

Age-related Macular Degeneration: Current concepts in pathogenesis and management

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ABSTRACT

Age-related macular degeneration, which was once thought to be a disease mainly found in Caucasian populations in Europe and America, is now also appearing more frequently among non-white populations in the developing world. Ophthalmic practitioners should be aware of this. This paper reviews current concepts in the pathogenesis and management of age-related macular degeneration as found in Pubmed journals over the past ten years with a view to recommending optimal treatment regimes for African populations.

Key words: age-related macular degeneration, pathogenesis, genetics, management, antiVEGF

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of visual impairment among the elderly in the developed world.¹ The disease was initially thought to be relatively rare in developing countries,² but recent studies have shown that it is more prevalent than earlier believed, particularly in India³ and Nigeria.⁴ Age-related macular degeneration is coming up more frequently in clinical studies as an important cause of low vision in the western^{5,6,7} and south eastern^{8, 9} parts of Nigeria. There is no accurate database on the prevalence of this disease in developing countries. This is probably due to the paucity of trained vitreoretinal surgeons and the non availability of equipment needed to make an accurate diagnosis of this important cause of low vision and blindness in the aging segments of African populations. As people are living longer due to improved health care, it is expected that the number of persons with the disease will continue to rise.

This review discusses current concepts such as the role of genetics in the aetiopathogenesis of AMD and the use of antiVEGF (vascular endothelial growth factor inhibitors) in its management and its suitability for African patients.

METHODOLOGY

A Pubmed search was conducted using the Internet. The search was limited to publications within the last ten years. Only studies that discussed pathogenesis and treatment were considered. The review of literature revealed very few studies from Nigeria and these studies only mention AMD as one of the causes of low vision in Nigeria.

AETIOPATHOGENESIS OF AMD

Genetics

AMD is a multifactorial disease.¹⁰ Its pathogenesis results from an interplay of genetics, the environment, and behavioural factors. Family-based studies and molecular genetics have consistently shown that complement factor H (CFH) and LOC387715 genes on chromosome 1 and 10 respectively are important in the pathogenesis of age-related macular degeneration.^{11,12} In complement factor H polymorphism, histidine is substituted with tyrosine at position 402 on chromosome 1 (Y402H).¹² This results in the production of an abnormal variant of complement factor H. Under normal conditions, this factor is involved in the inhibition of the alternate pathway of the complement through its ability to bind with C-reactive protein, thereby down regulating inflammation.¹² The abnormal variant of complement factor H produced from the defective gene binds sparingly to the C-reactive protein and this results in an increase in inflammation producing RPE damage and drusen formation, which are important stages in the pathogenesis of AMD.¹³ Increased levels of C-reactive proteins are associated with AMD.¹⁴ The exact role of the LOC387715 gene is still being investigated. It is associated with neovascular AMD.¹⁵

Environmental factors, such as solar exposure, are also implicated in the aetiopathogenesis of AMD.¹⁶ The Age-Related Eye Disease Study (AREDS)¹⁷ has shown the benefits of nutritional supplements in patients with AMD. Other factors associated with AMD development include, smoking,

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increasing age, hyperopia, a high body mass index, being Caucasian, hypertension, lens opacity and the presence of large drusens.¹⁸ The intake of fish is beneficial.¹⁹

CLINICAL PRESENTATION

Classification of AMD²⁰

The International Classification and Grading System differentiates age-related maculopathy (ARM), which includes all manifestations of age-related macular abnormalities that are not attributable to any other cause except AMD. The late stages of ARM are named age-related macular degeneration (AMD) and these include both 'dry' and 'wet' stages of AMD.²⁰

FEATURES

A defining feature of ARM is the presence of drusen. Drusen are 'discrete whitish-yellow spots . . . which are external to the neuroretina or retina pigment epithelium (RPE)'. 'Hard' drusen, however, are not necessarily a feature of ARM, as they may be present in the eyes without ARM. However, ARM will not be diagnosed if there are no drusen or if only small drusen (less than 63 microns) are present.

Features of early stages of ARM

1. Multiple small drusen and few intermediate drusen (63-124 microns in diameter).
2. Areas of hyperpigmentation associated with drusen.
3. Areas of hypopigmentation associated with drusen.

Intermediate ARM

According to the AREDS report, wherever a number of 'large' drusen (large drusen is defined as $\geq 125 \mu\text{M}$) were present in both eyes, there was a greater risk of development of AMD in either eye, than if the presence of large drusen occurred in only one eye. In the simplified severity scale described in the AREDS report number 18, drusen are considered a risk factor only if an individual drusen is large (defined as $>125 \mu\text{M}$). Drusen size is used instead of drusen area, because it is easier to estimate the size using an ophthalmoscope. The figure $125\mu\text{M}$ was selected because it approximates the size of a normal retinal vein at the disc margin.²⁰

The presence of multiple intermediate or any large drusen is considered an intermediate stage of ARM. The report also showed that patients with 'intermediate' drusen, (defined as any drusen $>63 \mu\text{M}$ but $\leq 125 \mu\text{M}$), or many small drusen, had only a 1.3% chance of developing advanced AMD over 5 years.¹⁷

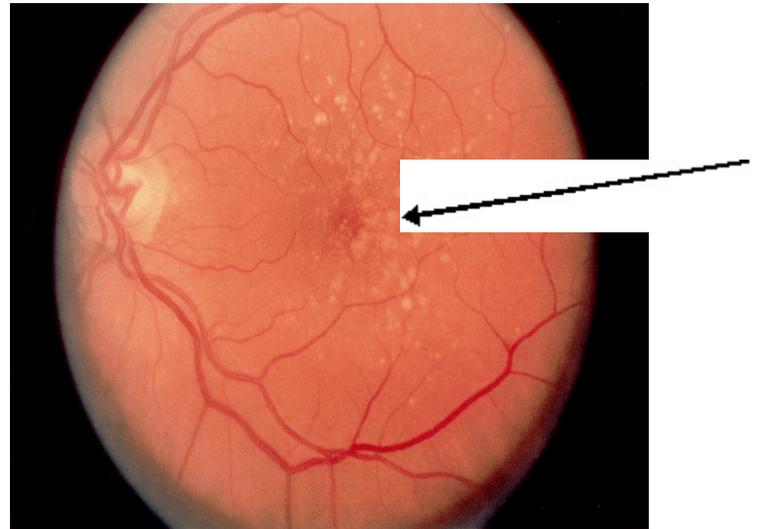


Figure 1. Intermediate ARM with multiple medium to large drusens (from Neil M Bressler MD, Johns Hopkins University School of Medicine).

LATE ARM (AMD)

Dry AMD (or 'geographic atrophy')

Dry AMD is characterized by sharply demarcated areas of hypopigmentation in which choroidal vessels (which are at least $175 \mu\text{m}$ in diameter) are more visible than in surrounding areas (see figure 2).

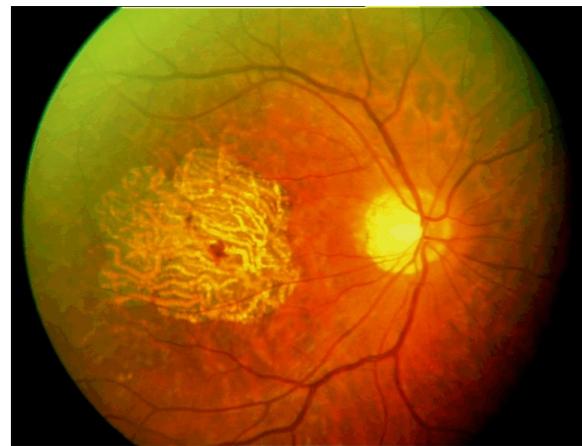


Figure 2. Intermediate ARM with multiple medium to large drusens (from Neil M Bressler MD, Johns Hopkins University School of Medicine).

Wet AMD ('neovascular', 'disciform', or 'exudative' AMD)

Wet AMD is also associated with the following features:

1. RPE detachments, which may be associated with neurosensory retinal detachment
2. Subretinal or sub-RPE neovascular membranes
3. Epiretinal, intraretinal, subretinal, or subpigment epithelial scar/glia tissue or fibrinlike deposits

4. Subretinal haemorrhages not related to other retinal vascular disease
5. Hard exudates (lipid) related to other ARM findings but not related to other vascular diseases



Figure 3. Subretinal neovascular membrane, with subretinal blood (From LV Prasad Eye Institute, Hyderabad, India)



Figure 4. Choroidal neovascular membranes with hard exudates. (From LV Prasad Eye Institute, Hyderabad, India)



Figure 5. Scarred choroidal neovascular membrane (from LV Prasad Eye Institute, Hyderabad, India)

MANAGEMENT OF AMD

Investigative procedures

Slit lamp biomicroscopy. A detailed slit lamp biomicroscopy with a contact (Goldman's 3-mirror lens) or non-contact fundus lens (+78 or +90D) with a bright thin beam is required for detecting choroidal neovascular membranes (CNVM) and fluid due to stereopsis offered by these lenses.

Flourescein angiography. This functional invasive test is an essential tool in making accurate diagnosis of classic and occult choroidal neovascular membranes. Indocyanine angiography(ICG) is useful in detecting occult CNVM especially when blood is blocking fluorescence.

Optical coherence tomography (OCT). Optical coherence tomography is a non invasive investigation that uses the reflection of infrared light to construct the histology section of the posterior pole similar to ultrasonography. It is an excellent tool for patients who are not suitable for flourescein angiography. OCT also helps to define the layers of the retina involved, it detects the presence of retinal oedema, cysts, and neovascular membranes. It also differentiates Type I (sub RPE) from Type II (sub neurosensory retina) CNVM. Patient follow up and education is made easier with OCT.

TREATMENT

Non-neovascular AMD

If AMD is at the intermediate stage, patients should be advised to start taking the nutritional/vitamin antioxidant supplements which were found effective in the AREDS study,¹⁷ provided the individual has not had any adverse reaction to taking any of the components of this formulation.

The antioxidants are taken at a daily dose of:

1. 500 mg of vitamin C
2. 400 International Units of vitamin E
3. 5 mg of beta carotene
4. Zinc supplement at a dose of 80 mg
5. Cupric oxide at 2 mg

Cupric oxide is added to reduce the risk of copper deficiency anaemia associated with taking a zinc supplement.¹⁷ Cigarette smokers should be warned of the risk of developing lung cancer with a high dose of beta carotene.²¹ Patients with bilateral advanced AMD, but with good vision in at least one eye should also be advised to start taking the above supplements. The AREDS report indicates that the above dietary supplement decreases the risk of vision loss in the eye with advanced AMD with visual acuity of 20/100 or better.¹⁷ Ophthalmologists in Nigeria should work together with the

pharmaceutical companies to investigate this vitamin formulation and explore the possibility of making it available as an eye supplement.

Neovascular AMD

It has been shown that vascular endothelial growth factors (VEGF) play a significant role in the pathogenesis of neovascular AMD.²² The new vessels formed can either be within the retinal, sub retinal or sub retinal pigment epithelium (RPE). Although it occurs in only 15% to 20% of AMD populations, it more commonly results in severe vision loss compared with non-neovascular AMD.²³ The origins of these new blood vessels include the choroid (choroidal neovascular membrane (CNVM)) or may start within the retina and proliferate downward, in which case they are called retinal angiomatous proliferation (RAP). Fluorescein angiography reveals patterns such as: predominantly classic (clearly defined neovascular network >50% of lesion area), occult (poorly defined new vessels), minimally classic (classic < 50% of lesion area), or predominantly scarred. Bleeding and exudation from these new vessels result in visual loss. The end stage is a fibrotic or disciform scar.²³

Prior to the year 2000, laser treatment was the standard for classic CNVM. This form of treatment, however, was not satisfactory and sometimes resulted in scotoma formation, especially for lesions close to the fovea. Secondly, neovascularization often recurred at the edges of the laser scar. In 2000, verteporfin photodynamic therapy (PDT) supplanted macular photocoagulation to become the dominant treatment for neovascular AMD.²⁴

However, patients receiving PDT still had loss of vision, and the 'benefit' of PDT is measured in terms of decreasing the loss of vision, rather than regaining lost vision. The limitations of PDT have led to more research efforts to find better methods for treating neovascular AMD. Steroids were the next choice of treatment.²⁵ Triamcinolone was combined with PDT with improvement or gain in vision.²⁶ Complications of intravitreal triamcinolone include cataract formation and glaucoma. This led to the development of angiostatic steroids with no glucocorticoid activity that could inhibit angiogenesis in an in-vitro model.²⁷ Anecortave acetate is an angiostatic steroid which is given as a subtenon's injection every 6 months in the treatment of neovascular AMD. It was found to be superior to no treatment²⁸ but inferior to PDT. In Nigeria, where PDT is not readily available, the need arises to look for more affordable treatment, such as intravitreal injections.

VASCULAR ENDOTHELIAL FACTOR INHIBITORS (ANTI-VEGF)

Investigators have shown that VEGF play a significant role in the pathogenesis of neovascular AMD,^{22, 29-31} hence, they are

the target of current treatment modalities. In the year 2005, the selective anti-VEGF aptamer pegaptanib (Macugen[®]) showed superiority over available treatment when given intravitreally.³¹ Pegaptanib is an RNA oligonucleotide aptamer that binds with VEGF. About a few months later, the nonselective antiBVEGF bevacizumab (Avastin[®]) molecule also became available.³²⁻³⁴ Bevacizumab (Avastin) is a full length antibody against VEGF and a humanized monoclonal antibody synthesized using recombinant DNA technology.³⁵

Intravitreal bevacizumab (at a dose of 1.25mg in 0.05ml) has many advantages over all the other treatments discussed so far. First, it seems to lead to an improvement in vision.³⁶ Second, it is safe, and third, it is less expensive than PDT or pegaptanib.³³ Several reports have described its efficacy.³⁶⁻³⁹ In July 2006, ranibizumab (Lucentis[®]) became commercially available in the United States, as the first medication which showed a proven improvement in visual acuity in a randomized controlled trial and was approved by the FDA for the treatment of neovascular AMD.⁴⁰ It is an anti-VEGF antigen-binding antibody fragment (Fab) that is specific for VEGF₁₆₅. Ranibizumab is administered as an intravitreal injection (0.3mg or 0.5mg), and it has now been tested in a number of clinical trials for the treatment of neovascular AMD.^{40,41} Two major phase 3 clinical trials for ranibizumab known as the **MARINA**^{*} and **ANCHOR**^{**} have demonstrated superiority of ranibizumab over sham and PDT.⁴²

Officials of The National Eye Institute (NEI), USA announced in October 2006 that they will launch their own clinical trials comparing outcomes of both Lucentis and Avastin as macular degeneration treatments. The *British Journal of Ophthalmology* in July 2006 reported results of one Internet survey among eye doctors who reported no adverse side effects related to the use of Avastin for macular degeneration, seemingly because relatively low doses of the drug are injected into the eye.⁴³ But other researchers commenting in the journal pointed out that long-term safety risks of Avastin remain unknown.

In May 2007, the *British Journal of Ophthalmology* published a cost analysis comparing the two treatments. Researchers concluded that Lucentis, which is about 50 times more expensive than Avastin, would need to be 2.5 times more effective to justify the additional cost.⁴⁴ Research indicates that at present, Avastin appears to be a better buy for the money.

In Nigeria, ophthalmologists should run a randomized trial using bevacizumab; if the results are positive, the

*Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the Treatment of Neovascular AMD.

**Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in AMD.

pharmaceuticals could manufacture bevacizumab as a cheaper alternative.

VEGF-trap (Regeneron^R)

The VEGF-trap consists of an Fc fragment linked to the extracellular portions of the VEGFR1 and VEGFR2 receptors. It is injected intravitreally, where it will bind with free VEGF and prevent activation of VEGF receptors. In-vitro studies are promising.⁴⁵⁻⁴⁶

Small inhibitory RNAs (siRNA)

These are short double stranded RNA molecules that inhibit translation of the native mRNA from which they are derived. In-vitro studies have demonstrated that anti-VEGF siRNAs were able to decrease the expression of the human VEGF gene and appeared to stop the growth of laser induced CNV.⁴⁷ A new anti-VEGF siRNA called **bevasiranib** or **Cand5**, which is injected intravitreally, is under investigation, and so far, has been shown to be effective.⁴⁸

The International Conference on Age-Related Macular Degeneration, held at Aravind Eye Hospital, India, in January, 2007 recommended the following treatment modality for neovascular AMD.

1. The treatment of extra foveal CNVM is laser treatment.
2. The first line treatment of subfoveal CNVM is intravitreal ranibizumab.
3. Bevacizumab is used when ranibizumab is not available, or when the patient could not afford the cost of ranibizumab.
4. Pegaptanib (Macugen) is considered when the above medications are not available.
5. The only consideration for PDT is when the patient has previously responded well to PDT, or the use of anti-VEGF is contraindicated.

CONCLUSION

Age-related macular degeneration is no longer a disease confined to developed countries, but occurs throughout the world. Ophthalmologists should carry out careful and detailed evaluations of the macular area in their elderly patients. The recent explosion in research and publications in this area worldwide is an indication of what to expect in the future.

In developing countries like Nigeria, ophthalmologists should work together with the pharmaceutical companies to conduct clinical trials using intravitreal injections, such as bevacizumab to determine the most effective treatment for subfoveal CNVM. Where this is not possible, intravitreal triamcinolone should be investigated, as this is readily available in Nigeria. The most commonly reported side effects

of intravitreal injections included red eye (conjunctival haemorrhage), eye pain, small specks in the fields of vision (floaters), increased eye pressure, and inflammation of the eye. Serious side effects, which were rare and often related to the injection procedure, included severe inflammation of the interior of the eye (endophthalmitis), intraocular inflammation, retinal detachment, retinal tear, increased eye pressure, and traumatic cataract.⁴⁹ These complications should be borne in mind when recommending this treatment. Multivitamins in AREDs recommended combinations are available and should be prescribed for patients with the intermediate stage of AMD.

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