Discussing treatment modalities for bilateral wet AMD

A 65-year-old lady with bilateral wet AMD and vision of 6/24 comes with an internet search about current therapies. How do you explain the various treatment modalities available?

There are two NICE approved treatments for wet age-related macular degeneration (AMD). Specifically, a series of intravitreal injections of either ranibizumab (Lucentis) or aflibercept (Eylea). Previous treatments for wet macular degeneration have included photodynamic therapy with Visudyne, which was first approved by NICE in 2001. Its effectiveness was limited and is no longer used routinely, except in a specific type of wet macular degeneration which is called idiopathic polypoidal choroidal vasculopathy (IPCV).

Before 2001 the only available treatment for wet AMD was retinal laser treatment. This was both a destructive treatment and ineffective and did not result in preservation of vision and is not used at all now.

Intravitreal injections of bevacizumab (Avastin), is also a well established treatment for wet AMD. However, it is not NICE approved and there is anecdotal evidence that there are increased cerebral vascular and cardiovascular adverse events with Avastin, which is now mainly used for non age-related wet macular degeneration. Since there are now two NICE approved treatments for wet AMD, this is what should be used and what the majority of consultants would recommend.

Which specific treatment is used depends upon the consultant's personal choice but once again there is some evidence to suggest that patients may need less injections of aflibercept than ranibizumab. This was confirmed by the clinical trials but whether it is true in real life remains to be seen.

Trials have been carried out showing that very localised radiotherapy (brachytherapy, ORAYA) may be of benefit in retaining vision when used in conjunction with a series of anti-VEGF injections (not instead of).

The benefit appears to be a possible reduction in the number of injections needed and less recurrence of wet AMD. This is not widely available on the NHS, not NICE approved and long-term safety (greater than two years) is not established. There are concerns about late development of radiation retinopathy.

My preferred advice would be:

1. Always do a fundus fluorescein angiogram, especially in bilateral disease. Although the diagnosis of wet macular degeneration may be obvious on the optical coherence tomography (OCT), fluorescein angiogram is necessary to define the true nature of the condition and any vascular abnormalities.
2. The consultant has a choice of either ranibizumab or aflibercept NICE approved injections to use for wet AMD. Consultant's choice may vary according to their personal experience but there is antedoctal evidence which suggests that aflibercept is more effective in patients with large pigment epithelial detachment (PED).
3. Nevertheless, if the patient has a large PED, they need to be cautioned on the possibility of a pigment epithelial rip post-treatment.
4. I would advise against doing bilateral injections on the patient's first visit for treatment. There is always the small risk of idiosyncratic reactions both due to the agent injected and to the actual injection procedure as well.
5. I would do sequential intravitreal injections for the first treatment episode with a few days between the injections and then subsequent injections can be timed to be bilaterally on the same day if the patient wishes.
6. If the patient is a primary non-responder, consider changing the type of anti-VEGF used.
7. If the patient continues to be a non responder (high flyer) then repeat the fluorescein angiography (FFA) +/- indocyanine green (ICG).
8. If the patient is phakic, make sure that a proper refracted visual acuity is carried out after the first series of injections so that any true improvement in vision can be documented.
9. In the younger patient always consider the possibility of a macular dystrophy, retinal angiomatous proliferation (RAP) or IPCV.

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TAKE HOME MESSAGE

Intravitreal anti-VEGF injections approved by NICE are the mainstay of treatment, although newer therapies are becoming available with varied responses.

I would explain about dry and wet AMD, rapid and unrecoverable loss of central vision in untreated wet AMD. Wet AMD needs investigations including vision, OCT and angiography depending on the clinical / OCT findings, including FFA and ICG. Consent for course of angiography to avoid reconsenting.

Treatment options

Mainstay is anti-VEGF. There are two licensed agents with different treatment regimens: Lucentis (ranibizumab) and Eylea (aflibercept). There is also one unlicensed: Avastin (bevacizumab).

Role of laser

Usually in the setting of a subset of wet AMD called polypoidal choroidal vasculopathy (PCV). Two options available in the NHS depending on the location of disease and can be used in combination with the anti-VEGF.

1. Photodynamic therapy (cold laser that can be used over / close to fovea which is area that provides fine vision centrally). Look for PCV if lot of exudates blood, serosanguinous or blood / serous PED, very steep high PEDs. Request ICG as the polyps show better on ICG.
2. Argon for any disease area away from the fovea.

For anti-VEGF before saying which drug and why, I would discuss local and systemic risks. I would explain about the risk of iatrogenic cataract, raised intraocular pressure, retinal detachment etc. and 1:1000 of loss of vision due to infection and the systemic risks including risk of stroke and myocardial infarction (MI). Also that this risk would be higher in the first three months after any previous cardiovascular episode and the general recommendation is to withhold treatment for three months after such a cardiovascular event unless the clinical situation and patient wishes after understanding enhanced risk. I would stress the need for the patient to inform us ASAP if they experience any cardiovascular event once treatment is started, as they could be reviewed in virtual clinics or booked for a course of injections with reduced opportunity for this information to be gathered.

Pros and cons of the two anti-VEGF options

Lucentis: Longer track record, it has been used extensively for around 10 years. The PRN regime after loading dose gives the possibility of injection free periods as the injection given only when needed and studies (PRONTO) have results comparable to more intensive fixed dosage, however, with the possibility of needing up to 12 injections in first year. The commitment to monthly monitoring visits will be explained. Explain the concept of virtual visits to monitor disease closely where vision and diagnostics are done, patient is sent home and the results reviewed and patient informed of outcome afterwards.

Eylea: Available in recent months, robust trials (VIEW) demonstrating that fixed dosing after loading dose demonstrated visual outcomes as good as monthly injections. This means that patient comes back every two months for diagnostics and injections and they can plan their life around these dates for the first year after starting treatment. There is some evidence in the literature suggesting slightly better anatomical results in some subsets of disease, though no difference in safety between the two drugs.

For either drug take consent for course of treatment. In a case of active AMD in one eye and high risk non-wet AMD, stress importance of self-monitoring and reporting of new symptoms from presently unaffected eye as 25% of patient can develop active disease in the second eye during the course of treatment.

New therapies

X-rays (ORAYA): New treatment, trials show that this reduces the need for injections when used in combination with injections. As radiation, hence used with caution, but overall good safety profile as low energy but very concentrated x-ray delivery to the wet AMD area. Suitable for some patients.

Other injections: Longer acting (DARPINS) and combination injections of anti-VEGF and anti-PDGF being investigated. Might become available in the near future.

In cases of non-wet AMD:

Discuss risk factors for AMD include age, gender, race, family history, genetics, weight and smoking. As individual's age, the risk for AMD increases. Women have a slightly higher risk for AMD than men. Genetic analyses have shown that a primary relative that has AMD can increase one's own risk of the disease.

Obesity is another significant, yet modifiable risk factor, and it has been shown that a 3% reduction in the waist-to-hip ratio decreases risk for AMD by 20%.

The most consistently reported risk factor for AMD is smoking, as it increases the risk for AMD up to seven-fold.

Supplements:

AREDS study found that increasing intake of micro nutrients was associated with a decreased rate of progression to central geographic atrophy over 12 years and progression to central geographic atrophy was also lowest. There is reduction in risk of progression to neovascular AMD. The evidence for utility of supplements is stronger for patients who have high risk changes as in first eye wet AMD, lots of large drusen, areas of atrophy. Smokers are at risk of Cancer of the lung with supplements with carotene, so to be avoided. For early AMD or even healthy elderly patients, a diet that is rich in fruits and vegetables, with sufficient fish, supports good retina health. Overall healthy lifestyles, including diet, appear to be beneficial for early AMD.

Information leaflets: Keep the clinics stocked with treatment leaflets about different anti VEGFs, supplements and information about support groups.

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