

## Review Article

## A brief review concerning age related macular degeneration

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Age related macular degeneration (AMD) is progressive non-curable disease primarily affecting the elderly. In addition to age the most important single contributing factor to the condition is an individual's genetic makeup. As with many diseases, genetic predisposition greatly increases the likelihood of developing the syndrome. This disease may manifest itself in families, not unlike cancer or cardiovascular disease. The development of AMD is also strongly linked to obesity and smoking. Gender has also been implicated but the data supporting this specific factor is more tenuous. Most of the current treatments involve the injection of a biologic into the posterior segment of the eye for the remainder of a person's life. These products have been shown to be effective in maintaining clarity of lines of vision. Supplements have also been recommended and shown promise in delaying disease onset in some individuals. Lutein and Zeaxanthin have been shown to maintain a person's lines of vision and thus retard progression of the disease.

**Introduction****Disease aspects**

There are two types of AMD referred to as wet or dry. Wet AMD occurs when blood vessels will appear growing from the choroid located approximately behind the retina. The development of these blood vessels is triggered by Vascular endothelial growth factor (VEGF) triggers the development of these blood vessels and intrusion of these blood vessels may cause retinal detachment or interference with the retinal segment. They may grow through Bruch's membrane leading to fluid leakage near or around the macula. Part of this fluid contains protein and with this leakage comes vision loss and photoreceptor damage. About 10% of the total number of AMD cases are this more extreme (wet) form of the disease [1]. Dry AMD occurs when cellular debris known as drusen accumulates between the retina and choroid, degrading the retinal pigment layer over time. The loss of the associated rods and cones in the eye causes vision degradation. Dry AMD is considered the less severe of the two disease forms. Drusen does buildup naturally with increasing age, and its appearance does not always lead to AMD [2]. The disease progresses slowly in older individuals with drusen being visualized as white or yellow-white areas under the retinal pigment epithelium. The pigments may remain small and not affect vision to a great extent. Other signs may include pigmentary alterations and loss of lines of vision. The affected individual may experience vision loss from the "center, outward". As such there is blurred or distorted vision. There may be a loss of contrast sensitivity, especially as related to color. The macula comprises only about 2% of the retina, but about 50% of the visual cortex processes information from the macula. So when the macula is compromised in any way, severe quality of life issues may result.

**Risk population**

The largest risk factor for developing AMD is age [3]. It is estimated that around 8 million Americans reaching age 54 will develop AMD and of those 13% will develop advanced AMD. In the United Kingdom 75% of the individuals who go blind will do so because of the development of AMD, and 30% of individuals who are affected occur in the 75-85 age range [4]. This percentage will increase with the

disease development within families (genetics). AMD development has also been correlated with cardiovascular risk factors [5]. Smoking is also a risk factor for AMD development as it is for cardiovascular disease. Research has also shown a tenuous link to Caucasian females, who appear to have a greater statistical risk for AMD development [6]. But this link is tenuous [1,6].

Other risk factors include hypertension, obesity, increased cholesterol levels and elevated HDL cholesterol. An individual's genetic makeup has also been linked to development of AMD, specifically the genes for factors H, B and 3 have been linked to the disease. These genes are part of the controlling mechanism of the complement activation system, and thus inflammation.

**Treatment****Drug therapy**

The first approved AMD drug treatment was Macugen (pegaptanib) was the first approved drug treatment for AMD that showed positive health benefits in patients [7]. It is comprised of a small sequence of mRNA and is administered by injection into the posterior segment of the eye. Additional approved posterior segment injection therapies are Avastin (bevacizumab) and Lucentis (ranibizumab). Bevacizumab (Avastin) has also been approved as a cancer treatment and is a monoclonal antibody [8]. Ranibizumab (Lucentis) is comprised of only the FAB region of the bevacizumab molecule. The Fc region of the antibody is not present. Thus, the molecule has a different (lower) molecular weight and stereochemistry. All these injectable products are given via the posterior segment on a routine basis to treat the disease. The primary negative side effect is discomfort during the injection.

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Aflibercept formulated as EYLEA is a more recent therapy for wet AMD. It is a recombinant fusion protein that is comprised of VEGF binding proteins thus preventing VEGF from stimulating blood vessel growth.

Once injected these drugs are free to interact with VEGF-receptor sites on cells. The desired effect is to retard the growth of blood vessels into the retinal and macula space, thus delaying disease onset. The major patient risk is in administration of the drug. All the drugs listed above are prescribed for monthly or bi-monthly use under a physician's care. The major side effects once delivered are retinal detachment (due to injection) and inflammation or infection.

## Supplements

Supplements are also used as effective treatment options. Lutein and Zeaxanthin have been shown to modulate the onset of AMD [9]. The compounds may be taken as dietary supplements or from eating green vegetables such as spinach. They modulate the disease processes for oxidant and light exposure. Lutein and Zeaxanthin tend to reduce inner eye exposure to short wavelengths of light, thus preventing damage to cell components including nucleic acid, by oxidant damage. Untreated, the alteration of cellular components may lead to optic nerve damage, via either inflammation or development of neovascularization in the retinal segment of the eye. These two supplements (along with Omega-3) are currently being marketed by Bausch and Lomb as Ocuvite. They are usually administered as once-a-day oral capsule or tablets. The Age-Related Eye Disease Study (AREDS) was designed to evaluate various supplements such as Vitamins C and E and beta-carotene on the progression of AMD and cataract. These compounds had no effect on cataract. However, they were effective at preventing AMD related vision loss. In a subsequent study Age-Related Eye Disease Study 2 (AREDS 2), lutein and zeaxanthin were evaluated for their ability to prevent AMD progression. These supplements taken together were found to be an effective substitute for beta-carotene in modulating AMD disease progression.

## Medical device/drug delivery

A study in New Zealand White rabbits has shown that steroids delivered via a hydrogel contact lens can reach the retinal space of the eye. The experiments were conducted separately. Inflammation due to VEGF administration (as shown in positive controls) was retarded in the case of steroid treatment [10]. The animals were treated with VEGF to induce inflammation, and then treated with either saline (positive control) or a steroid (modulator). Experiments showed that the steroids were able to decrease inflammation due to VEGF presence. Further, the analytical data demonstrated that the path of entry to the retinal space was not directly through the vitreous humor but around the globe of the eye. ELIZA was used to detect Lucentis delivered from a contact lens to the posterior segment [10].

## Laser surgery

Treatment with laser surgery can be successful in a limited number of cases provided certain conditions are met. Laser treatment will delay the development of choroid neovascularization by a few months in patients with unilateral advanced AMD [11]. But the symptomology will return in time. This is an effective treatment in severe cases where action to preserve vision must be taken immediately.

## Phototherapy

This is an option that has been used to treat wet AMD. The drug verteporfin is administered by intravenous injection followed by light

treatment [12]. The combination of drug in the correct location in the eye causes destruction of the blood vessels and thus disease treatment. As with laser surgery the disease progression may return in the form of blood vessel encroachment in the posterior segment over time. Neither treatment is a cure.

## Conclusion

Age related macular degeneration is a progressive disease with no overt signs or symptoms until actual visual loss. It affects millions of people world-wide, but there are specific risk factors such as age, smoking, obesity and importantly, genetic factors which lead to development of the disease [13]. It seems that the group which may be most at risk are overweight, chronic smokers. While genetics also seem to be the strongest link for disease development overweight, chronic smokers are also at risk. A combination of all these factors, genetic, smoking and obesity increase the risk greatly for potential onset of the disease. If visual decay which can be measured by loss of lines of vision can be halted or reversed, then the quality of life of an affected individual will improve. There is no cure but the treatment options which are available are effective in modulating the process of the disease in at least some people. This is what the newer therapies are designed to do. The sometimes extreme side effects of the treatments such as retinal detachment are rare, and are not necessarily related to the drug itself. Inflammation is more of a problem in terms of numbers of individuals affected, but a less serious complication. Increased public awareness coupled with better diagnostic techniques and improved treatment methods are the best techniques available at this time to prolong an individual's quality of life through the course of the disease. As product costs decline these current therapies should be more readily available for use [14].

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