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Review Article

A SYSTEMATIC REVIEW ON DECISIVE FACETS OF AGE-RELATED MACULAR DEGNERATION AND FUTURE PARADIGMS

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A B S T R A C T

Angiogenesis in the eye stands as a big reason for blindness and vision impairment in both developed and developing countries including age-related macular degeneration especially Exudative age-related macular degeneration, Proliferative Diabetic Retinopathy, Diabetic Macular Oedema, Glaucoma and Cataract. Amongst these, Age-related macular degeneration ranks third globally as a cause of visual impairment and central vision loss in industrialized and middle-income countries, raising a major concern for more effective and affordable treatment. Age-related macular Degeneration is a retinal disorder which occur due to low blood circulation in retinal and macular region causing degeneration in macular retina and central vision loss. For the treatment of disease, dosage forms used are administered through intravitreal route in the form of Pre-filled syringes and they are regulated as Combination product by USFDA (United States Food and Drug Administration) (21 CFR 3.2(e))in USA and by directive 93/42/EEC in European Union. This Age-related Macular Degeneration is associated with serious consequences in person's life starting from loss of independence, depression to even increased financial outcome, requiring more focus over effective therapies. For this, concerns for availability of New medications and also easy identification of patients with risk factors of Age-related Macular Degeneration is becoming more significant. This review article gives detailed information about Age-related macular degeneration, procedure for its diagnosis and various treatment options available along with regulatory requirements to be fulfilled for the dosage forms meant for treatment. This article also explains the challenges associated with macular degeneration market and future products in pipeline.

INTRODUCTION

Age-Related Macular Degeneration (AMD) is an acquired retinal condition occurring due to reduction in blood flow to retinal area of eye which results in development of degenerative lesions in macular retina and gradual loss of central vision. It majorly affects elder or older population ageing between 50-60 years. One of the estimates of World Health Organization says that globally, AMD ranks third as a cause of blindness after Cataract and Glaucoma. It is condition with prevalence of 8-7% in industrialized countries (USA, UK, Western European Countries, Belgium, France, Japan) as a primary cause of visual deficiency.[1,2]

Anatomy of Eye

Eye, organ of sight, surrounded by orbital bones consists of a thin, transparent layer called Conjunctiva covering its foremost part. Anterior chamber of the eye located behind the Cornea (clear at the front and center of eye) and in front of Iris (colored part of the eye). Lens, the clear flexible structure located just behind iris and pupil together with Cornea functions to focus light onto Retina (a film which create an image). Behind the Retina, Choroid is located which supply blood to Macula and Retina. There exists a Bruch's membrane which acts as a barrier between Retina and Choroid. The layer of pigmented cells which nourishes retinal visual cells is Retinal Pigment Epithelium located just outside the Retina. There are mainly two type of cells (Photoreceptors) in retina known as Rods, which allow to see in low light situations but not allow to see color and Cones, which allow to see color, require morelight. Macula located in central part of Retina, has highest concentration of Cones and this region is responsible for providing sharp vision.[3]

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Risk factors for AMD

1. **Ageing**- one of the major risk factor for developing AMD because this condition is likely to occur after 60 years of age.

2. **Oxidative Stress-** Retina is highly susceptible to oxidative stress which is caused due to consumption of oxygen and exposure to visible light.
3. **Apoptosis by Phototoxicity-** Damage to Choroid layer on exposure to Ultraviolet radiations of sunlight results in cell death of RPE which is another risk factor contributing to AMD. Thus, its important to wear sunglasses to prevent direct exposure of eyes to sunlight.
4. **Smoking-** Cigarette smoking appears to accelerate AMD since Tobacco smoke contains as many as 4000 active compounds, most of them are toxic and poisonous to ocular tissues and damage them through ischemic or oxidative mechanisms.
5. **Hypertension-** Hypertensive people on long term use of Thiazide diuretics are highly susceptible to AMD due to phototoxic effects caused by such medications.
6. **Race-** AMD is more common among Caucasians i.e. Europeans, Middle East Africans than Americans.
7. **Heredity and Genetics-** People with family history of AMD are at a higher risk of developing AMD.
8. **Diet-** People consuming diet lacking antioxidant vitamins are at a high risk of vision loss from macular degeneration. Generally Aqueous humour and corneal epithelium of eye is highly concentrated with Vitamin C which protect eye from damaging UV radiation and thus preventing AMD. Consuming Vitamin E containing food items help in preventing damage due to oxidative stress and free-radicals. Another factors such as low carotenoid intake and high fat intake also contributes to occurrence of AMD. [4,5,6,7,8]

Pathophysiology of Age-related Macular Degeneration

One of the theories suggests that dynamics of Choroidal blood circulation is the critical pathophysiological mechanism. Risk factors such as Vascular diseases contribute to cause blockage in choroidal blood vessels and result in elevated ocular rigidity and decreases choroidal blood circulation. This in turn lead to release of extracellular proteins and lipids that form accumulates known as Drusen.[5,9]

There are three stages of AMD on the basis of part by size and number of drusen under Retina:

1. ***Early AMD:*** People with Early AMD typically do not have central vision loss. It is characterised by presence of medium sized drusen.
2. ***Intermediate AMD*:** It causes some vision loss and is characterised by presence of large drusen or pigment changes in Retina or both.
3. ***Late AMD:*** It is characterised by presence of drusen and severe damage to Macula resulting in vision loss. There are two types of late AMD as discussed in following Table 1:

Deterioration in elastin and collagen in Bruch's membrane in addition to drusen formation causes calcification and fragmentation. These events in association with increased protein known as Vascular Endothelial Growth Factor (VEGF) causes small capillaries to grow up abnormally from choroid into retina thus resulting in blood and protein leakage below Macula. All this coupled to give to rise to serious form of AMD i.e. Wet Age-related Macular Degeneration.Another Theory also suggest that with ageing, there are chances of abnormalities in enzymatic action of aged RPE cells which causes accumulation of metabolic By-products. After RPE get distended, drusen is formed which leads to Neovascularization.

Diagnosis and Testing

Early and intermediate stages of AMD do not show any symptoms and are difficult to diagnose. However, two forms of late AMD can be diagnosed through following eye examination tests:[5,10,11,12]

1. ***Visual Acuity Test:*** This measure smallest letters you can read on a standardized chart or a card which is held 20 ft or 6 metres away.
2. ***Amsler Grid Test:*** Visual changes can be detected using amsler grid. People with AMD may experience wavy or disappearing lines in grid, a sign of change in central vision due to AMD.

The difference in view of amsler grid to a patient with and without AMD can be seen in figure 1 and figure 2 respectively.

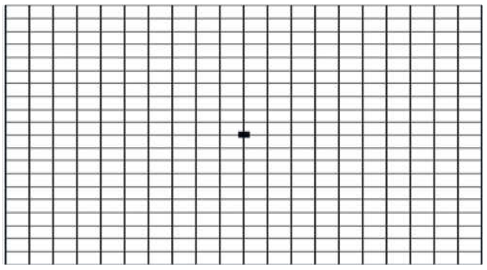

Figure 1 Amsler grid might appear like to this someone without AMD

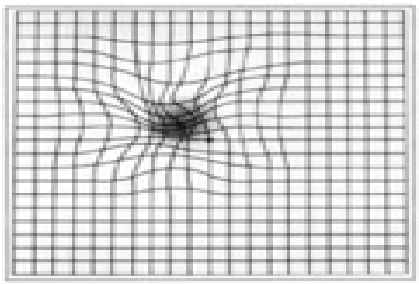

Figure 2 Amsler grid appear like this someone with AMD

Table 1 Comparison of two types of Age-related Macular Degeneration

DRY AMD (Geography Atrophy)	WET AMD (Neovascular AMD)
More common and less severe form of disease.	Most serious form of the condition.
Characterised by accumulation of drusen, damage to Retina and gradual breakdown of light sensitive cells in Macula that convey visual information to brain and supporting tissue underlying Macula.	Characterised by growth of abnormalbloodvessels (Neovascularisation/Angiogenesis) underneath Retina, and these vessels leak fluid and blood resulting in swelling and damage to Macula.
Early symptom is distortions in vision which is most apparent when reading.	Early symptom is that straight lines appear wavy.
Does not usually causes total loss of central vision.	Damage is rapid and severe causing rapid and permanent loss of central vision.

Dilated Eye Exam: After Dilating the eyes/pupil using dilating eye drops such as cyclopentolate drops can provide a better view of back portion of eye. Thus, eye care professional can look for signs of AMD by examining Retina and Optic nerve. Looking at the Figure 3, an ophthalmologist/optometrist can differentiate an AMD affected eye from normal eye.

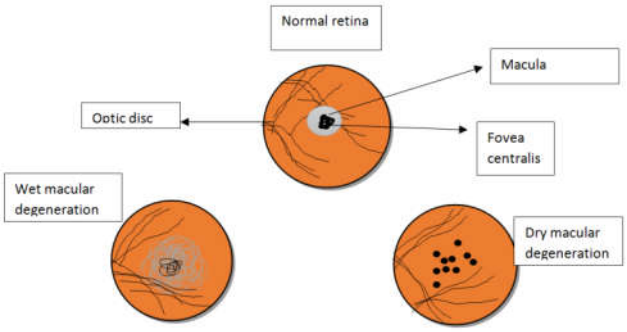

Figure 3 Macula in normal and AMD affected eye after dilation.

Fluorescein Angiogram: It is performed by an ophthalmologist. It starts with injecting a fluorescent dye into patient's arm. As soon as dye reaches blood vessels of eye, pictures are captured. This test makes possible to see leaking blood vessels which occur only in Wet AMD.

OCT (Optic Coherence Tomography): It is a non-invasive imaging test which uses light waves to capture high resolution pictures of tissues that can be penetrated by light. It aids in identifying intraretinal and sub retinal fluid and can help in assessing response to treatment.

Treatment for AMD

Pharmacological management of AMD

For **Geographic Atrophy (Dry AMD)**, National Eye Institute suggests supplementation with antioxidants and carotenoids such as lutein and zeaxanthin which slow down the progression of geographic atrophy and also improves vision. The conventional treatments for **Neovascular Age-related Macular Degeneration or Wet AMD** include drugs popularly known as Anti-VEGF agents i.e. Anti-Vascular Endothelial Growth Factor agents.

Mechanism of action of anti-VEGF agents for Wet AMD

Anti-VEGF medications namely Macugen, Lucentis, Avastin work in a similar way to bind and inhibit the activity of VEGF thus reducing formation of abnormal blood vessels. Macugen (Pegaptinib) is an aptamer, Lucentis (Ranibizumab) is an antibody derivative and Avastin (Bevacizumab) is a monoclonal antibody. VEGF is a signal protein which stimulates angiogenesis, overexpression of this protein results in vascular disease in retina of the eye.[13,14.15,16]

1. **Lucentis (Ranibizumab)** binds and inactivates VEGF and prevent its interaction with VEGF receptor on cell surface. It is administered intravitreal. It is available as pre-filled syringes in two dose strengths i.e. 0.5 milligrams and 0.3 milligrams.[17]
2. **Macugen (Pegaptinib)** selectively binds with VEGF with greater affinity and inhibits activation of ocular VEGF receptor thus inhibiting angiogenesis. It is available as pre-filled syringe and administered intravitreal into affected eye once every 6 weeks.
3. **Avastin (Bevacizumab)** is a humanized monoclonal antibody that recognizes and blocks VEGF. It was approved by USFDA firstly for the treatment of cancer and its use to treat wet AMD is an off-label use.
4. **Eylea (Afibercept)** a protein which binds with activated form of VEGF, thus inhibiting formation of abnormal new blood vessels. It is administered as injection into the eye once every 4 to 12 weeks.[18]

Adjunctive Therapies

Photodynamic Therapy

This involves laser treatment of select areas of retina. In this, a light sensitive medicine known as Visudyne is injected into bloodstream which after activation from an outside source of laser light get converted to its active form known as Verteporfin, blocks the abnormal blood vessels and seal the leaking blood vessels lining macula region. This therapy reduces central vision loss. [19]

Laser Surgery

Retinal Laser Photocoagulation is recommended when growth of abnormal blood vessels is restrained to a compact area in eye, i.e. away from central region of macula and can be easily targeted with laser. It uses an intense beam of light to burn that compacted area of retina, this burn seals the leaked blood vessels and slows down the central vision loss.[20]

Non-pharmacological management of AMD/ Dietary interventions

There are certain strategies suggested by National Eye Institute to reduce the risk of wet AMD through daily intake of high doses of certain vitamins and minerals as shown by AREDS (Age-Related Eye Disease Study). It suggests that a formulation with combination of vitamin C and E, beta-carotene, zinc, lutein and copper canslow down the progression of late AMD. It is being stated by one of the first trial conducted on AREDS formula that it reduces the chances of advanced or neovascular AMD in patients with early AMD by 25-30 percent who are given such formula containing following components[21,22]:

- 500 milligrams of vitamin C
- 400 international units of vitamin E
- 15 milligrams beta-carotene
- 80 milligrams zinc as zinc oxide
- 2 milligrams copper as cupric oxide

Further it was found that lutein, zeaxanthin and omega-3-fatty acids are also helpful in slowing the progression of macular degeneration thus a second trial, AREDS2 (Age-Related Eye Disease Study-2) was carried out. This trial explained that lutein and zeaxanthin are far better than beta-carotene so the original AREDS formula was changed. Additionally, it was also found that beta-carotene may increase the risk of lung cancer in smokers and ex-smokers as well. Based on both the trial studies, following daily formula was designed to slow down the progression of AMD:

- 500 milligrams of vitamin C
- 400 international units of vitamin E
- 10 milligrams lutein
- 2 milligrams zeaxanthin
- 25 milligrams or 80 milligrams zinc as zinc oxide
- 2 milligrams copper as cupric oxide

Regulatory Requirements for Dosage forms used in AMD treatment

Generally, the most common dosage form used for AMD patients are Pre-filled syringes which are administered via intravitreous route. In USA, USFDA regulates Pre-filled syringes as a Combination product and further define it under 21 CFR 3.2 (e) (1) as a product comprised of two or more regulated components i.e. drug/device, biologic/device, drug/biologic or drug/device/biologic that are physically, chemically or otherwise combined or mixed and produced as a single entity.[23,24] Medical device User Fee and Modernization Act, 2002, section 503 (g) mandated the FDA establish OCP (Office of Combination Products). OCP classifies combination product and assigns lead center i.e. CDER (Center for Drug Evaluation and Research), CDRH (Center for Devices and Radiological Health) or CBER (Center for Biologics Evaluation and Research) on the basis of Primary Mode of Action (PMOA) for submission of application. Regulations for cGMP of Combination product are set forth in 21 CFR part 4. However other specifications for pre-filled syringes development, USP monograph <661> is relevant.[24,27] Approval pathway is also determined by primary mode of action (NDA, BLA, PMA, 510(K)).[24,27]

In European Union, there are special rules for specific type of medical devices incorporating a medicinal product (drug or biologic). The three types of medical devices incorporated into combination products based on primary mode of action are: [25,26,27,28]

1. Devices regulated under Medical device Regulations for administration of medicines (eg. Empty single use-syringes, reusable spoons, droppers).
2. One which are not reusable that combine device and medicinal product to form a single, integral product used as a combination are regulated as per Directive 65/65/EEC. E.g. Pre-filled syringes. Such type of single product is regulated as medicinal product. However, safety and performance of such devices should comply with relevant essential requirements of Annex 1 of Medical Device Directive (MDD) 93/42/EEC. This means combination should be assessed by Drug Regulatory Authorities and Device needs to meet MDD, which is satisfied by use of CE mark. In this type, requirements of medical device should apply as far as device-related features of product are concerned, e.g. mechanical safety features of Pre-filled syringes and labelling should comply with requirement for medicinal product.
3. Devices incorporating a substance, which if used separately, may be considered as a medicinal product e.g. heparin coated catheter. In this, Notified Body assess the combination product and drug information is sent by Notified body to a Drug regulatory authority for assessing specific sections.[28,44]Market approval are conducted either through Mutual recognition or centralised or decentralised procedure depending on primary mode of action of combination.

Drivers for Age-related Macular Degeneration therapeutics market globally

One of the market reports of 2017 says that Globally, AMD market accounted for a revenue of $5,335.7 Mn in 2015 and is forecasted to grow at a CAGRof 7.6% in the coming years 2016-2022. In this forecast period, Wet form of AMD is predicted to dominate the market with faster growth. Key factors driving AMD market are increasing prevalence of hypertension, obesity and growing geriatric population. Among industrialized countries, North America is predicted to rank first in global AMD market during year 2016-2022 as this market is facing rapid increase in geriatric population thus demanding more drug treatment. After North America, European market and Asia-Pacific market are also expected to reach highest growth in AMD therapeutic market globally due to expansion in occurrence rate of different forms of AMD during forecast period. Key companies working in global AMD market include Novartis AG, F. Hoffmann-La Roche Ltd, Bayer AG, Regeneron Pharmaceutical, Inc; Acucela, Opthotech Corporation, Neurotech Pharmaceuticals Inc; GlaxoSmithKline plc, Stemcells Inc and Alimera Sciences, Inc.[29,32]

Challenges impacting the Age-related Macular Degeneration market

One of the Major restraining factors which is inhibiting the market growth is high cost of drug treatment, for instance, one single injection of Anti- VEGF agent (Eylea) for treatment of AMD costs about $1418, which means annual cost per eye for 7 injections is about $9,926. Another important factor is increasing off-label use which is hindering the market growth. High cost of drugs and treatment along with lack of trained ophthalmologists are some of the major restraining factors inhibiting the market growth over the review period. Also, strict mandates and growing off-label use are also hindering the market growth over the years. For instance, a single injection of anti-vascular endothelial growth factor agent for treating AMD costs very high.[30,31,32]

Future Approaches to AMD treatment

Inadequacy of FDA-approved medications for Dry AMD and treatment of Wet AMD requires intravitreal injections for prolonged time period are a big cause of inconvenience for patients suffering from AMD. Considering these problems, many pharmaceutical firms are taking initiatives to develop an affordable, easily accessible and convenient mode for treatment of AMD. Some of the companies are developing new molecules for an effective treatment as per details discussed in Table 2 below:

Table 2 Medications and Devices in pipeline for AMD treatment

S.no.	Manufacturer	Product	Clinical Trial Phase	Expected Completion of Study
1.	Genentech[33,34]	PortDelivery System (Device)	II	2019
2.	Novartis[35,36]	Brolucizumab	III	2019
3.	Allergan [37]	Abicipar	III	2019
4.	Regenxbio [38]	RGX-314	I	2020
5.	Graybug vision[35,39]	Sunitinib	I	2020
6.	Opthea[40]	OPT-302	II	2020
7.	Wills Eye [41]	Dorzolamide-timolol	III	2019
8.	Apellis PharmaceuticalsAPL-2[35,42]	APL-2	Ib/II	2020

According to one of the pipeline analysis report of 2018, Gene-therapy can be an emerging and efficient approach to treat Age-related Macular Degeneration. Companies covered under this report namely Retrosense Therapeutics, REGENXBIO and AGTC (Applied Genetic Technologies Corporation). This report has further space which will have an

enhance effect on target cells), Intravitreal (in which drug is administered directly into vitreous fluid). The drugs for gene therapy are in their pre-clinical development phase as per this pipeline analysis report.[43,44,45]Early detection and prevention of AMD can be a major contributing factor that can help to achieve a curtailment in Age-related Macular Degeneration population:[46]

Factors which can affect the prevention and early detection of AMD**:**

- Emphasizing the routine eye examination by an eye doctor (ophthalmologist/optometrist) i.e. individuals with eye problems must check their vision at a regular interval through Amsler grid at home or get it checked by retina specialist. People with a history of AMD need to have regular eye tests.
- Identification of biomarkers: A critical advancement in early detection of Wet AMD would be identification of blood biomarker.
- Utilizing research database: lack of adequate understanding about AMD is another reason for unsuccessful treatment of patients receiving interventions meant for AMD. Mainly two vision related electronic health registries are available for data mining in United States i.e. Vestrum Health Retina Research Dataset, which is an independent registry and IRIS (Intelligent Research in Sight) REGISTRY, which is administered by AAO (American Academy of Ophthalmology).
- Inculcating vision in National Health survey: example- NHANES (National Health and Nutrition Examination Survey).

CONCLUSION

For Age-related macular degeneration, the prominent factors associated to central vision loss must be given careful concern. The ultimate goal of an AMD research should be to develop a permanent cure for the progressive disorder at an affordable cost to the population since cost of drug treatment is very high. Moreover, the repeated administration of intravitreal injections for treatment are associated with increased risk of glaucoma, endophthalmitis, cataract, retinal detachment and choroidal or vitreous haemorrh age. So, it must be made important to develop novel drug delivery system (e.g. Gene or Cell therapy) with minimum adverse events and maximum patient compliance and those which are more targeted for retinal disorders. The action of developing a self-administrable dosage form such as eye drop, which does not require repeated doctors visit can be a good recommendation to give an effective and affordable treatment to the patient.

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