular endothelial growth factor (VEGF) (7). This ultimately leads to a breakdown of the blood-retinal barrier, angiogenesis and neovascularization (5). Notably, VEGF levels observed in CRVO cases are among the highest in all retinal disorders (4), and ME is the most frequent cause of vision loss in those who have the disease (5).

Historically, treatments for CRVO were unable to improve vision. The first available option, grid laser photocoagulation, was only ever intended to prevent complications in ischemic disease (8), and it's unclear if radial optic neurotomy (RON) has any benefit over and above natural history (9). Grid laser photocoagulation is no longer recommended for the treatment of CRVO (10). More recently, the GENEVA studies revealed that steroids do display some efficacy in the treatment of ME in patients with retinal vein occlusion, but their use commonly resulted in increases in intraocular pressure and cataract development (11). Latterly, anti-VEGF agents have been shown to provide significant vision improvements with a good safety profile (11). Figure 1 shows the historical progress that's been achieved to date in the treatment of CRVO-induced ME.

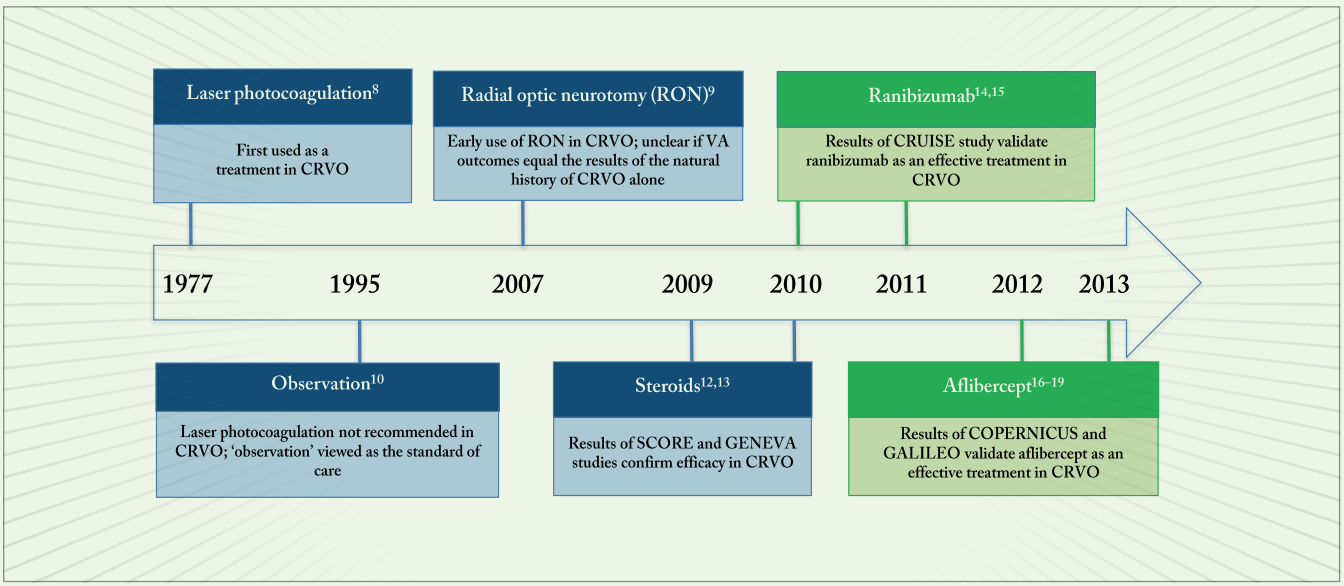

Figure 1. Timeline of advances in the management of CRVO-induced ME.

Aflibercept: leveraging efficacy and the window of opportunity

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Aflibercept is a fusion protein, designed specifically to be a potent and durable anti-VEGF and anti-placental growth factor (PlGF) agent (Table 1). The Phase III COPERNICUS (16,17) and GALILEO (18,19) clinical trials (Figure 2) demonstrated that aflibercept use rapidly improves both visual acuity (VA) and central retinal thickness (CRT) from baseline in patients with CRVO of both ischemic and non-ischemic origins, with a low incidence of adverse events.

Like all anti-VEGF agents used to treat the ME that's caused by CRVO, getting the timing right and minimizing delays to commencing treatment are critical to achieving the best possible outcomes for the patient. Untreated CRVO results in progressive and irreversible vision loss, and early aflibercept administration results in better anatomical and visual outcomes: patients treated within two months of diagnosis have better outcomes with aflibercept than those whose treatment was delayed (18,19). Furthermore, patients switched from sham injections to aflibercept do achieve VA gains, but

	VEGF-A_{121} IC_{50} at 20 pM (pM)	VEGF-A_{165} IC_{50} at 20 pM (pM)	hPlGF2 IC_{50} at 40 pM (pM)	VEGF-A_{121} IC_{50} at 20 pM (pM)	VEGF-A_{165} IC_{50} at 20 pM (pM)
Bevacizumab	854	1476	NB	630	1323
Ranibizumab	675	1140	NB	576	845
Aflibercept	15	16	2890	16	26

Table 1. Aflibercept strongly inhibits VEGF and PIGF (both potent promoters of angiogenesis) in cell-based assays (20). IC50 = 50 percent inhibitory concentration at 20 pM; NB = no detectable blocking under the assay conditions used. PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

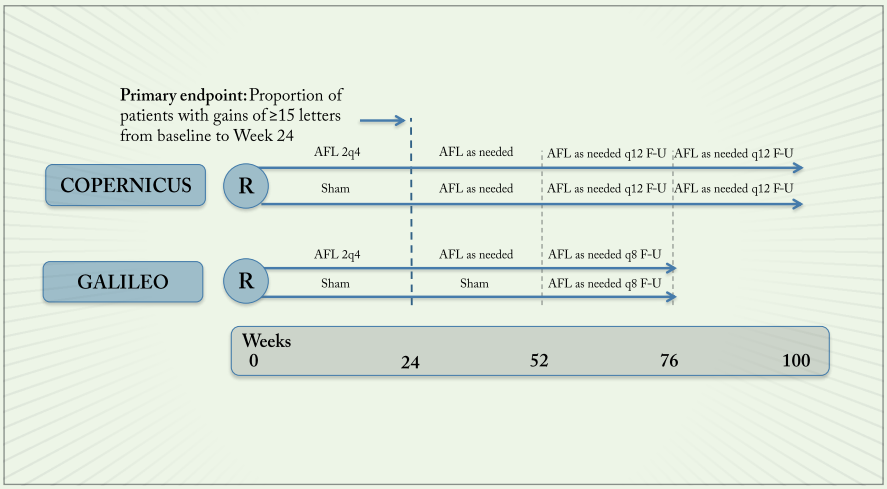

Figure 2. Copernicus and Galileo study designs (16–19).
AFL, aflibercept; F-U, follow-up; 2q4, 2mg every 4 weeks; q8, every 8 weeks; q12, every 12 weeks.

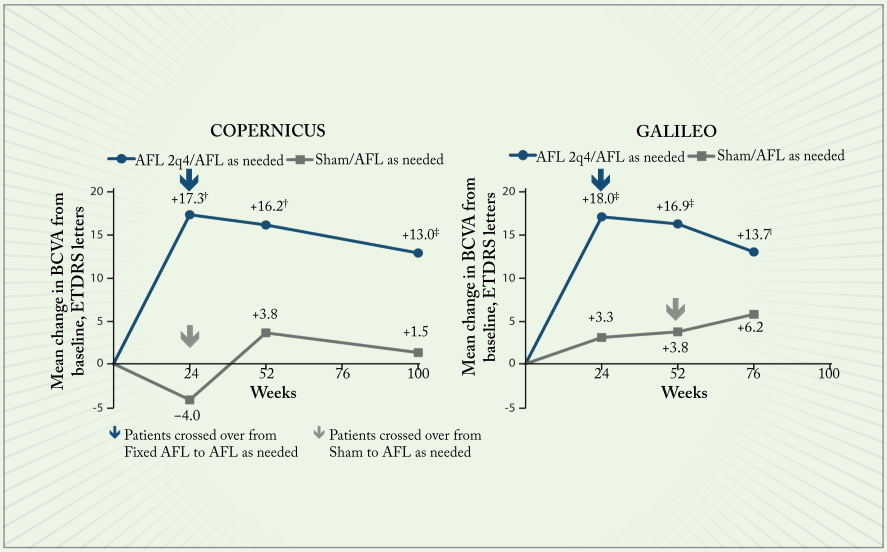

Figure 3. Vision gains were largely maintained with less frequent than monthly dosing (16-19).
2q4, 2 mg every 4 weeks; AFL, aflibercept; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; ‖ p<0.01; †p<0.001; ‡p<0.0001 vs. sham.

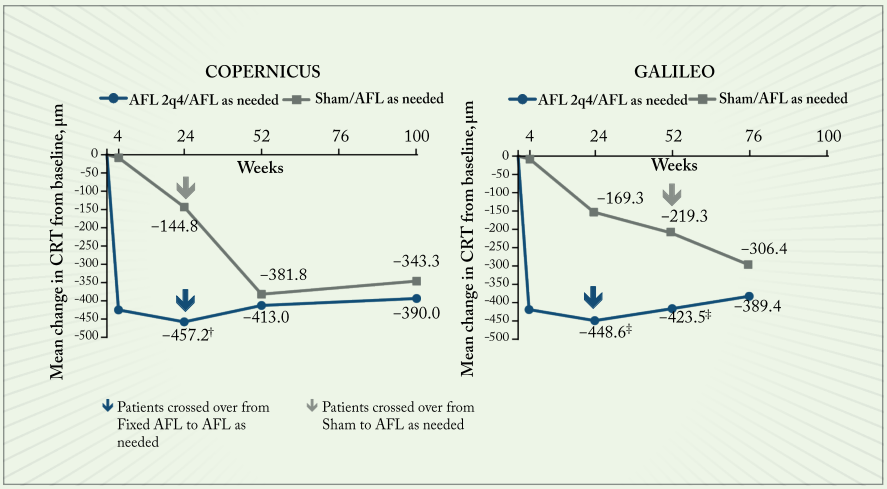

Figure 4. Aflibercept delivered rapid and durable improvements in CRT (22–23).

2q4, 2 mg every 4 weeks; AFL, aflibercept; CRT, central retinal thickness. †p<0.001; ‡p<0.0001 vs. sham.

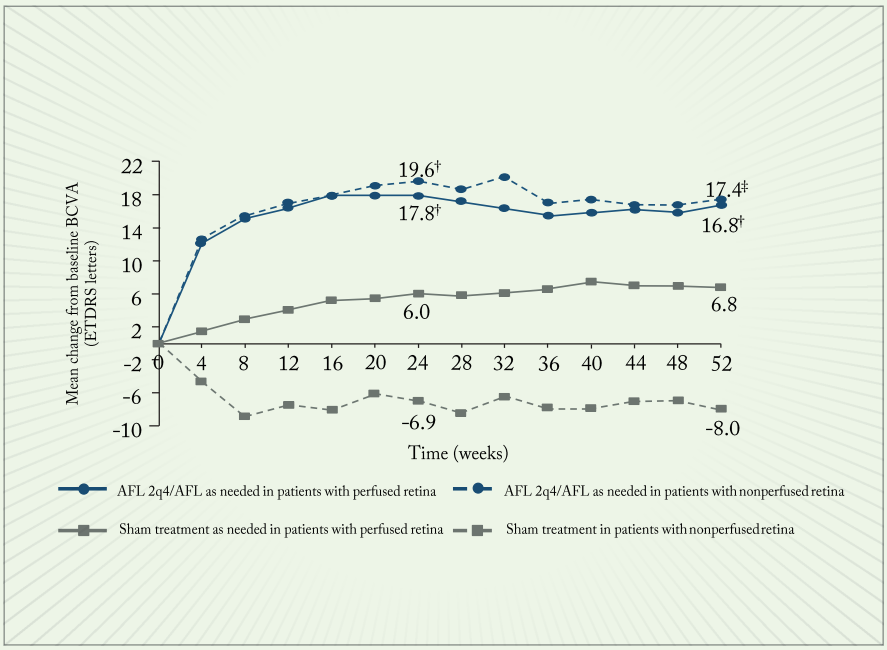

Figure 5. Visual outcomes during the 52 weeks of the GALILEO study. Mean change from baseline BCVA by the status of retinal perfusion at baseline (18).

Perfused: fewer than 10 disc areas of non-perfusion. 2q4, 2 mg every 4 weeks; AFL, aflibercept; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study. †p<0.0001 vs sham; ‡p<0.001 vs sham.

they never equal those achieved by patients who received aflibercept in the first place, underscoring the need for early intervention (16,18).

Importantly, the vision gains with aflibercept observed in the COPERNICUS and GALILEO trials are largely maintained with a dosing schedule less frequent than monthly regimens (Figure 3). Such a schedule still improved mean best corrected visual acuity (BCVA) by over 17 letters within 24 weeks (16–19), and most patients gained at least 15 letters within two months of diagnosis, with the mean gain in BCVA after the first dose being more than two lines. Furthermore, patients that received initial treatment with aflibercept maintained gains of at least 13 letters up to week 100 of treatment (21–23).

But just how far out can you spread aflibercept injection and still see functional improvements in vision? In both trials, patients received aflibercept as needed (pro re nata; PRN) from week 24 onwards (Figure 2). Treatment was considered warranted only if pre-specified changes in CRT, fluid accumulation, edema or BCVA occurred (18). The mean number of PRN injections in GALILEO was 2.5 over this 6-month period, and the median time to the first PRN intravitreal aflibercept injection was 83 days (18). CRT showed similar patterns (Figure 4) – for example, at week 24 in the COPERNICUS study, CRT was approximately three times greater in the sham group compared with the aflibercept-treated group (16,17). After this point, all patients received PRN aflibercept, and the CRT in the initially sham-treated group managed to catch up by week 52 (although this doesn't reflect the VA gains). In GALILEO, sham-treated patients were switched to PRN aflibercept later – at week 52 – and also showed rapid improvements in CRT once treated with the active drug (18), but even by week 76, they had not caught up with the aflibercept group, again underscoring the importance of timely intervention with aflibercept in patients with ME secondary to CRVO (23).

Furthermore, aflibercept treatment significantly improves visual outcomes relative to sham treatment, irrespective of perfusion status at baseline (Figure 5) (18).

Beyond clinical trials: the proactive treat-and-extend approach

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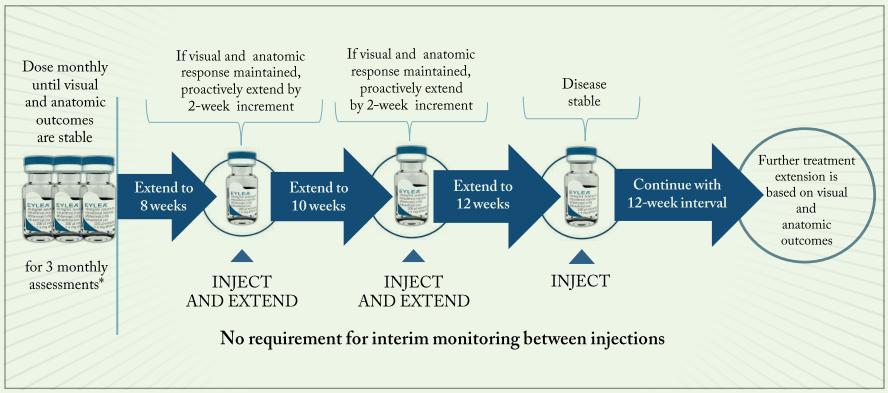

Figure 6. Specimen administration schedule for aflibercept therapy in patients with CRVO. The schedule should be determined by the treating physician based on patient response, and monitoring may be more frequent than the schedule of injections. *Discontinue treatment if there is no improvement in response after the first three injections.

When treating ocular diseases, we want to improve patients' visual and anatomic outcomes with the minimum amount of burden. Anti-VEGF treatment is effective for treating ME secondary to CRVO, but the burden can be treatment-associated adverse events or the hassle of frequent clinic visits for intravitreal injections – both stressful and inconvenient. On the other hand, drugs don't work if patients don't receive them – regimen adherence is absolutely crucial for treatment success. The question is therefore: how do we best achieve the desired treatment outcomes while minimizing patient burden?

There's also a big gap between what works in a clinical trial and what happens in the real world – the AURA study gives one such example (24). Investigators collected 'real-life' data on the clinical management and resource utilization of 2,227 patients from eight countries who had wet age-related macular degeneration and were treated with ranibizumab. The investigators found that real-life anti-VEGF therapy use was associated with poorer than expected visual outcomes when compared with what was observed in trials. Why? In the real world, monitoring occurred less than monthly and only a low number of treatments were administered per year, allowing fluid to accumulate. The success of PRN treatment depends on monthly monitoring in the clinic. So I asked myself: might there be a better approach that maintains the benefits achieved in the first six months of monthly aflibercept therapy, but maximizes the intervals between doses, thereby reducing patient burden?

Treat-and-extend regimens could be the answer. The concept is simple: initiate treatment with standard loading doses of aflibercept, then slowly extend the time between treatments until fluid recurs. This means that you understand what the patient's maximum fluid-free interval is and you can adjust the dosing regimen accordingly. Of course, if the fluid recurs, then it's always an option to treat more frequently in order to keep the retina dry and maintain VA. Like fixed regimens, treat-and-extend is a proactive approach, aiming to treat CRVO before fluid accumulates; however, it is flexible, allowing you to exercise your clinical judgment and identify the right treatment interval for each of your patients.

Most patients with CRVO attain maximum VA gains after three or four monthly aflibercept injections; the challenge is then to maintain those gains. In both COPERNICUS and GALILEO, those receiving aflibercept had their dosing based on visual and anatomic outcomes after week 24 of the trial. Furthermore, a post-hoc analysis of COPERNICUS and GALILEO revealed that a majority of patients required only three or fewer aflibercept injections in the second six months of the trials (25).

Aflibercept's estimated long intravitreal half-life (26,27) and prolonged suppression of VEGF (28) means that treatment intervals can be extended in many patients to eight weeks or more without compromising the VA gains achieved in the initial monthly dosing period. A flexible treat-and-extend posology for ME, secondary to CRVO, comprises an initial fixed monthly dosing period to gain control of the disease; the treatment intervals are then increased based on visual and anatomic outcomes (Figure 6).

Results from the COPERNICUS and GALILEO studies lead to the approved posology wording for the use of aflibercept for the treatment of ME secondary to CRVO. They recommend that (21):

- After the initial injection of aflibercept, treatment is given monthly – with the treatment interval being no

shorter than one month.
- If no improvements in visual and anatomic outcomes are observed over the course of the first three injections, then continued treatment is not recommended.
- If improvements are seen, monthly treatment should continue until visual and anatomic outcomes are stable for three monthly assessments – thereafter, the need for continued treatment should be reconsidered.
- If necessary, treatment may be continued with gradually increasing treatment intervals to maintain a stable visual and anatomic outcome. If treatment has been discontinued, visual and anatomic outcomes should be monitored and treatment should be resumed if these deteriorate.
- Usually, monitoring should be done at the injection visits. During treatment interval extension through to completion of therapy, the monitoring schedule should be determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections.

Aflibercept has, therefore, a flexible posology, which allows a treat-and-extend approach that is tailored to the individual needs of the patient – an approach pioneered with aflibercept that has now been adopted for ranibizumab use in this indication too (29).

In summary, the goals for treating ME secondary to CRVO are clear; the challenge is how we achieve them. Maximum VA and anatomic outcomes, as well as the prevention of irreversible vision loss, are achieved through intensive treatment at the early stages of disease – the greatest visual gains occur within 12 weeks of starting treatment. A treat-and-extend regimen using aflibercept, therefore, aims to prevent visual and anatomical decline by providing therapy immediately prior to disease breakthrough.

Treat-and-extend in the clinic: case study review

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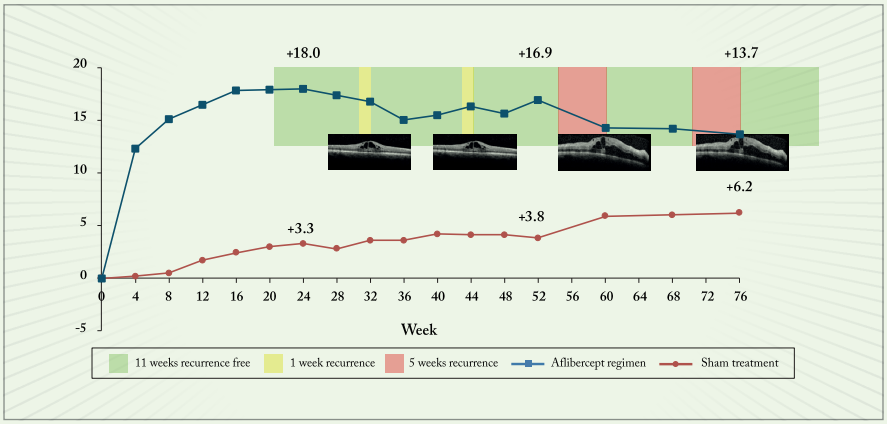


Figure 7. Eleven-week recurrence-free interval with aflibercept (adapted to GALILEO) (18,23). At the week 24 primary endpoint, patients receiving intravitreal 2 mg aflibercept every four weeks had a significantly greater mean change in BCVA than the sham-treated patients (18.0 vs 3.3 letters, respectively; p<0.0001) (18). At week 76, patients in the intravitreal aflibercept 2q4 group reported a mean change from baseline BCVA of 13.7 ETDRS letters, compared with sham-treated eyes, which gained 6.2 letters (23).
2q4, 2 mg every 4 weeks; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, pro re nata.

The COPERNICUS and GALILEO studies show us that a significant gain in VA of three lines in the first year of aflibercept therapy is possible, and that the first injection is associated with the most extensive reduction in edema and increase in VA (16,18).

However, treatment with six loading doses followed by variable-interval treatment PRN isn't necessarily the best approach in all patients because I believe that there are smarter, personalized treat-and-extend strategies that we can employ. We have also learned not to delay treating our patients; extending PRN can sometimes prove suboptimal (Figure 7).

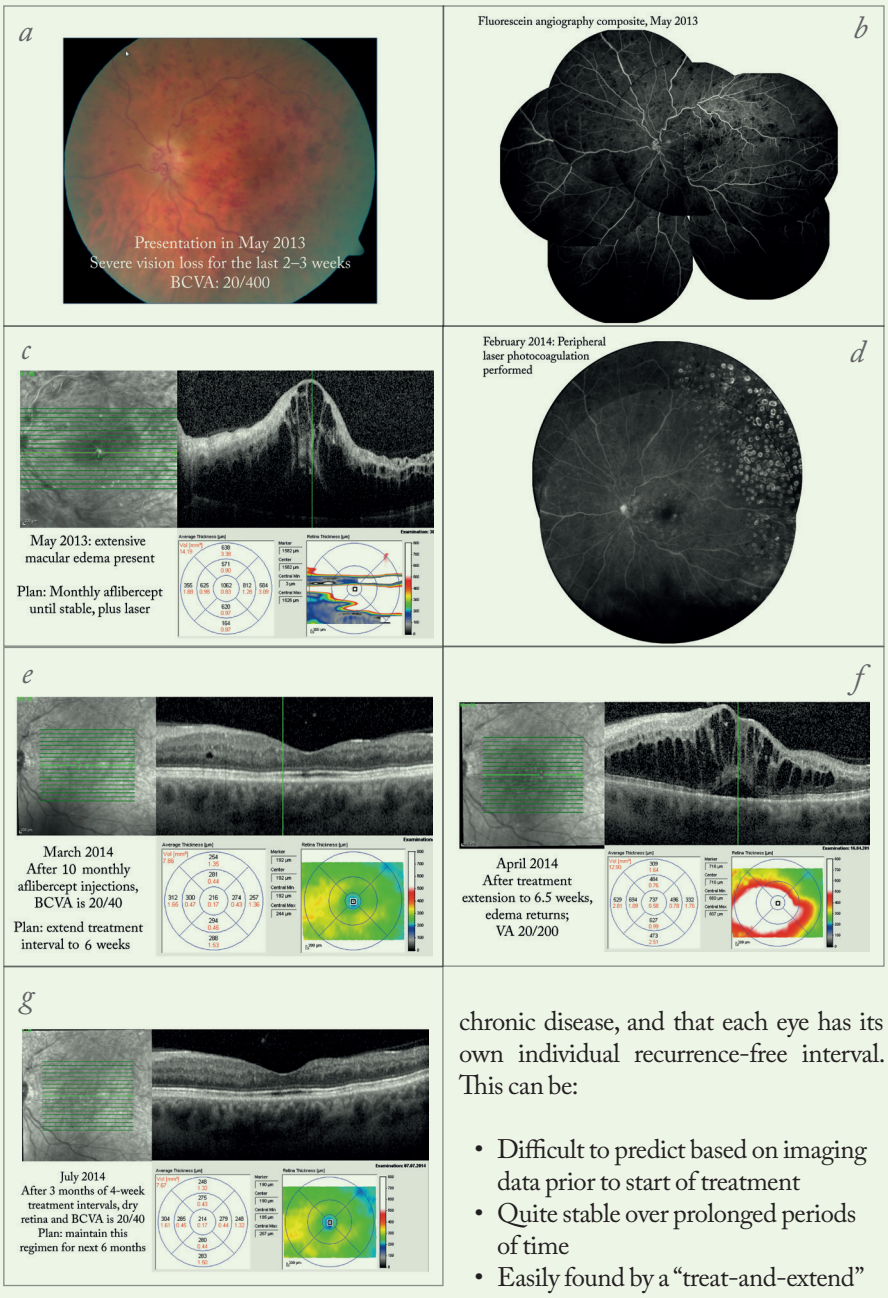
The following ischemic and non-ischemic CRVO case studies show the efficacy of aflibercept and how we developed appropriate treatment regimens for each patient.

The first case study (see Box) presents a treatment-naïve ischemic CRVO patient who had been experiencing severe vision loss for two to three weeks (a). The patient's VA was poor – 20/400, and the composite of the fluorescein angiography (FA) (b) showed large areas of non-perfusion. The ME was quite extensive (c), and we treated with monthly aflibercept – and we used a laser on the peripheral, non-perfused areas

(d). We did try to extend the treatment to six weeks (e), but we were unsuccessful (f) – it is likely that this patient has very high levels of VEGF. The FA charts the response to treatment (g); through maintaining monthly treatment intervals over six months, the patient had a VA of 20/40.

The second case study comes from 2012, and concerns a treatment-naïve patient with non-ischemic CRVO who presented to me two months after their initial vision loss. Their BCVA was 20/200, and FA and OCT imaging showed extensive ME. At that time, the approved therapy was ranibizumab, so we started the patient on monthly intravitreal injections of the drug. OCT imaging taken four weeks after the third injection showed that the patient had a nice response, although his BCVA never improved beyond 20/40 – possibly because of an irregularity in his photoreceptor inner segment/ outer segment junction. After his fifth monthly ranibizumab injection, we tried to extend the period between injections to six weeks. This resulted in significant ME, and his BCVA had degraded to 20/63. At this point in time, we were able to switch the patient to aflibercept.

We initially used quite an aggressive aflibercept regime – I used the maximum recurrence free interval under ranibizumab and added two weeks to that – in other words, he received the first injection of aflibercept, and he returned to the clinic six weeks later. His macula was dry, so we extended the treatment interval to eight weeks – successfully. We administered the third aflibercept injection, then again after eight weeks, then tried to push him a little further by extending the interval between the third and fourth injection to ten weeks – but edema returned and his visual acuity worsened. We reduced his treatment interval to eight weeks again, which kept his retina edema-free. At the patient's one-year follow up, eight weeks after the seventh aflibercept injection; his retina is dry and his BCVA is 20/32.



Typically we try to keep such patients on this recurrence-free interval for six months and then try to extend it again by two weeks – if that doesn't work, we keep the patient for another six months on their original interval. Accordingly, six months later, we tried to extend the treatment interval to nine weeks, but we started to see some edema return, so it seems that the patient's maximum fluid-free interval really is eight weeks.

What you have to remember when treating ME in patients with CRVO is that, in most cases, you're treating a chronic disease, and that each eye has its own individual recurrence-free interval. This can be:

- Difficult to predict based on imaging data prior to start of treatment
- Quite stable over prolonged periods of time
- Easily found by a "treat-and-extend" approach, and
- Dependent on the anti-VEGF drug used.

Because of these factors, fixed regimens – be it PRN, monthly or bimonthly dosing – can't fit the needs of all patients. If you do employ an aflibercept treat-and-extend regimen to treat ME in patients with CRVO, I have two tips I'd like to share. First, the best tool to detect recurrence is spectral domain OCT, and second, always remember that – just like wet AMD – function follows early anatomic changes… so intervene at the earliest opportunity.

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Prescribing info

▼Eylea® 40 mg/ml solution for injection in a vial (aflibercept) Prescribing Information (Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 1 ml solution for injection contains 40 mg aflibercept. Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. Indication(s): Treatment of neovascular (wet) age-related macular degeneration (AMD), macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) and visual impairment due to diabetic macular oedema (DMO) in adults. Posology & method of administration: For intravitreal injection only. Must be administered according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. Each vial should only be used for the treatment of a single eye. The vial contains more than the recommended dose of 2 mg. The extractable volume of the vial (100 microlitres) is not to be used in total. The excess volume should be expelled before injecting. Refer to SmPC for full details. Adults: The recommended dose is 2 mg aflibercept, equivalent to 50 microlitres. For wAMD treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. No requirement for monitoring between injections. After the first 12 months of treatment, treatment interval may be extended based on visual and/or anatomic outcomes. In this case the schedule for monitoring may be more frequent than the schedule of injections. For RVO (branch RVO or central RVO), after the initial injection, treatment is given monthly at intervals not shorter than one month. Discontinue if visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment. Treat monthly until maximum visual acuity and/or no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. Shorten treatment intervals if visual and/or anatomic outcomes deteriorate. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response. For DMO, initiate treatment with one injection/month for 5 consecutive doses, followed by one injection every two months. No requirement for monitoring between injections. After the first 12 months of treatment, the treatment interval may be extended based on visual and/or anatomic outcomes. The schedule for monitoring should be determined by the treating physician. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, treatment should be discontinued. Hepatic and/or renal impairment: No specific studies have been conducted. Available data do not suggest a need for a dose adjustment. Elderly population: No special considerations are needed. Limited experience in those with DMO over 75years old. Paediatric population: No data available. Contra-indications: Hypersensitivity to active substance or any excipient; active or suspected ocular or periocular infection; active severe intraocular inflammation. Warnings & precautions: As with other intravitreal therapies endophthalmitis has been reported. Aseptic injection technique essential. Patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients must report any symptoms of endophthalmitis without delay. Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection; special precaution is needed in patients with poorly controlled glaucoma (do not inject while the intraocular pressure is ≥30 mmHg). Immediately after injection, monitor intraocular pressure and perfusion of optic nerve head and manage appropriately. There is a potential for immunogenicity as with other therapeutic proteins; patients should report any signs or symptoms of intraocular inflammation e.g pain, photophobia or redness, which may be a clinical sign of hypersensitivity. Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors. Safety and efficacy of concurrent use in both eyes have not been systemically studied. No data is available on concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular). Caution in patients with risk factors for development of retinal pigment epithelial tears including large and/or high pigment epithelial retinal detachment. Withhold treatment in patients with: rhegmatogenous retinal detachment or stage 3 or 4 macular holes; with retinal break and do not resume treatment until the break is adequately repaired. Withhold treatment and do not resume before next scheduled treatment if there is: decrease in best-corrected visual acuity of ≥30 letters compared with the last assessment; central foveal subretinal haemorrhage, or haemorrhage ≥50%, of total lesion area. Do not treat in the 28 days prior to or following performed or planned intraocular surgery. Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection. Populations with limited data: There is limited experience of treatment with Eylea in patients with ischaemic, chronic RVO. In patients presenting with clinical signs of irreversible ischaemic visual function loss, aflibercept treatment is not recommended. There is limited experience in DMO due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. Eylea has not been studied in patients with active systemic infections, concurrent eye conditions such as retinal detachment or macular hole, or in diabetic patients with uncontrolled hypertension. This lack of information should be considered when treating such patients. Interactions: No available data. Fertility, pregnancy & lactation: Not recommended during pregnancy unless potential benefit outweighs potential risk to the foetus. No data available in pregnant women. Studies in animals have shown embryo-foetal toxicity. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last injection. Not recommended during breastfeeding. Excretion in human milk: unknown. Male and female fertility impairment seen in animal studies with high systemic exposure not expected after ocular administration with very low systemic exposure. Effects on ability to drive and use machines: Possible temporary visual disturbances. Patients should not drive or use machines if vision inadequate. Undesirable effects: Very common: conjunctival haemorrhage (phase III studies: increased incidence in patients receiving anti-thrombotic agents), visual acuity reduced. Common: retinal pigment epithelial tear, detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract (nuclear or subcapsular), corneal abrasion or erosion, corneal oedema, increased intraocular pressure, blurred vision, vitreous floaters, vitreous detachment, injection site pain, eye pain, foreign body sensation in eyes, increased lacrimation, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival or ocular hyperaemia. Uncommon: Injection site irritation, abnormal sensation in eye, eyelid irritation. Serious: cf. CI/W&P - in addition: blindness, endophthalmitis, cataract traumatic, transient increased intraocular pressure, vitreous detachment, retinal detachment or tear, hypersensitivity (incl. allergic reactions), vitreous haemorrhage, cortical cataract, lenticular opacities, corneal epithelium defect/erosion, vitritis, uveitis, iritis, iridocyclitis, anterior chamber flare. Consult the SmPC in relation to other side effects. Overdose: Monitor intraocular pressure and treat if required. Incompatibilities: Do not mix with other medicinal products. Special Precautions for Storage: Store in a refrigerator (2°C to 8°C). Do not freeze. Unopened vials may be kept at room temperature (below 25°C) for up to 24 hours before use. Legal Category: POM. Package Quantities & Basic NHS Costs: Single vial pack £816.00. MA Number(s): EU/1/12/797/002. Further information available from: Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, United Kingdom. Telephone: 01635 563000. Date of preparation: March 2015.

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