



BMH Medical Journal 2015;2(2):31-36 **Review Article**

## **The Use of Intravitreal Aflibercept in the Treatment of Wet Type of Age Related Macular Degeneration**

Rejith Rag, MBBS, FRCS, DO, FICO

Department of Ophthalmology, Royal Derby Hospital, Derby DE22 3NE

**Address for Correspondence:** Mr. Rejith Rag, MBBS FRCS DO FICO, Department of Ophthalmology, Royal Derby Hospital, Derby DE22 3NE. Email: [rejith.rag@nhs.net](mailto:rejith.rag@nhs.net)

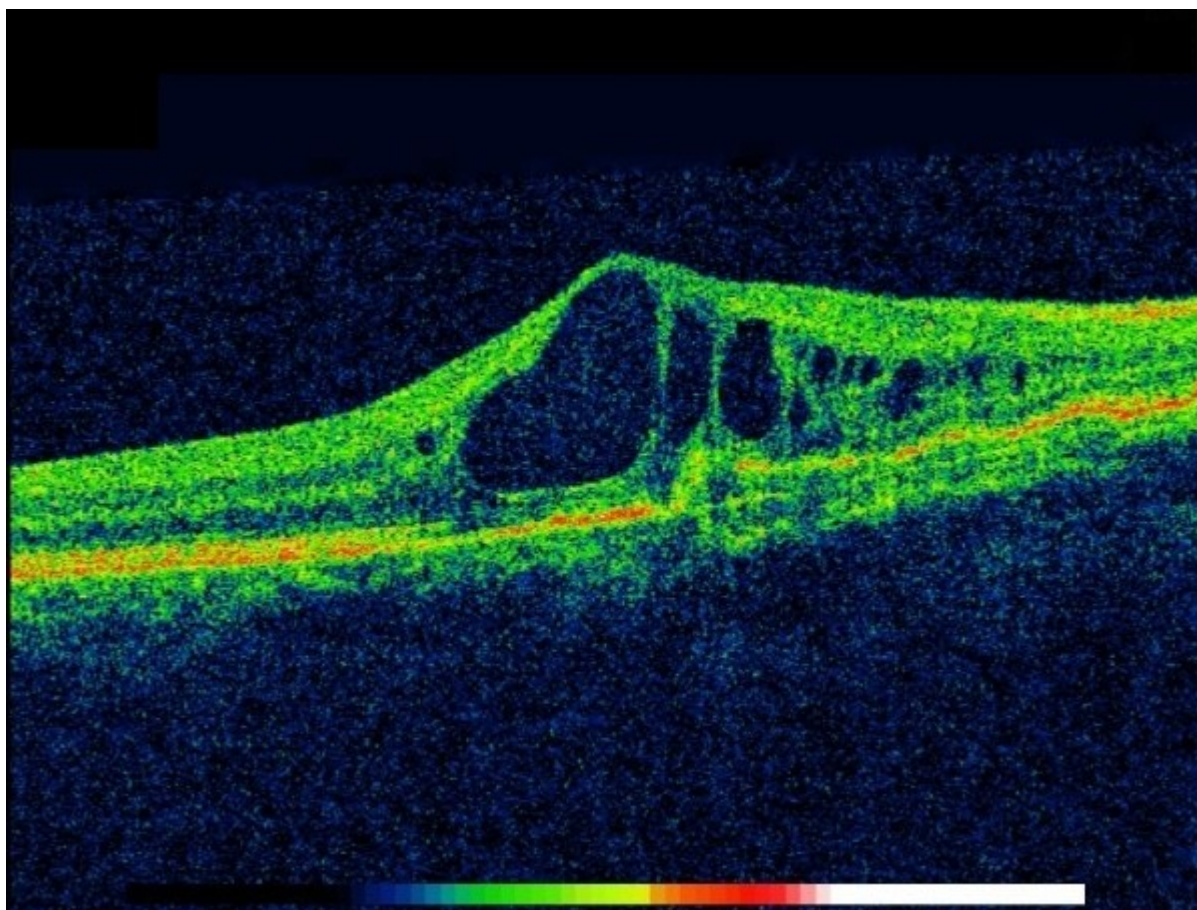
Aflibercept, an anti vascular endothelial growth factor (anti-VEGF) which was originally developed in the treatment of large bowel cancers, has been found to be effective in the treatment of wet type of age related macular degeneration (ARMD), a potentially sight threatening condition affecting the retina. Chemically this biological drug is C4318 H6788 N1164 O1304 S12 with a molecular weight of 96.9 KDa. This is manufactured as a lipid soluble recombinant fusion glycoprotein that binds with both forms of vascular endothelial growth factors, i.e. A and B as well as placental growth factors, thus blocking the angiogenic action and consequent neovascular membrane growth, the pathognomonic feature of wet ARMD.

### **Pathophysiology of wet ARMD and mechanism of action of aflibercept**

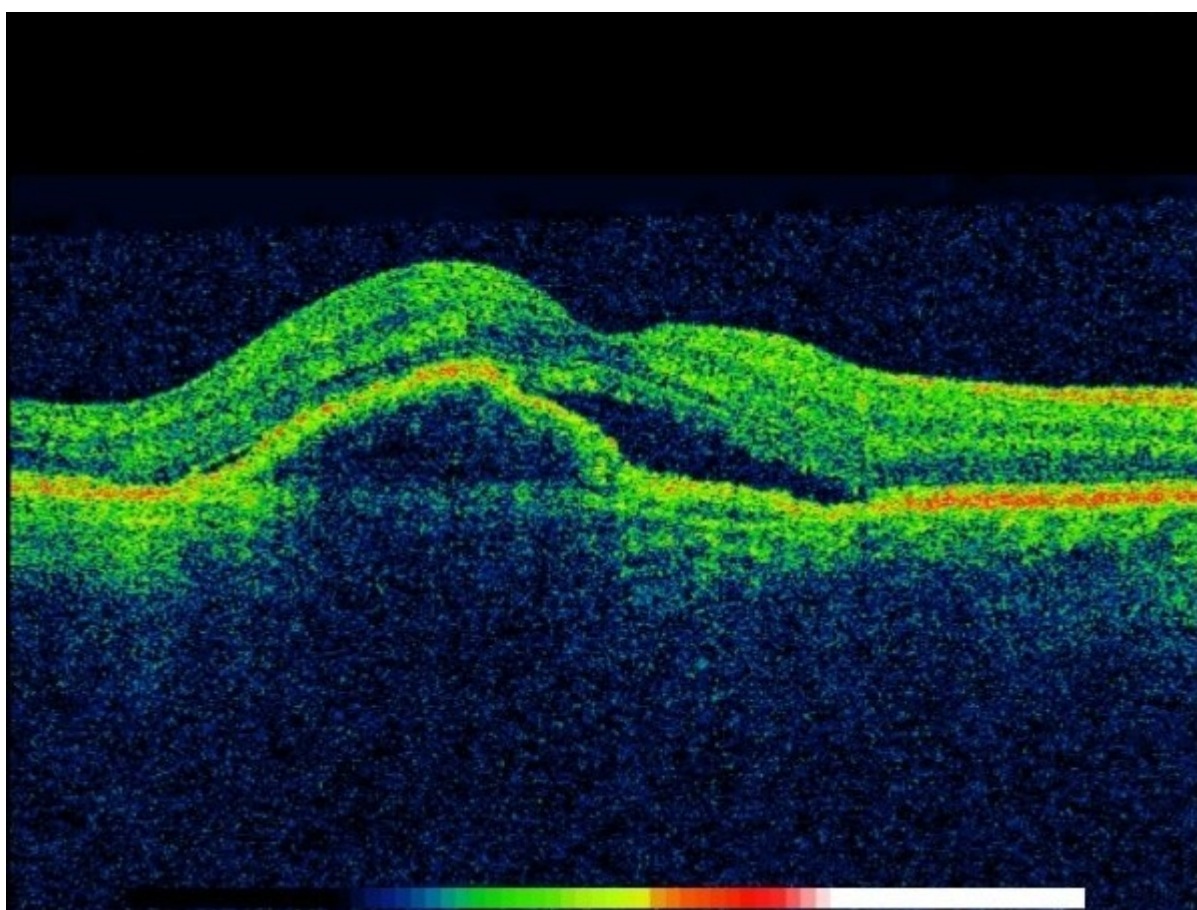
Basic pathology in wet ARMD is the formation of choroidal neovascular membrane (CNVM), beneath the macular area of the retina, at the level of choroid in response to growth factors like VEGF A, VEGF B and placental growth factors. In due course of time, CNVM would produce fluid within the retinal layers and beneath of them. These fluids are nothing but serous exudation from the active fibrous and new vessels embedded within the CNVM. As a result of the fluid collection, the macular area undergoes topographical changes and functional deterioration. On an Optical Coherence Tomography (OCT), these are manifested as bubbles within the retinal layers, called as intra retinal fluid (**Figure 1**) and a lenticular shaped opacity beneath the layer of rods and cones, termed as sub-retinal fluid (SRF) (**Figure 2**).

Of course, there are other reasons also there in culminating the loss of central vision like pigmentary epithelial detachment, popularly abbreviated as PED (**Figure 2**) and a rip in it. Sub macular bleeding, a serious condition affecting the vision, is not uncommon (**Figure 3**) as is macular scarring as its eventuality (**Figure 4**). Atrophy of the macula, although is more typical of dry type of ARMD, is commonly associated with scarring in wet form too.

Given intravitreally, the drug binds with the circulating VEGFs within the vitreous and stops their action of angiogenesis by forming an an inactive product. After the intravitreal injection of 2 mg aflibercept, the peak plasma concentration is 0.02mcg/l on the first day and almost disappears by 6th day.



**Figure 1:** Intra-retinal fluid collection at macula in the left eye



**Figure 2:** A PED and sub-retinal fluid (SRF) in left eye



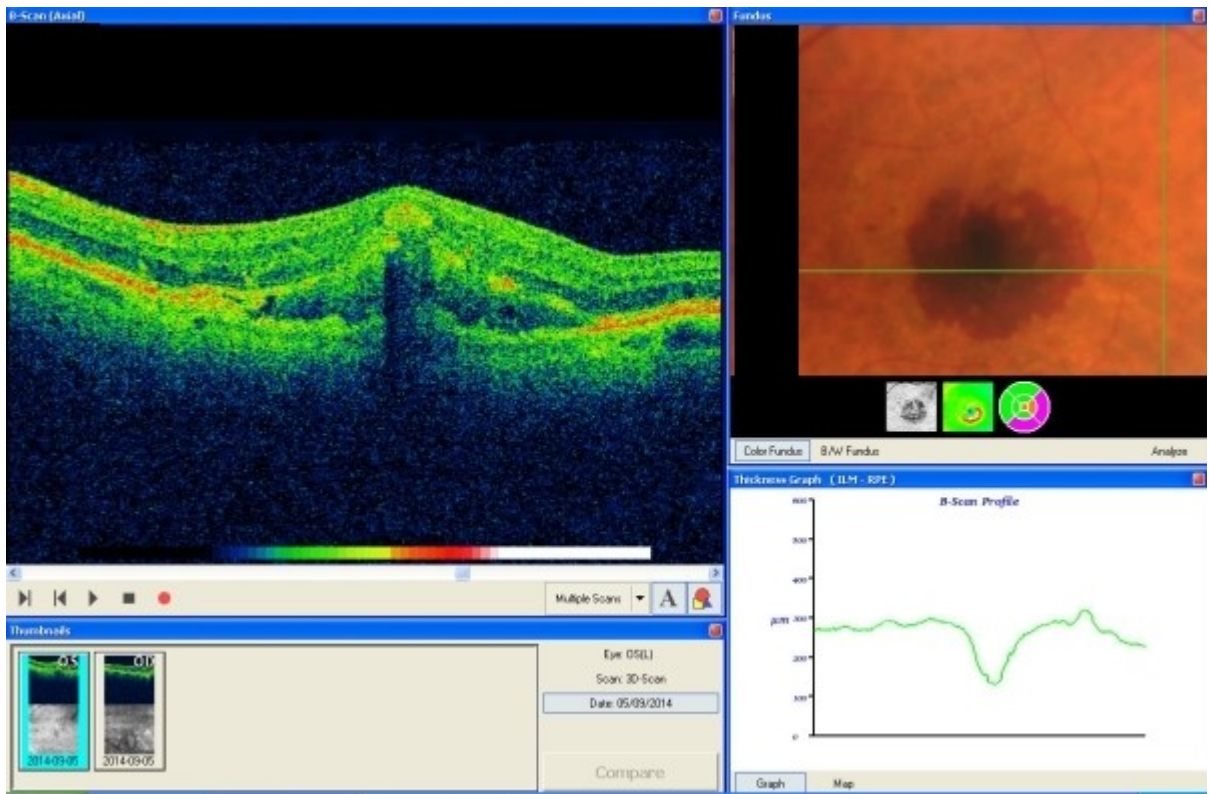


Figure 3: Sub-macular hemorrhage is seen as dark red lesion at centre of macula (top right photo)

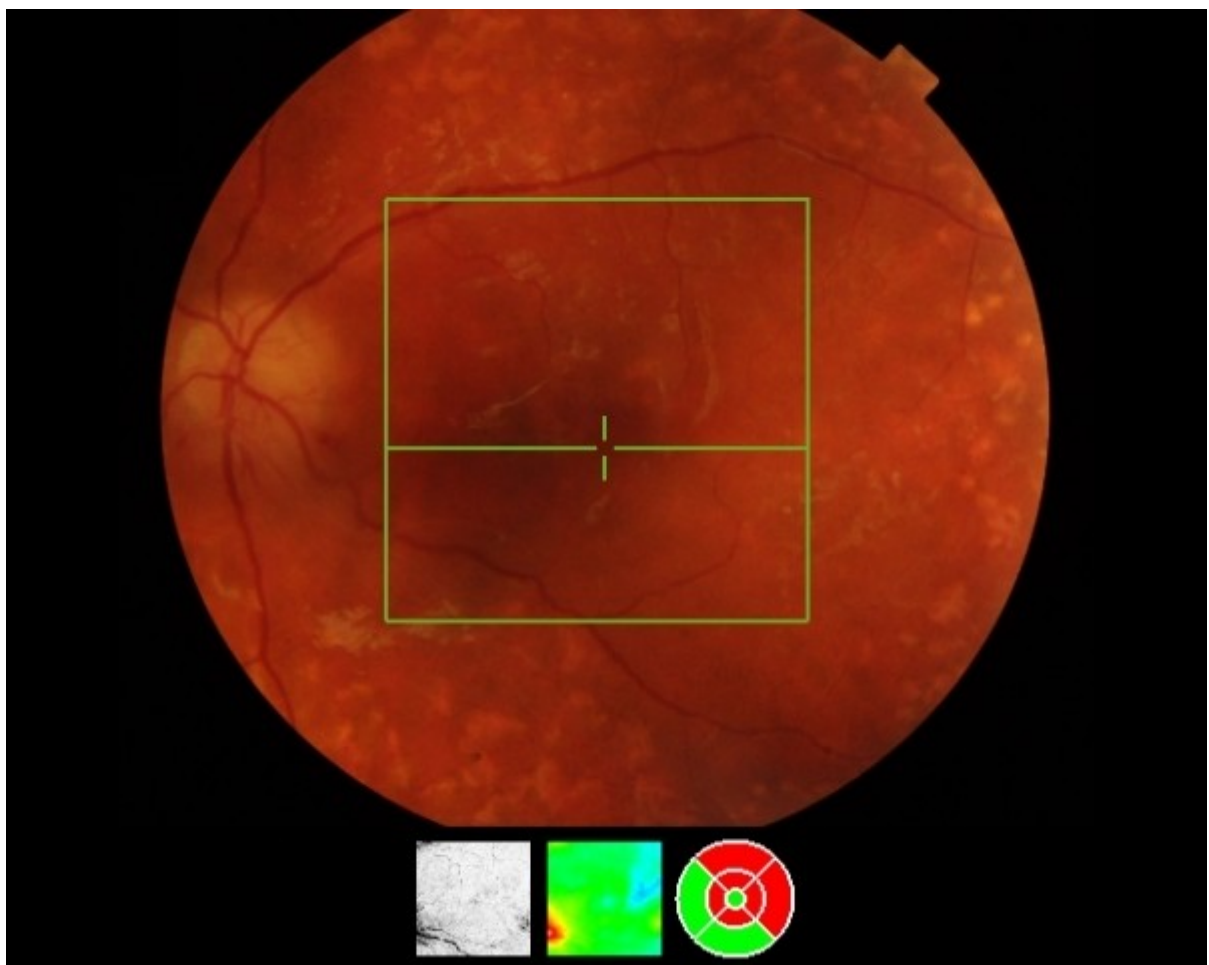


Figure 4: Sub macular scarring

## Guidelines for using the drug

### *NICE recommendation as the possible treatment in wet ARMD [1]*

The patient should follow the following criteria:

1. The best corrected visual acuity should be in between 6/96 and 6/12.
2. The macular area affected should be less than 12 disc diameter (one disc diameter is approximately 1.5 mm).
3. No signs of permanent damage.
4. No signs of worsening of the condition.
5. Treatment should be stopped if the vision gets worse and there are changes inside the eye which shows that the treatment is not working.

### *Recommended dosage [1,2,5]*

An injection of two mg of aflibercept intravitreally every four weeks interval for three consecutive months which is followed by one injection in the same dose on every second month, to be continued for one whole year. After one year we need to consider the visual and anatomical outcome of the eye. If the vision seems to be stabilized or there is a profound deterioration (in either case), the further treatment must be withheld.

### *Decision making on each visit [1,2]*

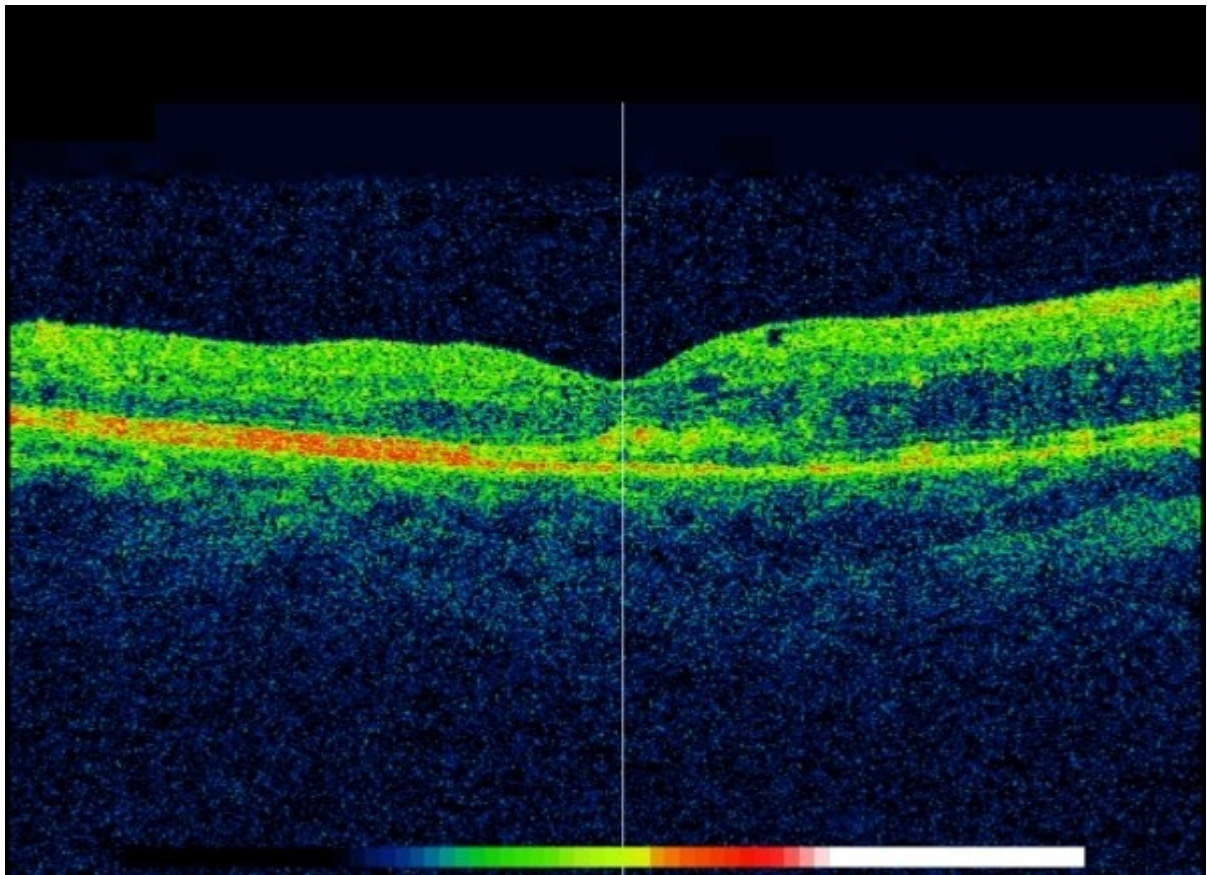
During the first three months, the patient shall be given injection regardless of visual or anatomical progression or regression. But after this, it is rather tricky as it involves not only the medical and ethical considerations but practical ones as well especially that of fiscal because this medicine is very expensive.

Scientifically, the visual acuity that is checked on EDTRS chart and the OCT are the two important parameters. That said, positivity on these would not be a sufficient reason for proceeding for injection unless there is any valid practical reason. For example, a presence of same level of fluid which looks as if a recalcitrant one but vision is stable, we do not inject even if fluid is present. On the other hand if vision deteriorates in that case, we need to give treatment. Generally, if the retina is 'dry' (**Figure 5**), we do not proceed, unless vision has gone down beyond five letters. To put in other words, the aim of treatment is to make the macula as dry as possible and to stabilize within five letters of change at least on three consecutive months after first three loading doses.

It is pertinent that other causes of visual deterioration also should be looked for, for example a recently developed cataract or corneal opacity. Decrease of vision of this sort should not be accounted as of ARMD, and thus medication should not be done. Of note, patient should always be examined for vision only with full refractive correction, lest bias be the result.

If the patient has already been listed for bilateral injection, even if, on later follow up, only one eye had the indication/s for treatment, it would be advisable to treat bilaterally. This is protocol is being followed up by some hospitals but some do not.

Treatment should not be instituted in the presence any local inflammation (eg. keratitis or iritis) or any focus of infection (eg. acute dacryocystitis or hordeolum). Likewise, the general condition also must be assessed. Aflibercept is contraindicated within three months of an attack of myocardial infarction and a cerebro-vascular accident. Brain tumor is an absolute contraindication. For those receiving warfarin, it is advisable to have INR between 2.5 and 3.5. Aspirin is not a contraindication like clopidogrel type of medicines. Safety in children is ambiguous but is so in pregnancy.



**Figure 5:** A dry retina, without any fluid, after five injections

### Complications

Complications are usually confined within the eye itself. Conjunctival hemorrhage and pain are the commonest ones however more sinister situations like endophthalmitis and retinal detachment are not unusual. Occasionally, due to sudden increase of intra-ocular pressure central retina artery can be compromised but in can be easily reverted by doing an anterior chamber paracentesis to drain a 0.5 ml of aqueous humour. Very few systemic complications are reported so far like cardio-vascular events and gastro-intestinal bleeds.

### Basis of evidence

Prior to being marketed, this drug's safety and efficacy were put into test by two studies - VIEW 1 and VIEW 2 - conducted simultaneously in the US and in the UK respectively [5]. In each study, patients were grouped into three. They were, those receiving 2 mg aflibercept every 4th week after the loading dose, those receiving 2mg aflibercept every 8th week after the loading dose and the third group has received standard ranibizumab (another anti VEGF already in practice). The primary efficacy point was defined as losing visual acuity fewer than 15 letters at week 52 compared to the base line. At 52nd week, it became evident that all the three groups performed in a more or less similar manner. So, cost effectively, the eight week regimen has been selected and licensed to practice.

### Conclusion

Even though expensive, aflibercept has already been emerged as a treatment modality for wet form of macular degeneration. Nevertheless, its efficacy and safety are largely depend upon the flexible and intelligent clinical judgment of the specialist involved.

## References

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