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AGE-RELATED MACULAR DEGENERATION, PHATOPHYSIOLOGY, CURRENT TREATMENT AND THERAPEUTIC PERSPECTIVES

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ABSTRACT

Age-related macular degeneration (AMD) is a disease leading to severe central vision loss and blindness in people over 60 years. [1] The pathogenesis of this disease is multifactorial and complex interactions of metabolic, functional genetic, and environmental factors - it is not fully known. [2] For the above reasons, the effectiveness of the therapies used is limited. Although the disease involves changes in the anatomical and functional complex, including photoreceptors, retinal pigment epithelium (RPE), Bruch's membrane, and choriocapillaris layer, the essence of the disorder and its earliest stage is the progressive degeneration and atrophv of the RPE cells. leadina conseauentiv to irreversible damaae to photoreceptors.
Four processes occurring within the mentioned complex contribute to the development of AMD: lipofuscinogenesis, drusogenesis, inflammation, and neovascularization. [3]

KEYWORDS

Pathophysiology of AMD Development, Neovascular AMD, Age-Related Macular Degeneration (AMD), Risk Factors of AMD

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The structure of retina

The macula is the central, posterior part of the retina. It is characterized by the highest density of photoreceptors in the retina, responsible for the sharpness and high vision resolution in the visual field's central part. Behind the photoreceptors there is the retinal pigment epithelium, it is a part of the blood-eye barrier and participates in the phagocytosis of photoreceptors, transport, and secretion of cytokines. Behind the retinal pigment epithelium is Burch's membrane– a semi-permeable barrier separating the retinal pigment layer from the choroid which supplies blood to the outer layers of the retina. [4]

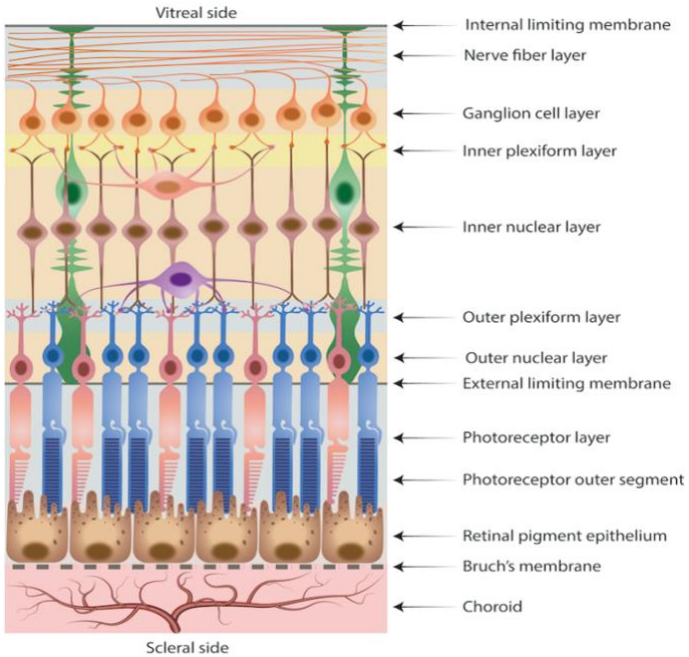

Fig. 1. *Image showing the microscopic structure of the retine. Based on - ophthalmologist R.C. Allen, R.A Harper Edra Urban & Partner*

Pathophysiology of AMD development

Neovascular AMD is a condition characterized by the formation of choroidal neovascular membranes (CNM). It's induced mostly by vascular endothelial growth factor (VEGF). [5] Vascular endothelial growth factor is a potent mitogen and permeability factor for endothelial cells and regulates angiogenesis, inflammation, and vascular maintenance. It interposes in homeostatic adaptation to hypoxic conditions by creating blood vessels. [6] The newly formed vessels create a form of "lace" vascular plate under the retina, they have thin, defective walls. Blood serum penetrates through these leaky walls and lifts the retina causing the patient to have the impression that the image is waving. When weak vessel walls burst blood spills under the retina, causing a gray or black spot in the field of vision, depending on the thickness of the hemorrhage. [7]

AMD is categorized using the WARMGS system (Wisconsin Age-Related Maculopathy Grading System). This is a very precise classification system of retinal changes based on color funds photographs. As a result, a detailed classification system was developed as part of the AREDES study. [8] [9] [10]

Table 1. AMD stage table based on – ophthalmologist R.C. Allen, R.A Harper Edra Urban & Partner

Group	stage of disease	type of changes
1	no AMD features	several small, hard drusen (diameter up to 63 µm)
2	early stage	numerous small drusen (>15 drusen) several medium ones (64-125 µm)
3	intermediate stage	numerous medium-sized drusen or at least 1 large drusen (>125 µm) or geographic atrophy.
4	advanced stage	geographic atrophy involving the fovea or any feature of neovascular AMD

The first three stages of macular degeneration according to AREDES and geographic atrophy (one of the advanced forms of this disease) is dry-type AMD. The second character is neovascular AMD. [11] Neovascular only accounts for 10% of all AMD cases. Until recently, the classification of neovascular AMD was based on the type of neovascularization visible in fluorescein angiography. The classification of wet AMD in force since 2019 is mainly based on the OCT examination. According to this classification, we distinguish the following types of neovascularization. [12]

Type 1 MNV - neovascularization originating from the circulation choroidal; abnormal vessels grow under the pigment epithelium.

Type 2 MNV - this neovascularization, also originating from the circulation choroidal; abnormal vessels grow in the space between the RPE, and the photoreceptor layer.

Type 3 MNV - neovascularization originating from the retinal circulation in deep capillary plexus (DCP), vessels grow towards the outer layers of the retina. [11] [12] [19]

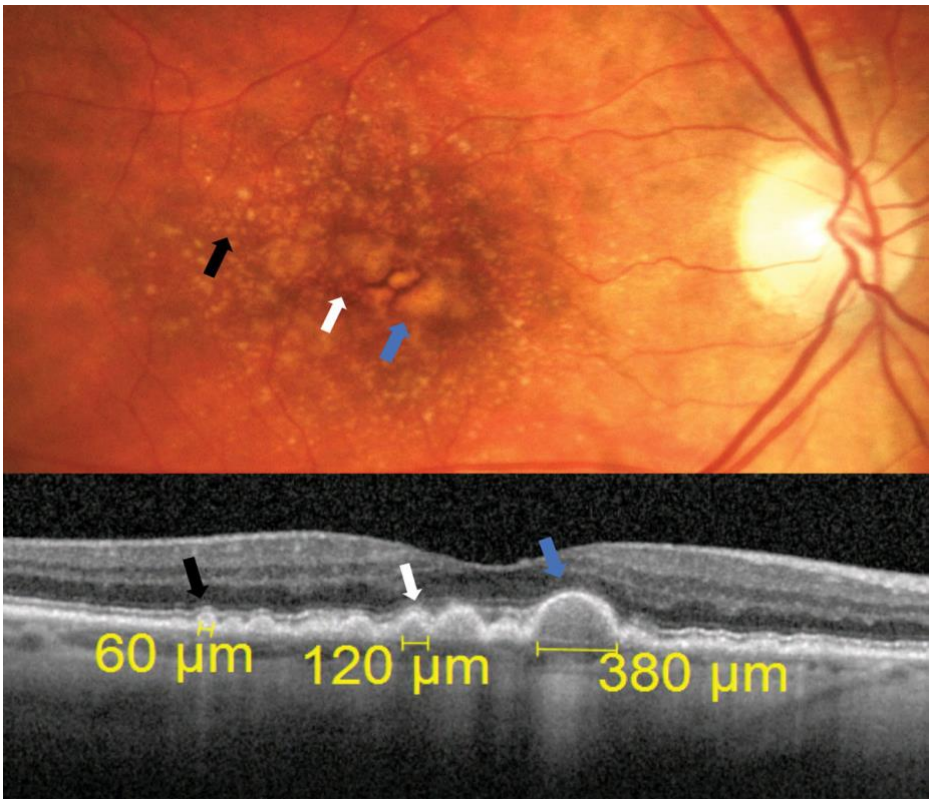

Fig. 2. *Black arrow - Small, yellow deposits of protein and lipids. White arrow - Areas of retinal pigment epithelium (RPE) atrophy. Blue arrow - Characteristic picture of AMD effusion*

Based on: „A comprehensive review on early detection of drusen patterns in age-related macular degeneration using deep learning models"

VEGF Cytokines

Vascular endothelial growth factor (VEGF) was discovered by Ferrara and Henzel in 1989. The VEGF group of cytokines includes VEGF-A, VEGF-B, -C, -D, -E, and PIGF. The common feature of these cytokines is the presence in the molecule of a fragment containing a sequence of cysteines. [13] VEGF-A is the best-known member of the VEGF; as a result of the expression of the gene located on chromosome 6 and alternative splicing VEGF-a isoforms are created. The basic biological function of VEGF is creating new blood vessels and increasing their permeability. The intensity of the biological effects of VEGF-A depends on the active isoform of the factor and its affinity for heparin. VEGF synthesis occurs in many types of body cells, including vascular cells, muscle cells, fibroblasts, and endothelial cells. [14] The interaction of the VEGF cytokine with a specific receptor activates several signaling pathways in the cell depending on the type of VEGF-R. The best-known signaling pathway has been described for VEGF-R2. The presence of VEGF induces autophosphorylation of VEGFR-2 receptor proteins, which enables the attachment of cellular proteins Shc and Grb2. These molecules forming the SOS-Rass complex, lead to the activation of the Ras-Raf-MAP cascade which is directly responsible for endothelial proliferation. [15]

Risk factors of AMD

In pathophysiology macular degeneration the main risk factor is age, with the disease being more prevalent in individuals over 60 years it is less common in younger individuals. [41] Since one of the most vital components of life is preserving one's senses, eye health is essential to a high standard of living. In older adults, one of the main causes of visual loss is age-related macular degeneration or AMD. The development of AMD, in both its dry and wet variants, is linked to several risk factors. Age is the main risk factor. The likelihood of acquiring AMD increases with age.[40] Genetics is also a major factor.[40] People who have a family history of the illness are more likely to have it. Another important risk factor is smoking.[39] AMD development is more common among smokers than in non-smokers. High blood pressure and cholesterol can

also raise the disease's risk. Dietary and lifestyle choices have an impact on AMD risk as well. AMD risk may rise with a diet heavy in saturated fats and deficient in fruits and vegetables. Another element that could play a role in the illness's onset is obesity. Furthermore, trans fat consumption and UV radiation exposure are acknowledged as risk factors. It's important to remember that dry AMD makes up the majority of cases, even though wet AMD frequently causes visual loss more quickly. The same risk factors may have an impact on both disease types. Maintaining good eye health and getting rid of or cutting back on risk factors like smoking and eating poorly can help lower the chance of AMD developing or slowing its advancement. Frequent ocular examinations are essential for the early diagnosis of the condition and the application of suitable preventive measures. [38]

Symptoms

While there are many different signs of macular degeneration, issues with central vision are the most typical. [38] Many times, patients detect distorted vision as their initial symptom. Reading and identifying faces when straight lines appear crooked could be challenging. Central vision loss deteriorates with the condition, resulting in hazy vision and challenging daily tasks like reading and detail recognition. AMD patients may also have trouble identifying colors and adjusting to changes in illumination. Low light vision is especially troublesome, and bright light may be necessary for patients to complete tasks that require visual attention. Large dark patches that appear in the central field of vision during advanced stages of the disease might severely impair one's ability to carry out daily tasks. Please keep in mind that the kind and severity of AMD can affect the symptoms. As a result, it's critical to conduct routine eye exams to identify any abnormalities as soon as possible and to put the right treatment in place. This can have a big impact on the patient's quality of life and the maintenance of visual function.[39] [40]

Diagnostics

When diagnosing dry age-related macular degeneration (AMD), the goal is to find the distinctive macula alterations connected to the illness. Using an ophthalmoscope, a clinician performs a fundus examination (fundoscopy) to determine whether drusen and pigmentary alterations are present in the macula. [40] Moreover, precise visualization of retinal structures is obtained by optical coherence tomography (OCT), which makes it easier to identify drusen and other AMD-related alterations. Another helpful diagnostic technique is fundus autofluorescence (FAF), which identifies aberrant autofluorescence patterns in the retina and may point to regions of retinal pigment epithelium dysfunction linked to dry AMD. It is also possible to evaluate functional alterations in the macula by using microperimetry, a technique that gauges retinal sensitivity to light stimuli.[40] [41]

Diagnostics for wet AMD aim to find aberrant blood vessel development under the retina. Currently, the foundation of diagnostics in many cases is angioOCT, setting clear paths for diagnosis and treatment. However, in exceptional situations where the issues become complex or ambiguous, it may be necessary to resort to fluorescein angiography. The use of indocyanine angiography, although rare, may be necessary in extreme cases, although in the context of its frequency of use, it is sometimes not even mentioned. Therefore, a better approach may be to rearrange the order of techniques discussed, starting with angioOCT, moving on to fluorescein angiography, and possibly mentioning the possibility of using ICG at the end. The precise diagnosis and evaluation of AMD progression made possible by the use of these diverse diagnostic techniques is essential for treatment planning and patient monitoring.[42]

Treatment

In therapies in wet AMD are currently approved three types of therapies: anti-VEGF preparations, photodynamic therapy, and laser photocoagulation of neovascular membranes. Due to the introduction of intravitreal therapy with anti-VEGF preparations, which provide better functional effects than PDT. A real revolution in the treatment of AMD was the introduction of preparations that inhibit the action of vascular endothelial growth factor by intravitreal injections. [19] [54]

In the VISION study, patients treated with pegaptanib lost 7 fewer letters on the ETDRS chart after one year than the control group not treated.[53] However, this drug has not yet been used more widely due to the introduction of the much more widely due to the introduction of the much more effective ranibizumab. Ranibizumab is a recombinant humanized FAB fragment of an antibody against all VEGF-A isoforms, registered for intravitreal use based on the ANCHOR and MARINA studies in 2006. [52] Ranibizumab is also the first drug that not only allowed for maintaining the initial visual acuity but also resulted in an improvement in vision by 8.1-10.7 letters after a year of therapy (intravitreal application, monthly). [51]

Pegaotanib sodium is a modified RNA oligonucleotide chain of 28 bases that binds with high affinity to the main isoform of VEGF (VEGF165). [16] Recently, the results of many randomized double-blind studies have been published which demonstrate that pegaptanib sodium (tested up to a dose of 3 mg/eye) produces a statistically significant, beneficial therapeutic effect in the treatment of AMD. An unexpected observation is that increasing the dose above 0.3 mg did not result in further improvement. In December 2004, the FDA recognized pegaptanib sodium as a drug that slows vision loss in all subtypes of wet AMD allowing the drug for commercial circulation while recommending a dose of 0.3 mg used for injections. [17] [18]

Studies show that the standard treatment of neovascular age-related macular degeneration (AMD) and diabetic macular edema is intravitreal injections of anti-VEGF drugs. Brolucizumab is used for the treatment of patients with neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME). [51] Brolucizumab is a fragment of humanized anti-VEGF antibody with a very low molecular weight of 26 kDa currently being introduced into therapy, showed similar therapeutic effectiveness to aflibercept in 50% of patients with longer intervals between drugs injections (12 weeks vs 8 weeks) The results of treatment with concept used in China, which binds VEGF-A, B and C PIGF isoforms. Researchers are also looking for other forms of treatment, independent or complementary. The effects of inhibiting other growth factors are being tested, e.g. angiopoietins (Faricimab). Analysis showed that the brolucizumab has significant visual improvement after 16 weeks of treatment, which then remains stable until the end of the first year. Brolucizumab has been effective in improving anatomical and functional parameters.[50] Long-term impacts of brolucizumab treatment include sustained visual improvement; which is a constant effect for up to 96 weeks. Inflammatory events associated with brolucizumab were mostly diagnosed within the first 6 months, but some can occur up to 18 months. 48% of the inflammatory cases associated with this treatment were diagnosed in the first 3 months of therapy. 74% of the events were diagnosed within 6 months of treatment; 12% of inflammation events occurred between 12 and 18 months after the treatment. In studies there is an estimated number of injections needed to achieve optimal outcomes - it's a range from a minimum of 5 to a maximum of 7 injections. Patients receive an average of 6.4 $\pm$0.9 IVIs of brolucizumab compared to 9.6$\pm$1.9 IVIs of other anti-VEGF.[49][48] The visual acuity remained stable during less quantity of IVIs. In the early phase of using brolucizumab side effects have been reported most often these were retinal vascular occlusions and intraocular inflammation. The medicine is given by intravitreal injection every 4 weeks for the 3 doses.[46] Then the doctor individually determines the intervals between doses depending on the activity of the disease, assessed based on visual and anatomical parameters. Analysis suggested that the disease activity should be assessed by 16 weeks after starting the treatment. In patients with an inactive disease, we should inject medicine after 12 weeks, in patients with an active disease every 8 weeks. [45]

Faricimab whose main advantage is the ability to extend the intervals between injections, without impairing the effectiveness and safety of treatment. [40] Faricimab is the bispecific antibody designed for intravitreal administration, which targets two different disease pathways - neutralization of both Ang-2 and VEGF-A by dual inhibition of ANG-2 and VEGF-a. [40] [43] This drug reduces vascular permeability, and inflammation inhibits pathological angiogenesis, and restores vessel stability. Better vascular stability is expected through the dual mechanism of action. Faricimab will provide comprehensive control of disease that will enable doctors to extend the intervals without making worse treatment effectiveness. At the same time, it is associated with less burdensome treatment regimens and patient monitoring schedules. The modern approach to the treatment of retinal diseases involves striving to reduce the frequency of drug dosing. [43] Faricimab can be used significantly for doses by increasing the intervals between subsequent administrations of the drug and the frequency of administration was reduced without affecting the deterioration of benefits obtained by patients. In patients with nAMD in 48 and 60 weeks almost 80% of patients achieved dosing every 12 weeks or less. A lower frequency of drug injections translated directly into a high degree of compliance with treatment by patients and consequently, limited the negative effects of discontinuation of treatment. However, meta-analysis did not demonstrate the superiority of faricimab over brolucizumab for the longest observation period. [42] [40]

Bevacizumab (Avastin) is a recombinant humanized anti-VEGF monoclonal antibody with a molecular weight of 149 kDa. The recommended dose of Avastin is up to 5 mg/kg body weight once every two weeks as a main injection. [54] Bevacizumab was also tested at a dose of 5 mg/kg i.v. in patients with exudative AMD and CNV secondary to pathological myopia with the possibility of using the effect (increasing visual acuity and reducing exudate form of CNV). [53] Recent results of trials using bevacizumab (Avastin) at a dose of 1 mg or 1.25mg directly to the results of medical supervision are promising. Bevacizumab has not been used as a drug for the treatment of ocular diseases, but it is available on the pharmaceutical market and can therefore

be used in treatment on an off-label basis. Currently available Avastin (25 mg/ml) can be used in patients with wet AMD as a ready-to-use solution at 50 µl/eye, equivalent to 1.25 mg per application. [52]

Qualification for treatment

There are multiple crucial processes involved in becoming eligible for therapy with anti-VEGF for AMD. First and foremost, thorough eye exams that involve fundus examinations, OCT imaging, angioOCT, and maybe fluorescein angiography are necessary to confirm the diagnosis of AMD. Finding the existence of active wet AMD becomes the main priority after the diagnosis has been made. Imaging studies can confirm this since it is characterized by aberrant blood vessel growth beneath the retina, which causes fluid leakage and may lead to bleeding. Determining the disease's severity is another essential component. This entails assessing the macula's lesions' size, location, and any related vision loss. Additionally, the disease's stability is a major factor. Doctors need to know if AMD is stable or actively advancing because this will affect the course of treatment. It's also critical to take the patient's general health into account. Comorbidities and overall health may have an impact on treatment choices and possible results. The doctor decides whether or not the patient is eligible for anti-VEGF therapy after taking all of these variables into account. Effective management of AMD requires routine monitoring of the disease's progression and the response to treatment. Although photodynamic treatment (PDT) was once widely used, its significance has decreased with the introduction of intravitreal anti-VEGF therapy. PDT is still an effective treatment option, nevertheless, especially for polypoidal choroidal vasculopathy (PCV) and other types of wet AMD that are not responsive to monotherapy, or where anti-VEGF medication is contraindicated. [42,43,40,45,47]

Prevention

Maintaining a healthy lifestyle and taking preventative action is crucial to lowering the risk of age-related macular degeneration (AMD).[46] Overall eye health depends on quitting smoking, maintaining a balanced diet full of fruits, vegetables, and fish that contain omega-3 fatty acids, and engaging in regular physical activity. Furthermore, routine eye exams, such as fundus exams, make it possible to identify any changes connected to AMD early on and start the right treatment right away. It is equally crucial to protect the eyes from damaging UV rays. Retinal damage can be prevented in part by donning a hat and sunglasses with appropriate UV protection. Preventing AMD also requires managing risk factors like diabetes, high blood pressure, obesity, and high cholesterol. The probability that a disease may manifest can be decreased by routinely monitoring these risk factors and treating them as necessary. In the AREDS 2 studies, the composition of dietary supplements was developed which, in certain stages of the disease, can reduce the risk of progression to advanced disease. This risk is reduced by approximately 25% in people with moderate disease in both eyes or moderate disease in one eye and advanced disease in the other eye. The current AREDS 2 formula is 500 mg of vitamin C, 400 IU. vitamin E, 10 mg lutein, 2 mg zeaxanthin, 80 mg zinc, and 2 mg copper taken daily.[50,51] While there is no complete prevention for AMD, these preventive steps can greatly lower the incidence of AMD or slow the disease's progression. As a result, those who are more susceptible to AMD—such as elderly people and those with a family history of the condition—must regularly follow these preventive guidelines. It is always advisable to speak with an ophthalmologist if you have any questions or concerns about preventing AMD. [50]

Conclusions, questions, and perspectives

In planing a therapeutic strategy, patients comfort should be considered but the main points to consider are safety and efficacy. Anti-VEGF treatment in wet AMD can not be completely efficient, VEGFA is the key regulator of normal and pathological angiogenesis, but it is not the only factor responsible for neovascularization in wet AMD. [48] [49]

The introduction of anti-VEFG treatment in wet AMD revolutionized the therapy of this disease, but this treatment, in most cases does not cure the wet AMD, it mainly stops the progression of the disease, preventing or delaying sight loss. However, therapy, which is characterized by lifetime intravitreal injections every 8 to 12 weeks after three monthly loading doses with relatively expensive substances, constitutes a serious burden for the patient. [49]

In essence, there is no cure for this illness. We must settle for slowing down the progression of the disease. Nevertheless, gene therapy is under investigation and is displaying encouraging outcomes. [50]

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