Pathogenesis and Management of Age-Related Macular Degeneration

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ABSTRACT
Age related macular degeneration (AMD) was responsible for 8.7% of all blindness worldwide in 2007, and this figure is expected to double by 2020 as a result of population ageing. Macular degeneration is defined by the NHS as a painless disease that leads to loss of central vision and is an umbrella term that denotes many eye disorders which lead to loss of detailed vision, the most common being AMD. AMD is the most common cause of severe vision loss in industrialised countries, with more adult Americans being affected by AMD than cataracts and glaucoma combined. This article will outline the pathogenesis and discuss the clinical management of this common and serious ophthalmology condition.

Key Words: macular degeneration; ophthalmology; education article

Introduction
Age related macular degeneration (AMD) was responsible for 8.7% of all cases of blindness worldwide in 2007, and this figure is expected to double by 2020 as a result of population ageing.¹ Macular degeneration is defined by the NHS as a painless disease that leads to loss of central vision and is an umbrella term that denotes many ocular disorders which lead to loss of detailed vision, the most common being AMD.² Indeed, AMD is the most common cause of severe vision loss in industrialised countries with more adult Americans being affected by AMD than cataracts and glaucoma combined.³ The risk of developing AMD is in excess of 35% by the age of 75, and is increased by a family history of the disease or environmental factors such as cigarette smoking, nutritional deficiency, excessive sunlight exposure and hypertension.⁴ It could also present as the late-onset of genetic disease, but age is the most significant of all risk factors.⁵

This article is a study of current research into the relevant anatomy and predisposing factors for the onset of AMD and the current management algorithm for AMD specific to Tayside. Possible alternative treatment methods that could improve prognosis and retard the pathogenesis of this disease will also be discussed. In addition, the article will discuss two hypothetical patients highlighting the differences between the two forms of AMD.

Anatomy of the Eye
A more detailed understanding of the anatomy of the eye is required to fully appreciate the pathogenesis of AMD (Fig 1). The eye consists of 3 main layers. The outer coat is known as the Fibrous Layer and comprises of the tough, fibrous sclera and the transparent, avascular cornea for focusing light.⁶⁷
The layer internal to this is the Vascular Layer and consists of 3 structures; the choroid layer which contains dark pigment to prevent internal reflection of light, the ciliary muscle which contracts under parasympathetic control making the lens more convex and focusing light onto the retina and finally the iris which is the coloured part of the eye and contains sphincter papillae and dilator papillae smooth muscles which alter the diameter of the pupil to regulate the amount of light entering the eye to prevent damage to the sensitive cells of the retina.

The innermost layer is the Inner Layer, otherwise known as the retina (Fig 2). The retina is a thin sheet of receptor cells that is located between the choroid layer and vitreous body. It lines the posterior three-quarters of the eyeball and is the beginning of the visual pathway. The retina is made up of two layers known as the optic-part and the non-visual retina. The optic part is further subdivided into a pigmented layer and a neural layer.

The pigmented layer is found between the choroid and neural layer and consists of a sheet of melanin-containing cuboidal epithelial cells called the Retinal Pigment Epithelium (RPE). Due to the melanin component these cells aid the action of the choroid layer in ensuring visual acuity by preventing light scattering. The melanin granules also act to absorb free radicals and protect the light sensitive structures of the retina. Thus the decrease in melanin associated with aging impairs protection against short wave radiation and the toxic effects of free radicals. The RPE is adherent to the neural layer but, due to the varying embryological origins of the two layers, they are not firmly attached via junction complexes and are thus easily separated in cases of trauma or disease. The tips of rod outer segments are deeply inserted into invaginations in the RPE and numerous microvilli on the cell surfaces project between the outer segments of the rods or cones.

The RPE also plays a major role in removal of waste products from rod and cone degradation. Once shed, the aged outer rod and cone segment discs are absorbed into the cell cytoplasm which carries out lysosomal destruction to form lipofuscin granules. The RPE then acts as a selectively permeable barrier by releasing the resulting metabolic waste at the basal side to be taken up by the blood vessels in the choroid into the blood stream. In contrast to melanin, lipofuscin granule levels increase and accumulate in the lipofuscin compartments of RPE cells with age. This lipofuscinogenesis is thought to be due to antioxidant deficiency or pro-oxidant conditions, as it is caused by the decreasing melanin levels leading to free radical build up. Many blood components are harmful to the retina and are kept away from it by this filter function of the RPE. The choroidal vascular supply to the RPE cells also means they help to nourish and support the rods and cones by transferring nutrients from the blood. Other roles of the RPE include regeneration of bleached visual pigment, production of immunosuppressive factors and antioxidant action. Failure of any of the numerous functions of the RPE would result in diminished retinal function and eventually blindness.
The Neural layer is a multi-layered outgrowth of the brain that processes visual data to convert the optical image into neural activity by sending impulses into axons that form the optic nerve. There are 3 distinct layers of retinal neurones; the photoreceptor cell layer, the bipolar cell layer and the ganglion cell layer. Light passes through the ganglion and bipolar cell layers before contacting the photoreceptor layer. The second layer of the retina, or the non-visual retina, is a continuation of the pigmented layer and is a layer of supporting cells extending over the ciliary body and posterior surface of the iris.

The macula lutea is a small oval area of the retina rich in photoreceptor cells, or Cones, which are specialised for acute vision, specifically colour perception and for daylight vision. It is temporal and inferior to the optic disc (the ‘blind spot’ at which the optic nerve exits the eye), and is seen fundoscopically as an avascular area with a yellow tinge [Fig 3]. The central area of the macula is a small depression called the fovea centralis which contains only cones and is not covered by the layers of pigmented cells which scatter light such that it is the point of highest visual acuity or resolution. As the macular region is rich in cones it grants central vision, whilst rods are much more plentiful in the surrounding retina so the peripheral retina accommodates peripheral and lower light intensities.

**Pathogenesis of Macular Degeneration**

Age-related macular degeneration is characterised by the build-up of cellular debris between the retina and choroid. This process is also associated with both hyperpigmentation and hypopigmentation of the retina due to morphological changes. These early conditions alone are not associated with loss of central vision, but visual loss may occur if the disorder is allowed to progress causing retinal atrophy and eventually wet macular degeneration. There are two forms of this illness, wet and dry macular
degeneration. Early macular degeneration can progress pathologically to either of these forms that have completely different clinical outcomes and management methods.

**Dry AMD**

Dry or atrophic macular degeneration accounts for 85% of AMD cases and is equally common in males and females. Dry macular degeneration is characterised by the accumulation of deposits of waste products or drusen beneath the RPE within Bruch's Membrane. Bruch’s membrane is an acellular membrane beneath the RPE formed of 5 layers that acts as the barrier between the retina and the choroid. Nutrients and oxygen diffuse from the underlying choriocapillaris through Bruch’s membrane to the RPE and retina, whilst waste products of metabolism are voided in the opposite direction into the choroid. Bruch’s membrane undergoes many morphological changes with increasing age, including thickening, calcification, degeneration of collagen and elastin fibres and splitting. Transport between the retinal RPE and choroid can also be impaired by incomplete clearance of waste with age leading to the accumulation of lipid-rich metabolic products. This drusen can be seen as pale yellow dots upon fundoscopic examination [Fig 4].

![Figure 4: Fundoscopic image to show drusen accumulation deep to the macular region](image)

There are two types of drusen - soft drusen and hard drusen. As the disease progresses, small discrete drusen coalesce into larger deposits to form soft drusen. Soft drusen is considered to be an early indicator of macular degeneration and is the form most associated with loss of vision and separation between the retinal layers. This soft form presents as large pale yellow deposits with ill-defined borders [Fig 5]. If an individual has a strong family history of macular degeneration, regular fundoscopy should be carried out to monitor these soft drusen deposits.

![Figure 5 : Optical Coherence Tomography (OCT) and fundoscopy showing a large area of soft drusen deep to the RPE](image)

Hard drusen appears as a well-defined, small, round deposits in the RPE. They are very common with age and can develop into the soft kind. Hard drusen is not indicative of exudative changes in the RPE and so the patient will generally have minimal change in visual acuity. Optical Coherence Tomography (OCT) can show other characteristic morphological changes associated with AMD, such as geographical atrophy. Geographical atrophy is the end stage of dry macular degeneration where pigmentation is disrupted across large areas of the macula and areas of the RPE atrophy and breakdown, leading to cell death. As a
result, irregular areas of thinner retina can be observed by OCT [Fig 6] and the patient will begin to notice attendant loss of central vision.\textsuperscript{16}

\textbf{Wet AMD}

Wet or neovascular AMD is an alternative pathway of early AMD progression where separation of the RPE and choroid layer alongside an increase in vascular endothelial growth factor (VEGF) stimulates angiogenesis of choroidal blood vessels into the retina beneath the macula.\textsuperscript{3} Angiogenesis begins with vasodilatation and increases in vascular permeability, followed by activation and proliferation of vascular endothelial cells. Accompanying degradation of the surrounding extracellular matrix facilitates endothelial cell migration, which assemble to form cords and develop lumens. Further differentiation and remodelling to accommodate local requirements eventually forms a complex vasculature.\textsuperscript{17} Choroidal neovascularisation breaches the normal anatomical barrier of Bruch’s membrane and invades the subpigment epithelial and or subretinal spaces.\textsuperscript{18} These newly formed blood vessels are fenestrated and frequently bleed causing the macula to bulge or form a mound, often surrounded by small haemorrhages and tissue scarring.\textsuperscript{5} This ultimately leads to the separation of Bruch’s membrane, the RPE and the retina from each other and so the accumulation of intraretinal fluid and generalised thickening of the retina or the formation of cystic spaces. These pathological manifestations cause the photoreceptors to become misaligned and eventually degenerative changes occur with cell loss and eventual fibrosis.\textsuperscript{19} These processes will present clinically as distortion of central vision and the appearance of dark spots. Neovascularisation can also arise \textit{de novo} in the macular retina and is referred to as retinal angiomatous proliferation.\textsuperscript{20} The progression of dry AMD may take place over years, whilst wet AMD can progress in mere months or even weeks.

\textbf{Causes of AMD}

A number of factors have been discovered to predispose to the development and progression of AMD (Fig 7). They include age, smoking, obesity, positive family history, hypertension, cardiac disease, heavy alcohol consumption, Alzheimer’s disease, hearing loss and low circulating levels of endogenous antioxidants.\textsuperscript{21} Smoking is the most consistent risk factor for the development of late AMD with current smokers more than doubling their risk of developing AMD. Individuals with a genetic susceptibility are also more likely to develop the disease if they smoke. These factors in themselves do not directly cause macular degeneration, but rather the chemical and pathological reactions they induce.\textsuperscript{22} The progression and severity of macular degeneration, as with all age-related diseases, are exacerbated by factors such as oxidative stress, inflammation, hyperglycaemia and poor vascular health.\textsuperscript{5} It is thought that the retina may be particularly vulnerable to oxidative stress because of a combination of exposure to visible light and high oxygen concentrations.\textsuperscript{3} Normal structural changes in the retina that occur with aging, such as the thickening of Bruch’s membrane, could elevate oxidative stress by producing poorer perfusion of RPE cells by the choroidal circulation. Oxidative damage could also occur through the accumulation of reactive waste products such as A2E, a component of lipofuscin that is formed during the catabolism of photoreceptor outer segments by RPE cells.\textsuperscript{22} As a result, particular interest
has focused on the possibility of prophylactic treatment of individuals who have been identified as high risk for developing AMD with antioxidant micronutrients.

Macular pigment is composed of two carotenoids, lutein and zeaxanthin, which are solely of dietary origin and are found in a wide variety of green leafy plants such as spinach and kale, and in some animal products such as egg yolks. It is thought that they protect the retina from the harmful effects of free radicals released by visible light. Studies such as the Beaver Dam Eye Study, the Blue Mountains Eye Study, and the Carotenoids and Age-related Eye Disease Study (CAREDS), show that diets higher in carotenoids, zinc, vitamin C and vitamin E are associated with a lower risk of AMD. These observational studies form the basis for further research into the relationship between dietary intake or serum levels of antioxidant nutrients and risk of AMD. Indeed, clinical trials carried out in the USA have established a link to the carotenoid lutein further implicating a role of nutritional supplements and vitamins in delaying the progression of AMD and vision loss. Unfortunately, antioxidant trials have many limitations as researchers are unable to manage the composition of control groups, so they often suggest correlations where there are none. Furthermore, the trials do not last long enough as it may not be possible to show the benefits of antioxidant treatment over several years if the therapy is trying to reverse the effects of decades of oxidative stress. As a result, there have been no major changes in AMD treatment algorithms towards the use of carotenoid supplements in clinical practice.

It has also been suggested the complement system may have a key role in AMD pathogenesis, as several genes which code for proteins involved in the complement cascade have been identified to significantly increase the risk of AMD including factor H (CFH) and complement component 3 (C3). The Wilkinson study in 2005 showed for the first time that the mutation of CFH is strongly associated with AMD, and variation in C3 was shown to increase the risk of developing AMD up to 2.6 fold.

Figure 7: Summary of factors that predispose to and accelerate AMD progression

This article will discuss two hypothetical patients, Ms Watson and Mr Jones in order to outline the key differences between the diagnosis, clinical management and long-term outcomes of the dry and wet AMD.
Patient 1: Ms Watson

59 year-old female who works as an accountant in West Scotland. She has a BMI of 29 and has a very limited diet of high fat convenience foods, saying she has little time to shop for fresh vegetables and meat as her job is very time consuming and stressful. She has no medical history of diabetes, epilepsy, but was diagnosed with hypertension aged 39 and angina at 48 years old. Her father died of myocardial infarction at 74 years old, and her mother was diagnosed with AMD aged 62. Her current medications are Bisoprolol (10mg orally once daily), Lisinopril (20mg orally once daily) and GTN PRN. She does not drink any alcohol and has never smoked cigarettes.

Patient 2: Mr Jones

77 year-old male from South England. He previously worked as a building merchant but retired 10 years ago by choice, and currently lives with his wife in their own home. He has no medical family history, and no previous complaints himself other than he was prescribed glasses 6 years ago that he only uses for reading. He does not suffer from diabetes, epilepsy or cardiovascular problems, but was diagnosed with hypertension 15 years ago. His current medications consist of Bendroflumethiazide (2.5mg orally once daily) and Simvastatin (40mg orally once daily). He does not consume any alcohol and he does not smoke, having given up at 45 years of age when he had smoked 30 cigarettes daily.

Diagnosis of AMD

The eye has very few mechanisms to convey a diseased state and so a careful and detailed history gives the key information needed to make a working diagnosis. Patients with dry macular degeneration where atrophy of the retina is bilateral and involves the fovea of both eyes generally present with deterioration of central vision, commonly noticing increasing difficulty with reading initially with the smallest sizes of print and then later with larger print or words. Diagnosis of dry macular degeneration is normally confirmed by stereo biomicroscopy using a high definition fundus lens. This will reveal characteristic areas of pallor with sharply defined and scalloped edges, large choroidal vessels within the area and usually areas of drusen and focal hyperpigmentation adjacent to the patch. OCT can also be used for diagnosis to identify areas of geographical atrophy that cannot be seen clinically by biomicroscopy. Monitoring the progression of dry AMD is necessary as the early identification of progression to wet AMD can significantly improve prognosis and reduce vision loss. The system used was created by AREDS (Age-Related Eye Disease Study) and consists of 4 stages (Table 1).

Table 1: AREDS classification to monitor progression of wet AMD

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Image</th>
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<tr>
<td>1</td>
<td>No AMD: none or a few small drusen</td>
<td>Patients are essentially free of age-related macular abnormalities, with a total drusen area less than five small drusen and minimal deterioration of visual acuity in either eye</td>
</tr>
<tr>
<td>2</td>
<td>Early AMD: Patient will present with any of multiple small drusen, few intermediate drusen (63 to 124 μm in diameter), or RPE abnormalities</td>
<td>Cases have these mild or borderline, age-related macular features, still with little change in visual acuity</td>
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### Intermediate AMD: Individual will have extensive intermediate drusen, and at least one large drusen (125 μm) or geographic atrophy, not affecting the fovea

The patient must not have advanced AMD in both eyes, or at least have one eye with visual acuity of 20/32 or better.

### Advanced AMD: Geographical atrophy affecting the fovea and/or any of the features of neovascular AMD

These patients have visual acuity of 20/32 or better and no advanced AMD in one eye, whilst the other has lesions of advanced AMD, or visual acuity less than 20/32 with AMD abnormalities sufficient to explain reduced visual acuity.

This classification system allows easy monitoring of disease progression so people at high risk of developing late AMD are identified and made aware of certain lifestyle changes they could make to reduce their risk.

Wet macular degeneration presents differently with the appearance of central visual blurring and distortion. As AMD causes the impairment of central vision, patients generally have complaints such as difficulty with close-work activities, straight lines appearing wavy or distorted and dark patches in the central field of vision. **An Amsler grid test should be carried out to quantify the degree of visual distortion and locate early visual problems related to macular disease.** It simply involves holding the grid 30cm from the patients eye and asking if they can see all four corners of the grid and if any of the lines appear blurry, wavy, bent or are missing, whilst looking at the central dot.

GPs, nurses and optometrists need to be aware of the urgent nature of referral for patients with recent onset of distortion and visual loss, as these patients may still have treatable disease and so must be referred to an ophthalmologist. **For confirmation of wet macular degeneration diagnosis, examination of the macula will usually show an exudative macular lesion along with other features of early AMD, for example drusen and pigmentary irregularities.** These features are often only seen soon after development of wet AMD, and begin to disappear as the disease progresses. **As a result, both eyes must always be examined, even if the patient has not experienced concomitant symptoms in both eyes, as the other eye usually exhibits some of these early clinical signs and can help confirm that the neovascular lesion is due to AMD.** It is essential to monitor the progression of wet macular degeneration using OCT imaging as the morphological changes seen will determine whether treatment is efficacious, or if the dosage of medication should be increased or decreased to improve prognosis. The areas of fluid, appearing as a dark black area within the retinal layers [Fig 9], can only be estimated in size and need comparative values to quantify the severity. Thus, these areas of leaking and swelling are observed over time to determine if the condition is improving, worsening or is stable.

![Figure 9: OCT scan of Wet AMD showing leakage and swelling](image-url)
An accurate Snellen visual acuity must also be recorded in all patients with an eye problem as this categorises the level of visual acuity and allows monitoring of deterioration or improvements in future.  

<table>
<thead>
<tr>
<th>Patient 1: Ms Watson</th>
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<tr>
<td>Diagnosed by her optician with dry AMD following a routine appointment. She reported that she had noticed increasing problems whilst doing numerical work and had to concentrate much harder to ensure she did not get the numbers mixed up.</td>
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<tr>
<th>Patient 2: Mr Jones</th>
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<tr>
<td>Presented to his GP after noticing that the edges of door frames and walls appeared wavy. He noticed himself that his right eye was much worse and that any straight objects appeared out of focus and distorted. Mr Jones GP referred him to the ophthalmologist for more specialised testing. Over the next two months required for these tests to be undertaken, Mr Jones noticed a mistiness forming ‘over’ his right eye that became progressively darker until he could only see what he described as a ‘black blob’ in his central vision.</td>
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### Intervention or Chemical and Surgical Management

#### Dry AMD

The management of dry AMD aims to minimise visual loss and disability in order to maintain independence, rather than actually treating the pathology of the disease. Dry AMD itself cannot be reversed, so management is to prevent progression of the disease to late macular degeneration. Current strategies include careful monitoring by examining fundus photographs and using the AREDS model to observe large drusen formation and the development of hypopigmentation followed by geographical atrophy. This ensures that the progression of the disease is quantified such that suitable prophylactic treatment can be administered to minimise disease development. Laser treatment is currently being studied as a prophylactic treatment option. Focal laser treatment has been shown in multiple studies to be able to disintegrate drusen, but in most cases has also increased the risk of choroidal neovascularisation. As a result, research is ongoing into the alternative use of large spot size lower power laser treatment. As the full benefits of antioxidants on the pathology of AMD has not yet been proven, some ophthalmologists may advise patients to take vitamin, zinc or lutein supplements, but again there is no definitive proof at present that this is an efficacious prophylactic treatment.

#### Wet AMD

Angiogenesis has a role in many vascular disorders, including wet AMD. Since the rapid angiogenesis into the choroid layer causes the leakage of immature vessels between the RPE and choroid in wet AMD patients, the management of this underlying pathological...
angiogenic process is vital. The main regulators of angiogenesis are vascular endothelial growth factor (VEGF), fibroblast growth factor 2, pigment epithelium-derived growth factor, angiopoietins and extracellular matrix molecules. Identification of these has facilitated the development of novel therapeutic agents, most importantly Bevacizumab that blocks VEGF-A. Although these multiple growth factors have been attributed to angiogenic processes, VEGF appears critical for a number of reasons: it is triggered by hypoxia, is involved in multiple aspects of the angiogenic process, and causes vascular dilatation and promotes vasopermeability which facilitate the growth of new vessels. Its discovery triggered a new therapeutic era, with the utilisation of VEGF blockade for the management of chorioretinal diseases with vascular hyperpermeability or neovascularisation. All of the anti-VEGF medications work in a similar fashion by binding to VEGF and inhibiting its biologic activity, so reducing the formation of abnormal blood vessels. They also reduce the amount of leakage and therefore reduce swelling in the macula. These actions lead to preservation of vision in patients with wet macular degeneration. Currently two drugs, pegaptanib sodium and ranibizumab, have successfully qualified all the necessary phases of drug development to obtain licensing approval by regulatory bodies and form the mainstay of treatment for neovascular AMD. Lucentis, or Ranibizumab, is an antibody fragment able to target all VEGF-A isoforms when administered monthly via intravitreal (IVT) injection. Ranibizumab was licensed for use in the USA following the MARINA and ANCHOR studies. In the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) trial, patients were randomised to receive monthly injections of IVT Ranibizumab or monthly placebo injections. 12 months into the study, visual acuity was found to have improved by 15 or more letters in 33.8% of the 0.5 mg group, with only 5% similar improvement in the placebo group. In addition, the 94.6% of patients receiving IVT Ranibizumab in the trial reported no visual loss and only 62.2% of the control group managed to do so.

In the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularisation in AMD) trial, individuals with leaking choroidal neovascularisation received either 24 monthly Ranibizumab IVT injections of Ranibizumab or photodynamic therapy with verteporfin. Visual acuity improved by 15 letters or more in only 5.6% of individuals treated with verteporfin. As in the MARINA trial, those receiving Ranibizumab also demonstrated a mean increase in visual acuity whilst the control group experienced a mean decrease. Similarly, 96.4% reported no visual loss compared with 64.3% of individuals in the verteporfin group.

Current NICE guidelines recommend Ranibizumab as treatment for wet AMD if the patient has all of the following criteria:

1. The best possible visual acuity after correction with glasses or contact lenses is between 6/12 and 6/96.
2. There is no permanent damage to the fovea
3. The area affected by AMD is no larger than 12 times the size of the optic disc

The second approved drug, Pegaptanib sodium, is an RNA aptamer that only targets the VEGF isoform responsible for pathological ocular neovascularisation, VEGF 165. Despite the apparent efficacy of this drug, it does not provide the extent of VEGF blockade necessary for optimal clinical outcomes, and as a result recent NICE guidelines do not recommend Pegaptanib as a management option for patients presenting with wet AMD.

Although Ranibizumab and pegaptanib are the only two drugs with licensing approval, Bevacizumab, a recombinant humanised monoclonal antibody against all VEGF-A isoforms, has shown considerable promise as an off label treatment method. It was originally
developed to treat metastatic carcinoma of the colon and rectum and is derived from the same monoclonal antibody as Ranibizumab, therefore it recognises the same epitope on VEGF as Ranibizumab but binds with a different affinity. Trials have shown that Bevacizumab can penetrate through all layers of the retina, and it has been used off licence as AMD treatment to positive effect. A case series by Michaels et al on the systemic administration of Bevacizumab in the management of choroidal neovascularisation demonstrated this treatment’s benefits, with recordings showing reduced retinal thickening and improved visual acuity. These findings encouraged further studies, such as the Cleveland Clinic trials, reporting similar outcomes when administered by IVT injection.

In 2011, the results of the CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) study provided further evidence for the efficacy of Bevacizumab in neovascular AMD. In this trial, 31.3% of patients treated with Bevacizumab monthly gained 15 or more letters from baseline visual acuity and 94% of patients lost fewer than 15 letters of visual acuity from baseline. Furthermore, mean visual acuity increased by 8 letters over the study period in those receiving Bevacizumab monthly. This study also allowed comparison of outcomes with Bevacizumab or Ranibizumab management; 34.2% of patients treated with Ranibizumab monthly gained 15 or more letters from baseline visual acuity, with 31.3% of patients treated with monthly Bevacizumab IVT injections. 94.4% of patients receiving Ranibizumab monthly lost fewer than 15 letters of visual acuity from baseline, whilst 94% of patients reported similar results with monthly Bevacizumab injections. This trial concluded that there was little clinical evidence to determine if Bevacizumab or Ranibizumab would be the most efficacious treatment for wet AMD as the difference between percentage of visual acuity regained was inconsequential. Considering the outcome of these trials alongside the fact that the drug cost to the NHS will be considerably less, Bevacizumab would appear as the logical primary treatment for wet AMD. Despite this, the drug companies who produce Bevacizumab have yet to apply to the European Medicines Evaluation Agency to license Bevacizumab as a treatment option for wet AMD. Instead, continued use of the costly but licensed Ranibizumab injections is advised. The decision to register Ranibizumab as a primary treatment for wet AMD can only be made by the drug production company and to do so would greatly reduce their financial income. Many practitioners chose to administer Bevacizumab regardless, but its continued unlicensed use raises both ethical and legal questions.

Over the past decade, there have been extensive developments in AMD treatments necessitating new guidelines to ensure the best therapeutic options are available to all patients in the NHS, whilst ensuring efficient use of NHS resources. The Tayside treatment algorithm does this by managing neovascular AMD with IVT Ranibizumab injections. In the first year following diagnosis with wet AMD the patient is administered 3 loading doses of IVT Ranibizumab 1 month apart with follow up and/or booster injections every 6 weeks for the rest of that year. In the second year following diagnosis the patient should only receive the IVT injections if necessary so treatment efficacy is monitored with 2 monthly reviews [Appendix 1]. The frequency of injections and reviews is progressively decreased as the patient responds to the treatment. If the patient has no signs of disease or does no longer require the Ranibizumab injections after these 2 years of treatment, they are discharged.

**Patient 2: Mr Jones**

Mr Jones was diagnosed with wet AMD and immediately treated with IVT Ranibizumab injections. Gradually after 2-4 injections he noticed definite improvements as the blackness began to disappear and the ‘mist began to clear’ and after 5 months of injections he reported that only a light mist remained, slightly obscuring his central vision. He still has problems focusing and identifying fine detail, but he has regained the ability to read and drive. His main concern was that the wet AMD would also affect his left eye but he has had no symptoms in that eye.
Conclusion

AMD is the leading cause of vision loss in industrialised countries, and so clearly is an extensive health problem. Whilst research is on-going as to new treatment options and prophylactic management for this disease, further trials are required to provide definitive treatment options for either wet or dry macular degeneration. At present causative factors have been researched considerably more and guidelines have been defined, so patients should be advised on the modifiable predisposing factors discussed earlier to aim to prevent the disease, rather than treating it retrospectively. Changing lifestyle factors such as these can improve the patient’s prognosis and delay disease progression significantly.

Drug treatments are still developing rapidly, with seemingly effective drugs such as pegaptanib sodium being discarded for an even more efficacious drug, Ranibizumab. Recent trials identifying Bevacizumab as an alternative to Ranibizumab further show that drug advances for AMD treatment are still very much ongoing. Under the current economic pressures and cost/benefit criteria practised in the medical environment, Bevacizumab is a cheaper alternative to the more refined Ranibizumab and has the potential to become a standard treatment for wet AMD treatment. Considering it would cost the NHS up to 100 times less to administer this drug, it would be the best option to optimise NHS resources and ensure that society as a whole benefits from other possible uses of these funds.32 As to whether drug companies will choose to apply to licence Bevacizumab, or to not and so majorly increase their net profit by continuing to advise the considerably more expensive Ranibizumab, is yet to be seen.

References