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RECENT ADVANCEMENTS AND FUTURE PROSPECTS IN THE MANAGEMENT OF ARMD

Shrinkhal[1] and Arvindgautam[2]

[1]Junior Resident, Department of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi and [2]Junior Resident, Department of Shalakya, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Corresponding Author: Shrinkhal

Abstract: *Age-related macular degeneration (AMD) is one of the leading cause of visual impairment in people above the age of 50 years in developed nations. There are various factors involved in etiology of AMD in which genetic and non-genetic factors have major role. And some other factors involve are like multiple gene variants and lifestyle factors such as smoking have associate with the disease. The basic pathology involve in AMD is still not very clear but due to advancement of genetic knowledge and treatment some opportunities are still there to treat AMD. In this article we discuss the recent advances in knowledge, treatment and future prospective of AMD patients.*
Keywords: *AMD, Genetic, Lifestyle.*

Introduction: Age-related macular degeneration (AMD) is the most common cause of visual impairment and blindness in the elderly in the industrialized nations [1]. In 2000, more than nine million individuals were estimated to have AMD in the United States [2]. Its prevalence is predicted to double by 2020 [3]. AMD is classified into two main forms: non-neovascular (also known as "dry" or "nonexudative") or neovascular (also known as "wet" or "exudative"). The clinical hallmark of non-neovascular AMD is drusen, which are yellowish deposits at the level of the retinal pigment epithelium (RPE) which lies just under the neurosensory retina."Geographic atrophy" is the advanced stage of non-neovascular AMD, where areas of atrophy become confluent and cause visual loss. Neovascular AMD is also an advanced manifestation of AMD, characterized by choroidal neovascularization (CNV)—abnormal blood vessels typically arising in the choriocapillaris and often invading the subretinal space. CNV is the hallmark of neovascular AMD. The gold standard for diagnosing CNV is with fluorescein angiography, where CNV is seen as hyperfluorescent lesions deep in the retina that increase in intensity and size over time as the fluoresce in leaks from the neovascular membranes.

The major risk factor for any stage of AMD is old age. Advanced AMD is seen more frequently in Caucasian patients. In the Baltimore Eye Study, 30% of bilateral blindness in Caucasians was caused by AMD, compared to 0% in African Americans [4]. Smoking and obesity are perhaps the only well-established risk factors that are modifiable. The Age-Related Eye Disease Study (AREDS) showed that the risk for neovascular AMD was doubled for participants who had ever smoked [5].

Till date, there have been considerable advancement in the management of wet AMD, but there is still no established treatment for the most prevalent dry form of AMD. Left untreated, patients with dry AMD are at risk for significant vision loss and progression to wet AMD. The National Eye Institute (NEI), the Macular Degeneration Foundation, Inc., the Macular Degeneration Partnership and Macular Degeneration Support provide the following recommendations for slowing down, or preventing the progression of, both dry and wet AMD.

Diet and weight control: Studies suggest that eating antioxidant- rich foods such as fresh fruits, dark green leafy vegetables (a good source of lutein) and at least one serving of fish (omega3 fatty acid) per week may delay the onset or

reduce the severity of dry AMD; in addition, obesity may increase the risk for progression to advanced AMD.

Nutritional supplements: Supplements containing high doses of antioxidant vitamins, copper, and zinc may reduce the risk ofdeveloping advanced AMD by approximately 30%.

Blue Light: Avoid ultraviolet and blue light (particular light waves that make the sky, or any object, appear blue) as much as possible and wear sunglasses that block blue light.

Control blood pressure: Individuals with hypertension are more likely to have wet AMD than persons without hypertension.

Wet AMD

1. **Laser Photocoagulation*:*** Panretinal photocoagulation was the earliest treatment for Wet AMD. But persistent and recurrent neovascularization associated with severe visual loss were the drawbacks observed with laser treatment [6]. Other limitations include destruction of overlying retina causing permanent visual loss, making it unsuitable for subfoveal CNV as well as for occult CNV.
2. **Verteporfin Photodynamic Therapy*:*** With PDT, a light-sensitive dye (Verteporfin) is injected intravenously. It gets accumulated in the choroidal vessels that are growing abnormally. A blue laser beam is then shone onto the macula to activate the dye. It releases reactive oxygen species, destroying the leaking blood vessels without damaging the healthy tissue around them.
3. **Intravitreal Corticosteroids*:*** Corticosteroids act by reducing inflammation, blocking the up-regulation of VEGF, reducing vascular leakage as they close up the gaps between endothelial cells in the capillary walls. They also inhibit fibrosis, reducing the scarring in the retina. Intravitreal triamcinolone acetonide is used.
4. **Anti-VEGF Treatment:** These agents do not appear to cure the condition. Rather, they halt or slow progression of AMD in most cases. The drugs currently used are Macugen (pegaptanib sodium), Lucentis (Ranibizumab). It is an antibody fragment derived from a murine antibody to VEGF that specifically binds all active isoforms of VEGF) and Avastin (Bevacizumab). It is a humanized monoclonal antibody derived from the same murine antibody as ranibizumab and also specifically binds all biologically active isoforms of VEGF).
   Bevacizumab is approved by the Food and Drug Administration for the treatment of advanced colorectal cancer in combination with 5-fluorauracil [7]. Bevacizumab has off label use intra vitreally.
5. **VEGF Trap-Eye:** VEGF Trap is a recombinant protein in which the binding domains of VEGF receptors 1 and 2 are combined with the Fc portion of immunoglobulin-G. The receptor portion of the molecule has a high affinity for all VEGF-A isoforms, placental growth factors 1 and 2, and VEGF-B50. Therefore, VEGF Trap is distinguished from ranibizumab by its higher binding affinity for all VEGF-A isoforms and its ability to inhibit other VEGF family members. It also binds VEGF more tightly than all other anti-VEGF agents. Example: Aflibercept
6. **VEGF Receptor Tyrosine Kinase Inhibition*:*** Vatalanib® (formerly PTK-787, Novartis International AG, Basel, Switzerland) is a potent inhibitor of all known VEGF receptor tyrosine kinases, VEGFR1 (sFlt-1), VEGFR2 (KDR), and VEGFR3 (Flt-4). Its satisfactory oral bioavailability makes it an attractive alternative to intravitreally or intravenously injected medications [8].
7. **Surgical Treatment**: Submacular surgical removal of CNV [9], pneumatic displacement of large subretinal haemorrhage [10], and macular translocation [11] have been tried for AMD associated with CNV.
8. **Squalamine Lactate*:*** It is a intracellular VEGF inhibitor. It inhibits plasma membrane ion channels with downstream effects on VEGF, and has shown promising results with systemic administration.
9. **Anecortave Acetate*:*** Anecortave acetate has also been used in patients with AMD-related CNV.
10. **Designed Ankyrin Repeat Proteins (DARPins):** It is also a VEGF inhibitor.
11. **PDGF Blocker:** FOVISTAT+Ranibizumab.
12. The interaction between *the transmembrane integrin α5β1 receptor and its natural ligand, fibronectin* in the angiogenic cascade is critical to endothelial cell survival. Inhibiting this interaction may disrupt the process of neovascularization [12]. One such agent, Volociximab (M200), is undergoing a

phase one trial in combination with Ranibizumab[12].

13. Attempts to target retinal and choroidal new vessel formation using *the small molecule inhibitor carboxyamidotriazole (CAI),* known for its anti-angiogenic and anti-tumor effect support the potential of developing it for treatment of proliferative retinopathies in humans such as proliferative diabetic retinopathy, exudative AMD, and retinopathy of prematurity [13].
14. **Radiotherapy:** It is a promising adjunctive tool to antiangiogenesis therapies for control of CNV in AMD.
15. **Combination Therapies**

Dry AMD

1. There is no effective interventional therapy for maintaining or improving vision associated with dry AMD. The current recommendation is an oral supplement containing high doses of antioxidants and zinc. *The Age-Related Eye Disease Study (AREDS),* a randomized controlled clinical trial of high-dose antioxidant vitamins (vitamins C, E, and β-carotene) and minerals (zinc and copper), demonstrated that the combination of antioxidant vitamins and zinc treatment reduce the risk of progression to advanced AMD by 25%.[14]
2. **Neuroprotectives:** CNTF (ciliary neurotropic factor). Eg- Serotonin-1A agonists (eg- Tandospirone)
3. **Alfa-2 Adrenergic Agonists:** Brimonidinetartarate
4. **Complement Factor Inhibitor**
    - LGF316(C5 inhibitor)
    - POT-4(C3 inhibitor)
    - Eculizumab(C5 inhibitor)
      Note: Eculizumab is FDA approved for the intravenous treatment of paroxysmal nocturnal hemoglobinuria, however, its chronic systemic use is associated with increased risk of Neisseria meningitides infection
    - GSK-337706(C3 inhibitor)
    - Rapalizumab(Factor D inhibitor)
5. **m TOR Inhibitor:** SIROLIMUS (Rapamycin). Its spectrum of actions includes inhibition of inflammation, angiogenesis, fibrosis, and hyperpermeability.
6. **Glatirmer Acetate**

Role of Nanotechnology: Nanotechnology involves using nanoparticles (NPs) which are microscopic particles whose size is on the nanometer scale [15]. They can be synthesized with organic, inorganic polymers or a combination of both polymers in various molecular sizes and conformations allowing for encapsulation of specifically adapted formulations. Also, they can be made biodegradable. These properties of NPs have encouraged research into their possible application in the treatment of AMD by continuous intraocular drug release through coupling the desired drugs to liposomes, microparticles (1–1000 μm) or nanoparticles (1–1000 nm, generally 20–300 nm). Nanotechnology may offer several advantages for administration of drugs in vivo, such as controlled release, injectable and sterilizable formulation, and long shelf-life after lyophilization. In addition, drugs and genetic materials embedded or encapsulated into the NPs can be protected from immediate dilution and degradation and also overcome drug solubility issues. NPs may be used to deliver these drugs for sustained release in a longer time period, which may reduce the frequency of intravitreal injection.

Hormone Therapy: There are few reports of role of hormone therapy on AMD [16-18]. Treatment with conjugated equine estrogens (CEE) or with CEE combined with progestin (CEE+P) does not affect early stage AMD, but treatment with CEE+P may reduce the risk of soft drusen or neovascular AMD [18].

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