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Scientific understanding of advanced therapeutic strategies for nonexudative age-related macular degeneration in 2025

Hanna Wołodkiewicz[1], Marta Wolszczak[1], Grzegorz Gruba[2], Joanna Przybek-Skrzypecka[2], Michał Post[2], Jacek P. Szaflik[2], Justyna Izdebska[2]

[1] Member of Ophthalmological Student Organization in Independent Public Teaching Ophthalmological Hospital SPKSO, Faculty of Medicine, Medical University of Warsaw
Head: prof. Jacek P. Szaflik, MD, PhD

[2] Department and Clinic of Ophthalmology, Medical University of Warsaw, Independent Public Teaching Ophthalmological Hospital SPKSO
Head: prof. Jacek P. Szaflik, MD, PhD

HIGHLIGHTS

This review provides an update on prospective treatment options for the management of dry AMD and preventing the progression of geographic atrophy.

ABSTRACT

Age-related macular degeneration is one of the most common causes of severe vision loss in the developed world. Advanced forms of age-related macular degeneration are seen in primarily 2 types, exudative type involving the presence of choroidal neovascularization, and nonexudative age-related macular degeneration with geographic atrophy. The more prevalent form of age-related macular degeneration is nonexudative type, yet with less definitive treatment options. The emergence of anti-VEGF has revolutionized the treatment of exudative type. For nonexudative age-related macular degeneration, vitamins and minerals supplementation known as the AREDS 2 formulation remains a primary care strategy. Recently, two intravitreal anti-complement factors have been approved as a novel treatment – pegcetacoplan and avacincaptad pegol. Many other therapeutic pathways are still being investigated, including stem cell therapy, gene therapy, laser treatment, photobiomodulation, neuroprotective and antioxidant agents, and also surgical options. In this review, we provide an update on prospective treatment options for the management of nonexudative age-related macular degeneration and preventing the progression of geographic atrophy.

Key words: age-related macular degeneration, non-exudative age-related macular degeneration, dry AMD, geographic atrophy, complement pathway inhibitors, visual cycle modulators

INTRODUCTION

Age-related macular degeneration (AMD) is one of the leading causes of irreversible vision loss in developed countries [1]. It is a degenerative retinal disease that causes macular aging and deterioration, which has consequences in the loss of central vision [2]. AMD damages the outer retina, which contains the retinal pigment epithelium (RPE), Bruch membrane, the choriocapillaris, and the underlying choroid [3]. In the course of this disease, there is an accumulation of retinal deposits, called drusen, which are inextricably linked to this disease and may be its first symptom. In the nonexudative type, which is called dry AMD, atrophic scars form in the macula, taking the form of geographic atrophy (GA). Dry AMD is the most common type of this disease, but in many cases, it can progress to wet AMD, with a much worse prognosis. In this neovascular form of AMD, new vessels and central choroidal neovascular membranes (CNV) are formed, which can lead to bleeding and exudation, destroying the macula. Currently, no treatment would completely cure AMD and reverse all of the lesions. The only available therapies allow for slowing down the progression of the disease. For this reason, the search for innovative therapy for AMD in recent years has been very intensive. However, this is a difficult task, because the pathogenesis regarding the progression of the disease has not been fully discovered [4].

METHODS

A retrospective review of the literature from PubMed (1984–2025).

EPIDEMIOLOGY AND CLINICAL SIGNIFICANCE

With the population aging worldwide, AMD is a leading cause of severe, irreversible vision loss worldwide, affecting 10–20% of adults over age 65, with 288 million individuals expected to be affected by 2040 globally [5, 6]. The rising prevalence figures may also be due to better ascertainment through improved diagnosis [7]. The annual incidence for late AMD stage is 0.5 cases per 1000 individuals under 70, and 6.7 cases per 1000 individuals over 70 years old. In addition, this prevalence is higher in women than in men [8]. Nowadays, AMD affects more than 50% of people over 80 worldwide [4]. Dry AMD accounts for almost 80–85% of all cases and generally carries a more favorable visual prognosis. Neovascular AMD affects the remaining 15–20% and is associated with a much worse prognosis and more frequent vision loss [4, 9]. The strongest risk factor for developing AMD is aging, but smoking, elevated body-mass index (BMI), cardiovascular disease, and hyperlipidemia also play significant roles. Additionally, factors such as lifestyle or race can influence the risk [1, 3]. AMD prevalence is highest among Caucasians compared to Asians, Hispanics, and Africans [5].

STAGES OF DRY AMD – EARLY, INTERMEDIATE, AND ADVANCED

However, AMD is the most common eye disease, and it covers different types of lesions affecting the macula [4]. AMD is defined by the deposition of focal yellow extracellular deposits known as 'drusen.' The presence of macular drusen may be the first sign of the dry form of the disease, and patients may often be asymptomatic [3]. There are 4 stages of AMD:

1. First stage includes the usual changes associated with aging, namely drusen <63 μm in diameter and no pigment abnormalities.
2. Second stage (early AMD) includes intermediate drusen with a diameter of 63–124 μm, but still without RPE cell abnormalities.
3. Third stage (intermediate AMD) includes extensive, moderate, at least one large drusen (diameter 125 μm) and RPE abnormalities.
4. Fourth stage (advanced AMD) is synonymous with the development of a disciform scar of the fovea (geographic atrophy GA) or any neovascular degeneration of the macula, causing vision loss.

In early AMD, visual impairment is mild, characterized by difficulty in reading and a black spot in the central field of vision. In intermediate AMD, large or moderate vitreous wart membranes or imperfect pigmentation with significantly affected central vision may occur [1]. Clinically, advanced AMD is divided into two types – dry AMD and wet AMD. Dry AMD is characterized by confluent atrophy of photoreceptors, RPE, and choriocapillaris, which is also known as GA. Dry AMD causes impaired vision, disordered macular pigmentation in both eyes and the disappearance of the foveal reflex. Atrophic changes cause loss of outer retinal tissue and the surrounding vascular network, specifically the RPE layer, Bruch membrane, and the choriocapillaris, with the occurrence of yellowish-white drusen between Bruch's membrane (BrM) and RPE [1, 3, 10]. If retinal neovascularization occurs, leading to the formation of a CNV membrane, we classify it as wet AMD [2]. At some point throughout the disease course, for all forms of dry AMD, there is a 10–15% risk of progression to wet AMD. Interestingly, both atrophic and neovascular features can sometimes coexist, as wet (neovascular) AMD may develop into GA, and vice versa. [3, 11].

DIAGNOSTIC EVALUATION OF DRY AMD

Diagnosis of the dry form is based on a general interview (risk factors) and an ophthalmological examination, assessment of best corrected visual acuity (BCVA), examination of the fundus of the eye after dilating the pupils with possible extension of the examination by fundus imaging, fluorescein angiography (FA), indocyanine green angiography (ICGA), optical coherence tomography (OCT), optical coherence

tomography angiography (OCTA) and artificial intelligence (AI). Fundus imaging techniques, such as color and monochromatic photography, autofluorescence, and angiography, are valuable for diagnosing AMD. Microperimetry is a non-invasive test that evaluates central visual field defects and fixation, offering advantages like real-time imaging and eye tracking compared to standard perimetry. Each of these techniques has its advantages and is used to monitor the retina, RPE, and choroid morphological changes [1]. The test that allows for self-diagnosis and monitoring of the disease progression is the Amsler test. The visual acuity can also be evaluated using the ETDRS scale score (Early Treatment Diabetic Retinopathy Study) [4]. During the examination of the fundus, in the context of AMD, the ophthalmologist will evaluate the macula for deposits of drusen, pigmentary changes, GA, hemorrhage, fluid, exudate, scar formation, and fibrosis. Attention is given to the size, number, and distribution of drusen [3, 12].

DIETARY AND LIFESTYLE MODIFICATIONS

The primary therapeutic measure for treating dry AMD remains vitamin supplementation as established by the AREDS 2 protocol. The initial formula proposed by AREDS 1 had to be altered because of the content of β-carotene, which was linked to the prevalence of lung cancer in smokers. In AREDS 2 β-carotene was replaced with lutein (10 mg) and zeaxanthin (2 mg). The protocol also comprises vitamin C (400 mg), vitamin E (400 IU), copper (2 mg), and zinc (80 mg). Those compounds indicate a 25% decrease in progression to advanced AMD. The implemented AREDS 2 protocol is the most effective in treating patients with intermediate AMD or early AMD in one eye and advanced AMD in the other. However, the protocol is not recommended for patients with early-stage dry AMD in both eyes or as a measure of prophylaxis. Neither was it beneficial for patients presented only with a family history without a qualifying diagnosis. All patients are advised to adopt lifestyle changes, among which the most significant are smoking cessation and increased intake of antioxidant-rich foods, omega-3 and omega-6 fatty acids. Evidence on UV's role in AMD is contradictory, but avoiding the sun can be a possible precaution [3].

COMPLEMENT PATHWAY INHIBITOR

The first drug ever officially accepted for therapy for GA is intravitreal pegcetacoplan (Syfovre), which was approved as such in February 2023 by the FDA. Pegcetacoplan course of action is based on inhibiting the C3 complement pathway by binding to C3 and its cleavage product C3b, preventing it from being split into C3a/C3b. The C3 protein holds a key role in the activation of the 3 complement pathways, making it an important target for the potential treatment of AMD. As a result of halting the excessive complement activation, retinal tissue is protected from inflammatory damage, which plays a crucial role in slowing down and potentially limiting the progression of GA. Syfovre was investigated in two phase III studies – OAKS and DERBY over 24 months. Both studies involved a total of 1258 patients with GA, at first, they were randomized to four groups in a 2 : 2 : 1 : 1 ratio. Some patients received pegcetacoplan monthly (n = 419) and every other month (n = 420). Sham groups had 208 and 211 participants. Both OAKS and DERBY trials demonstrated reduced GA lesion growth with pegcetacoplan compared to placebo. After the initial 6 months of treatment, GA lesion growth was reduced by a mean of 12–13%, efficacy increased with time after 18–24 months, showing a reduction of GA lesions by a mean of 24–30% with more favorable effects connected to monthly dosage. Pegcetacoplan is usually administered as an intravitreal injection every 25–60 days. The recommended dosage is 0.1 mL which contains 15 mg of pegcetacoplan. The most experienced adverse reactions were eye discomfort reported by 13% of patients, floaters (~10%), vitreous detachment (4–6%), and redness/swelling of the eye (8%). Another notable side effect is progression to wet AMD experienced by 12 % of patients, as vision distortion and deterioration [13]. Avacincaptad pegol (Izervay™, formerly Zimura) exhibits a different approach to inhibiting complement pathways that was also recently approved by the Food and Drug Administration (FDA). It is an anti-C5 aptamer binding to the complement protein C5 and halting its cleavage into C5a and C5b. Firstly, the GATHER1 trial (phase II/III) enrolled 286 participants with GA secondary to AMD in a double-masked trial using 2 mg/0.1 mL and 4 mg as two separate injections of avacincaptad pegol. Patients were reviewed at 12 and 18 months. Outcomes were similar in both 2 mg and 4 mg cohorts showing a reduction in GA growth rate by 27.4% (p = 0.0072) and 27.8% (p = 0.0051) respectively. Also, the prevalence of choroidal neovascular membrane did not seem to be dose-dependent, occurring in 9% of cases for the 2 mg cohort vs. 9.6% (4 mg). After 18 months, the decrease in GA growth rate remained similar to outcomes at 12 months, showing 28.1% (2 mg) vs. 29.9% (4 mg) of reduction. In that study, the treatment exhibited minimal adverse effects, mostly associated with the injection procedure. BCVA and low luminance BCVA remained unaltered. Less favorable outcomes were presented in GATHER2 trial (phase III) which enrolled 448 patients demonstrating a 14.3% reduction in the mean rate of GA growth with 2 mg avacincaptad pegol compared to placebo (p = 0.0064) at the 12-month assessment [14]. Due to the lack of effects on BCVA, the European Medicines Agency (EMA) decided against authorisation of marketing for both drugs in Europe [15]. An additional reason against pegacetacoplan is a high risk of inflammation, vasculitis, and nonarteritic ischemic optic neuropathy (NAION), which

happens more often when using pegcetacoplan than with avacincaptad pegol [16].

REGENERATIVE THERAPIES

Stem cell therapy

Stem cell therapy has the potential to reverse the degeneration of the retina. Stem cells can be administered in many ways, including intravenous, subtenon, retrobulbar, and subretinal injections. Sources may vary from human embryonic stem cells (MA09-hRPE), pluripotent stem cells (iPSC) taken from the patient, and also the patient's bone marrow-derived stem cells (BMSCs). These therapeutic approaches can be categorized into two groups, one can help regenerate retinal cells, and another can transfer trophic factors to deter retinal and RPE atrophy [17–20].

MA09-hRPE

MA09-hRPE is designed to regenerate retinal cells via subretinal transplantation.

A completed phase I/II safety and tolerability study (NCT01344993) was followed by a long-term follow-up study (NCT02463344) [17, 21]. 13 participants diagnosed with dry AMD obtained different doses of MAO9-hRPE cells based on their vision loss from 50,000 up to 200,000 cell transplants. In a preliminary report, no signs of hyperproliferation, abnormal growth, or immune-mediated transplant rejection were identified [21]. Findings show an increase in general and peripheral vision, near and distance activities in vision-related quality of life, improving by 16–25 points 3–12 months after transplantation [17]. Ocular treatment-emergent adverse events were experienced by 36.4% of patients [17].

iPSC-derived RPE

Currently iPSC-derived RPE is in progress of a phase I/II study (NCT04339764). This approach is based on reprogramming a patient's somatic cells into iPSCs and then differentiating them into RPE cells. Inserted subretinally iPSC-derived RPE are meant to regenerate retinal cells in patients with GA. The most important factors considering the scaffold of iPSC-derived RPE grown on poly(lactic-co-glycolic acid) (PLGA) are proper thickness to avoid altering the eye's focal length, transient mechanical stability to withstand implantation, flexibility to accommodate the eye's curvature. The trial is currently recruiting and is expected to conclude by May 2029 [18].

Bone marrow-derived stem cells

Both SCOTS I and SCOTS II investigated the usage of bone marrow-derived stem cells for various retinal and optic nerve disorders. BMSCs were harvested from the posterior pelvis and processed to form an autologous stem cell concentrate [19]. CD133 progenitor cells can differentiate into RPE-like cells and support visual function recovery [22]. SCOTS II involved 32 eyes in the macular degeneration subgroup. Promising results were obtained in 20 eyes (63%) showing a mean visual acuity improvement of 27.6% (logMAR), $p < 0.001$. No treatment-emergent adverse events were reported, which may indicate a favorable safety profile [20].

Gene therapy

The main focus in gene therapy for dry AMD is to inhibit the expression of complementary pathways and therefore slow or ultimately halt the progression of GA. The most broadly studied gene therapy for dry AMD is GT005 undergoing several clinical trials. GT005 is delivered via AAV2 – virus vector and administered as a surgical treatment – transvitreal subretinal injection intended as a one-time treatment. GT005 is supposed to induce the expression of complement factor I (CFI) resulting in downregulation of the alternative complement pathway [14]. Overactivation of the complement pathway leads to the formation of the membrane attack complex (MAC) located on the cell surface, which can promote tissue damage and atrophy as a part of GA progression. The initial trial on GT005 showed a positive safety profile (focus trial), and further studies focused on selected patients by genotype (explore trial) or broader GA populations (horizon trial). Another gene therapy is HMR-1001 trial, also reducing MAC – driven retinal damage by increasing sCD59. High doses showed a slower GA progression rate in comparison to controls. The safety profile was satisfactory, no dose-limiting toxicity or conversion to nAMD was reported [22]. HMR-1001 in comparison to GT005 could be more acceptable by patients, because it requires a single intravitreal dose [14].

LASER AND LIGHT THERAPIES

The main focus of laser therapy is to slow down or preferably stop the progression of early-stage dry AMD to GA. The biggest advantage of that therapy is that it provides a non-invasive treatment option, lessening the risk of surgical treatments. Currently, several types of laser are being tested with 3 of them at the Centre for Eye Research Australia (CERA) [14]. The LEAD study focuses on using a 2RT subthreshold nanosecond laser (SNL) for patients with bilateral large drusen (>125 μm) and no signs of atrophy on OCT. The study was a randomized controlled clinical trial with 292 participants randomly assigned to 2RT laser or sham treatment at 6 monthly intervals. At first the 2RT laser did not present a significant lessening of the progression to GA compared with sham treatment ($p = 0.122$), but post hoc analysis showed a modified effect by reticular pseudodrus-

en (RPD). For participants without RPD at baseline (76% of participants) 2RT slowed the progression rate to dry AMD with a statistical significance of p = 0.002. However, in the case of participants with RPD at baseline (24.0% of participants) 2RT laser was associated with an increased progression rate, but not statistically significant (p = 0.122). The safety profile in both groups was satisfactory [23]. A different laser modality investigated was the Pascal Synthesis 577 system. In that study, 20 patients with iRPD secondary to dry AMD were treated with a yellow subthreshold laser over a 1.27 mm^2 extrafoveal area. The treatment showed a significant decrease in RPD distribution in stage 3 (p = 0.020), but also a significant increase in stage 1 (p = 0.002). Anatomical improvement was mainly associated with an increase in outer nuclear layer (ONL) thickness (p <0.001) suggesting disease regression rather than progression. A comparison of untreated areas indicates no changes in RPD stages or ONL thickness, reinforcing the effectiveness of this laser treatment. There was no alteration in BCVA and fixation stability. The treatment demonstrated favorable tolerability with no significant retinal damage, visual loss, or adverse effects during the 3-month follow-up. However, the primary limitation of this study is the small sample size and short follow-up period [24]. A separate course in photonic interventions is photobiomodulation (PBM). PBM exerts its effect by increasing mitochondrial function, reducing oxidative damage, and decreasing complement activation, ultimately leading to limitation in apoptosis. Two clinical trials took place, TORPA 1/2 and LIGHTSIGHT I/II/III. TORPA 1 focused on treating patients (18 eyes) with dry AMD in grade 2–4 AREDS. Patients initially presented with visual acuity between 6/6 and 6/60 and with the treatment managed to improve from 0.25 to 0.13 logMAR at 12 months. Those initial results encouraged expansion into TORPA 2 study [14]. TORPA 2 included 42 eyes from 24 patients grade 2–4 AREDS to whom PBM was implemented using yellow (590 nm), red (670 nm), and near-infrared (790 nm) wavelengths. Treatment was administered over a 3-week course and each eye received 9 treatment sessions. Functional outcomes presented improved BCVA by a mean of 5.9 letters post-treatment (p <0.001), sustained at 5.14 letters after 3 months (p <0.001). Furthermore, an increase in contrast sensitivity was significant at 3.0 and 6.0 cycles per degree levels (p = 0.02 and p = 0.003, respectively). Anatomical outcomes indicate reductions in drusen volume (mean decrease of 0.024 mm^3 post-treatment, p <0.001) and central drusen thickness (mean decrease of 3.78 μm, p <0.001). Concerning adverse events, PBM revealed no progression to GA progression or choroidal neovascularization (CNV) during 3-month follow-up, also retinal volume and thickness remained stable [25]. LIGHTSIGHT III was a double-masked, randomized, sham-controlled trial with 148 treated eyes. A series of 9 sessions over 3 to 5 weeks every 4 months over 24 months of multiwavelength PBM treatment was delivered to the patients using 590 nm, 660 nm, and 850 nm wavelengths. The primary effect was an improvement in BCVA in the range of 5.4 letters compared to 3.0 in the sham group (p = 0.02) meaning that approximately 55% of PBM-treated eyes gained ≥5 letters, compared to 41% in the sham group. New-onset GA was notably lessened in comparison to sham at the degree of 1.1% vs. 10% respectively (p = 0.024). Moreover, a hallmark of AMD progression, macular drusen stayed constant in the treated group in opposition to the sham group where it increased [26]. Functional improvements in visual acuity coupled with no GA progression, support PBM as a promising non-invasive treatment for dry AMD [25, 26].

NEUROPROTECTION AND ANTIOXIDANTS

Another promising field of research focuses on substances that act as neuroprotectors. Neuroprotective factors preserve RPE and photoreceptor cells from oxidative stress damage [4, 27]. Success in this domain offers hope for reducing GA-related apoptosis [14]. Substances whose neuroprotective effects are being investigated are brimonidine tartrate, tandospirone, risuteganib, and ciliary neurotrophic factor [4, 14]. Brimonidine tartrate (Alphaganâ), developed by Allergan, Inc. (Dublin, Ireland), is a small-sized 2-adrenergic receptor agonist [4, 28]. Brimonidine is commonly used in the treatment of ocular hypertension and glaucoma [14], as it is reported to reduce intraocular pressure (IOP) [4, 29]. In addition, this drug stimulates the secretion of neurotrophins such as BDNF (brain-derived neurotrophic factor), CNTF, and b-FGF (basic fibroblast growth factor) [30]. Clinical trials (NCT00658619, 2008–2018) have proven that injecting 200 μg or 400 μg of brimonidine as an intravitreal biodegradable implant for 24 months, resulted in a decrease in GA lesions size, especially the larger ones [31, 32]. In the BEACON study (NCT02087085, 2014–2019), the implant was administered every 3 months up to the 21st month, also showing a reduction in GA lesions [33, 34]. Tandospirone (AL-8309B, Sedielâ), developed by Alcon Laboratories, Inc. (Geneva, Switzerland) is a 1A serotonin agonist that has both antioxidant and antidepressant effects [27]. Since tandospirone slows down the activation of microglia and the complement system in the outer retina, it protects RPE cells and photoreceptors against oxidative stress and prevents apoptosis of retinal cells [35]. In the phase 3 study (GATE, NCT00890097, 2009–2014), where it was administered as eye drops, although it turned out to be safe, no beneficial effect on GA lesions was proven [36, 37]. Risuteganib (ALG-1001, Luminate) is a small pseudopeptide targeting heterodimers involved in angiogenesis, vascular leakage, and inflammation. Therefore, it has a protective effect on the RPE [4, 14]. In a phase II clinical trial (NCT03626636,

Allegro Ophthalmics, San Juan Capistrano, CA) [38] groups receiving 1.0 mg risuteganib injected intravitreally, instead of placebo showed improvement in BCVA, color vision metrics and mesopic microperimetry. The only ocular treatment-related adverse event was vitreous floaters, which resolved [14, 39, 40]. However, there has been no update since 2020. Another molecule that has a protective effect on photoreceptors and RPE is IL-6 type cytokine – CNFT (developed by Neurotech Pharmaceuticals, Cumberland, RI, USA) [4, 41, 42]. In humans, CNTF shows a delay in the symptoms' aggravation of neurodegenerative diseases. Moreover, in animals suffering from RPE, it has been proven to slow down the degradation of the retina. A phase II study (NCT00447954, 2007–2016) examining the efficacy of a polymer implant containing CNFT, revealed positive pharmacokinetic results [4, 43]. Oxidative stress and mitochondrial dysfunction lead to RPE damage and photoreceptors' apoptosis resulting in exacerbation of dry AMD. For this reason, substances that interfere with reactive oxygen species (ROS) production, or have antioxidant properties are being tested [4, 44]. An example of a substance, that may act as an antioxidant and anti-inflammatory factor, is OT-551 (Othera Pharmaceuticals; Exton, PA, USA), which was well tolerated in 2 promising phase 2 clinical trials (NCT00306488, 2006–2011; OMEGA, NCT00485394, 2007–2010), but has not been proven to have a positive effect on visual acuity and reduction of AMD markers such as (lesions size, retinal sensitivity, and drusen area). Yet, its strength is that administered in the form of eye drops, it has a great ability to penetrate the cornea, which allows it to reach the macula [45–49].

SURGICAL OPTIONS

Submacular surgery and surgical excision of neovascular lesions were initially considered as a therapeutic option, but studies did not demonstrate their benefits and proved an increased risk of surgical complications [3, 14]. At this point, surgical options for GA management include the PRIMA Bionic Vision System, SING-IMT implant, and the OcuDyne neurointerventional treatment.

The PRIMA vision system is a wireless photovoltaic retinal implant. Thanks to the built-in camera, the implant receives infrared light and then stimulates the retinal nerve cells. A PRIMA feasibility study (PRIMA-FS) showed that the implant can generate white–yellow prosthetic visual patterns with adjustable brightness in the area of atrophy, but the final results turned out to be below the expected level [50, 51]. Currently, two further studies are being conducted (PRIMAvera, PRIMA-FS-US) [52, 53].

Another innovative idea is SING-IMT implant (VisionCare, Inc.). It works on the principle of a telescope that enlarges images in the patient's central visual field, while the peripheral field is reduced [14, 54]. During the CONCERTO study, which is currently recruiting patients, the implantation of the SING-IMT can be performed, during extracapsular cataract removal, which takes a total of 45 min. Primary results showed improvement in visual acuity and preservation of endothelial cell density at safe levels [2, 34, 35].

OcuDyne system is a neurointerventional treatment for AMD [14], which improves ocular perfusion, by acting intravascularly on the ophthalmic artery. Better blood supply inhibits complement activation and slows down the progression of macular degeneration [14, 55]. The NCT05091476 clinical trial for this method was scheduled to end in 2024, but there have been no updates since August 2023 [56].

NEW DIRECTIONS AND EARLY-STAGE RESEARCH

The visual cycle consists of the regeneration of the retinal-11-cis from its all-trans isomer, thanks to a succession of enzymatic reactions occurring in the photoreceptor cells and in the RPE cells. The precise turnover of the visual cycle is deeply altered in atrophic AMD patients. Visual cycle modulators, which are various forms and derivatives of vitamin A, are currently a researched therapeutic option for patients suffering from dry AMD. An example of 5 substances that have been developed to improve the functioning of the visual cycle is: emixustat or ACU-4429, CU239, fenretinide, A1120, and ALK-001. All of them are administered in the form of oral tablets [4, 14].

Eximustat or ACU-4429 inhibits the conversion of all-trans retinyl ester into 11-cis-retinol catalyzed by RPE65 [4, 57]. In a clinical trial (SEATTLE, NCT01802866, 2013–2017) patients were administered the drug at doses of 2.5–10 mg for 24 months, however, regardless of the dose, the development of GA was not inhibited by the drug [4, 58, 59]. In 2018, a new compound CU239 was identified to inhibit RPE65 as emixustat [4, 60].

Fenretinide, which mimics vitamin A, in a phase 2 study (NCT00429936, 2007–2010), was administered to patients with atrophic AMD at doses of 100 mg for 24 months. This study showed a slowdown in the growth of GA lesions and a decrease in neovascularization, suggesting that fenretinide may inhibit the conversion of dry AMD to wet AMD [4, 61]. A1120 is a small molecule that, thanks to its action on the visual cycle, induces retinol conformational changes and leads to the blockade of lipofuscin formation in an Abca4 mouse model [62]. Due to the poor human liver microsome (HLM) stability of A1120, several new antagonists have been designed and can be a promising oral treatment for atrophic AMD [63].

ALK-001 is a modified form of vitamin A that is designed to reduce the dimerization of vitamin A. This process decreases the accumulation of toxic byproducts [64]. ALK-001 was primarily developed by Alkeus Pharmaceuticals, Inc. (Boston, MA, USA) to slow down or stop vision loss in atrophic AMD

and Stargardt disease [65]. A phase 2/3 study is currently being conducted (SAGA trial, NCT03845582, Alkeus Pharmaceuticals) evaluating the efficacy and safety of ALK-001 in participants with GA secondary to AMD. ALK-001, taken once a day as a capsule, replaces natural vitamin A in the body with one that forms vitamin A dimers more slowly [66]. Research also targets mitochondrial enhancers. An example of such a substance is elamipretide (also known as MTP-131 or Bendavia) which is administered subcutaneously [14]. This drug protects cardiolipin and has a protective effect on mitochondrial cristae. Animal models have proven that elamipretide can reverse mitochondrial dysfunction [67]. A study that has been assessing the impact of elamipretide on patients with dry AMD and non-central GA or high-risk drusen is the ReCLAIM study (NCT03845582) [68].

CONCLUSION

Many new strategies are emerging in the management of dry AMD, but, to this date, the AREDS 2 protocol remains a paradigm in treatment of this disease [3]. Two new drugs – pegcetacoplan and avacincaptad pegol were recently approved by the FDA that showed a reduction in GA growth over 24 months of administration. However, no improvement in BCVA and a questionable safety profile inclined EMA to decide against authorization of marketing for both drugs in Europe. Inhibition of complement pathways is a promising strategy in mitigating AMD progression, but there is still a dire need for larger population trials assessing the risk of endophthalmitis, intraocular inflammation, and secondary macular neovascularization [13, 15]. Nowadays stem cell therapy for dry AMD comprises two main strategies, which are regeneration of retinal cells and transfer of trophic factors to prevent retinal and RPE atrophy, that can be achieved through MA09-hRPE compound. Also, bone marrow-derived stem cells have shown encouraging results improving general and peripheral vision. Those agents are still in research to ensure their efficacy [21]. Nowadays, gene therapy in dry AMD therapy works through inhibition of the complement pathway expression. Two main agents showed optimistic results with high doses limiting GA progression in comparison to the control groups. HMR-1001 therapy with HMR-1001 may be more acceptable by patients than GT005 as it requires a single intravitreal dose. Satisfactory safety profile and its effect advocate in favor of those treatments, yet more research is needed to confirm these results [14]. Laser therapy provides a non-invasive alternative, limiting the potential risks associated with surgery. Many different laser modalities were tested, but 2RT and the Pascal system, and PBM exhibited the most promising effects. PBM especially resulted in enhancement of visual function and stability, additionally reducing GA onset [23]. Neuroprotective approach aims to minimize oxidative stress damage, which is linked to GA-related apoptosis in dry AMD. Some agents like brimonidine tartrate and risuteganib have shown optimistic results in clinical trials, others such as tandospirone and OT-551 require further investigation to establish their efficacy [4, 14]. Current surgical options have displayed ambiguous effects. Trials like PRIMAvera, PRIMA-FS-US, are still ongoing. However, CONCERTO study shows promising results with improved visual acuity and preservation of endothelial cell density. It is essential to fully determine the long-term safety and effectiveness, so that further analysis is required [50–54]. The main approaches depicted in early-stage research are visual cycle modulators and mitochondrial enhancers. Various forms and derivatives of vitamin A can potentially improve visual cycle function, which malfunction is linked to dry AMD. Mitochondrial dysfunction is one of the proposed mechanisms of pathogenesis of dry AMD, regarding that, some preclinical trials examine the potential of mitochondrial enhancers as a future treatment of dry AMD, but clinical trials are necessary to determine those effects in human [4, 14, 66, 68]. Until now, no treatment has been able to reverse the progression of dry AMD. Nonetheless, emerging research and development in therapies for dry macular degeneration is beginning to show promise in slowing progression of the disease, which is the paramount concern for an increasingly aging society [14].

CORRESPONDENCE
med. stud. Hanna Wołodkiewicz
Ophthalmological Student Organization in Independent Public Teaching Ophthalmological Hospital SPKSO, Faculty of Medicine, Medical University of Warsaw
03-709 Warszawa, ul. Józefa Sierakowskiego 13
e-mail: hwolodkiewicz@gmail.com

ORCID
Hanna Wołodkiewicz – ID – https://orcid.org/0009-0000-5166-6855
Marta Wolszczak – ID – https://orcid.org/0009-0005-6072-8524
Grzegorz Gruba – ID – https://orcid.org/0000-0003-4722-6544
Joanna Przybek-Skrzypecka – ID – https://orcid.org/0000-0001-6310-7516
Michał Post – ID – https://orcid.org/0000-0002-0166-3696
Justyna Izdebska – ID – https://orcid.org/0000-0002-5289-6860
Jacek P. Szaflik – ID – https://orcid.org/0000-0001-9100-0847

References

1. DLeng Y, Qiao L, Du M et al. Age-related macular degeneration: Epidemiology, genetics, pathophysiology, diagnosis, and targeted therapy. Genes Dis. 2022; 9(1): 62-79.
2. Xie D, Chen Y, Hu S et al. CRISPR-based gene therapy for wet age-related macular degeneration in mouse model. Clin Transl Discov. 2024; 4(1): e278.
3. Thomas CJ, Mirza RG, Gill MK. Age-Related Macular Degeneration. Med Clin North Am. 2021; 105(3): 473-91.
4. Fabre M, Mateo L, Lamaa D et al. Recent Advances in Age-Related Macular Degeneration Therapies. Molecules. 2022; 27(16): 5089.
5. Trincão-Marques J, Ayton LN, Hickey DG et al. Gene and cell therapy for age-related macular degeneration: A review. Surv Ophthalmol. 2024; 69(5): 665-76.
6. Wong WL, Su X, Li X et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014; 2(2): e106-16.
7. Stahl A. The Diagnosis and Treatment of Age-Related Macular Degeneration. Dtsch Arztebl Int. 2020; 117(29-30): 513-20.
8. Li JQ, Welchowski T, Schmid M et al. Prevalence, incidence and future projection of diabetic eye disease in Europe: a systematic review and meta-analysis. Eur J Epidemiol. 2020; 35(1): 11-23.
9. Ferris FL 3rd, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol. 1984; 102(11): 1640-2.
10. Fine SL, Berger JW, Maguire MG et al. Age-related macular degeneration. N Engl J Med. 2000; 342(7): 483-92.
11. Grunwald JE, Pistilli M, Daniel E et al. Incidence and Growth of Geographic Atrophy during 5 Years of Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology. 2017; 124(1): 97-104.
12. Fritsche LG, Igl W, Bailey JN et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. Nat Genet. 2016; 48(2): 134-43.
13. Nadeem A, Malik IA, Shariq F et al. Advancements in the treatment of geographic atrophy: focus on pegcetacoplan in age-related macular degeneration. Ann Med Surg (Lond). 2023; 85(12): 6067-77.
14. Girgis S, Lee LR. Treatment of dry age-related macular degeneration: A review. Clin Exp Ophthalmol. 2023; 51(8): 835-52.
15. Liakopoulos S, von der Emde L, Biller ML et al. Geographic Atrophy in Age-Related Macular Degeneration. Dtsch Arztebl Int. 2025; 122(3): 82-8.
16. Vakharia P, Eichenbaum D. Geographic atrophy: current and future therapeutic agents and practical considerations for retinal specialists. Curr Opin Ophthalmol. 2024; 35(3): 165-9.
17. Schwartz SD, Regillo CD, Lam BL et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. Lancet. 2015; 385(9967): 509-16.
18. Rizzolo LJ, Nasonkin IO, Adelman RA. Retinal Cell Transplantation, Biomaterials, and In Vitro Models for Developing Next-generation Therapies of Age-related Macular Degeneration. Stem Cells Transl Med. 2022; 11(3): 269-81.
19. Bone marrow derived stem cell ophthalmology treatment study II. ClinicalTrials.gov, ID: NCT03011541. https://clinicaltrials.gov/ct2/show/ NCT03011541.
20. Weiss JN, Levy S. Stem Cell Ophthalmology Treatment Study (SCOTS): Bone Marrow-Derived Stem Cells in the Treatment of Age-Related Macular Degeneration. Medicines (Basel). 2020; 7(4): 16.
21. Schwartz SD, Hubschman JP, Heilwell G et al. Embryonic stem cell trials for macular degeneration: a preliminary report. Lancet. 2012; 379(9817): 713-20.
22. Khan H, Aziz AA, Sulahria H et al. Emerging Treatment Options for Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration. Clin Ophthalmol. 2023; 17: 321-7.
23. Guymer RH, Wu Z, Hodgson LAB et al. Subthreshold Nanosecond Laser Intervention in Age-Related Macular Degeneration: The LEAD Randomized Controlled Clinical Trial. Ophthalmology. 2019; 126(6): 829-38.
24. Querques G, Sacconi R, Gelormini F et al. Subthreshold laser treatment for reticular pseudodrusen secondary to age-related macular degeneration. Sci Rep. 2021; 11(1): 2193.
25. Merry GF, Munk MR, Dotson RS et al. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration. Acta Ophthalmol. 2017; 95(4): e270-e7.
26. Boyer D, Hu A, Warrow D et al. LIGHTSITE III: 13-Month Efficacy and Safety Evaluation of Multiwavelength Photobiomodulation in Non-exudative (Dry) Age-Related Macular Degeneration Using the Lumithera Valeda Light Delivery System. Retina. 2024; 44(3): 487-97.
27. Leung E, Landa G. Update on current and future novel therapies for dry age-related macular degeneration. Expert Rev Clin Pharmacol. 2013; 6(5): 565-79.
28. Damico FM, Gasparin F, Scolari MR et al. New approaches and potential treatments for dry age-related macular degeneration. Arq Bras Oftalmol. 2012; 75(1): 71-6.

29. Walters TR. Development and use of brimonidine in treating acute and chronic elevations of intraocular pressure: a review of safety, efficacy, dose response, and dosing studies. Surv Ophthalmol. 1996; 41(Suppl 1): S19-26.
30. Kuno N, Fujii S. Biodegradable intraocular therapies for retinal disorders: progress to date. Drugs Aging. 2010; 27(2): 117-34.
31. Safety and Efficacy of Brimonidine Intravitreal Implant in Patients with Geographic Atrophy Due to Age-Related Macular Degeneration (AMD). ClinicalTrials.gov, ID: NCT00658619.
32. Kuppermann BD, Patel SS, Boyer DS et al. Phase 2 study of the safety and efficacy of brimonidine drug delivery system (brimo dds) generation 1 in patients with geographic atrophy secondary to age-related macular degeneration. Retina. 2021; 41(1): 144-55.
33. A Safety and Efficacy Study of Brimonidine Intravitreal Implant in Geographic Atrophy Secondary to Age-Related Macular Degeneration. ClinicalTrials.gov, ID: NCT02087085.
34. Freeman WR, Bandello F, Souied E et al.; BEACON Study Group. Randomized Phase IIb Study of Brimonidine Drug Delivery System Generation 2 for Geographic Atrophy in Age-Related Macular Degeneration. Ophthalmol Retina. 2023; 7(7): 573-85.
35. Collier RJ, Wang Y, Smith SS et al. Complement deposition and microglial activation in the outer retina in light-induced retinopathy: inhibition by a 5-HT1A agonist. Invest Ophthalmol Vis Sci. 2011; 52(11): 8108-16.
36. Geographic Atrophy Treatment Evaluation. ClinicalTrials.gov, ID: NCT00890097.
37. Jaffe GJ, Schmitz-Valckenberg S, Boyer D et al. Randomized Trial to Evaluate Tandospirone in Geographic Atrophy Secondary to Age-Related Macular Degeneration: The GATE Study. Am J Ophthalmol. 2015; 160(6): 1226-34.
38. Allegro Ophthalmics LLC. A Randomized Controlled, Double-Masked, Crossover Clinical Trial Designed To Evaluate The Safety And Exploratory Efficacy Of 1.0 Mg Luminate® (Alg-1001) As A Treatment For Non-Exudative Macular Degeneration. ClinicalTrials.gov, ID: NCT03626636.
39. Lad EM, Boyer DS, Heier JS et al. Color Vision and Microperimetry Changes in Nonexudative Age-Related Macular Degeneration After Risuteganib Treatment: Exploratory Endpoints in a Multicenter Phase 2a Double-Masked, Randomized, Sham-Controlled, Crossover Clinical Trial. Ophthalmic Surg Lasers Imaging Retina. 2022; 53(8): 430-8.
40. Boyer DS, Gonzalez VH, Kunimoto DY et al. Safety and Efficacy of Intravitreal Risuteganib for Non-Exudative AMD: A Multicenter, Phase 2a, Randomized, Clinical Trial. Ophthalmic Surg Lasers Imaging Retina. 2021; 52(6): 327-35.
41. Rhee KD, Nusinowitz S, Chao K et al. CNTF-mediated protection of photoreceptors requires initial activation of the cytokine receptor gp130 in Müller glial cells. Proc Natl Acad Sci USA. 2013; 110(47): E4520-9.
42. Li Y, Tao W, Luo L et al. CNTF induces regeneration of cone outer segments in a rat model of retinal degeneration. PLoS One. 2010; 5(3): e9495.
43. A Study of an Encapsulated Cell Technology (ECT) Implant for Patients with Atrophic Macular Degeneration. ClinicalTrials.gov, ID: NCT00447954.
44. Woodell A, Rohrer B. A mechanistic review of cigarette smoke and age-related macular degeneration. Adv Exp Med Biol. 2014; 801: 301-7.
45. Zarling JA, Brunt VE, Vallerga AK et al. Nitroxide pharmaceutical development for age-related degeneration and disease. Front Genet. 2015; 6: 325.
46. OT-551 Antioxidant Eye Drops to Treat Geographic Atrophy in Age-Related Macular Degeneration. ClinicalTrials.gov, ID: NCT00306488.
47. Wong WT, Kam W, Cunningham D et al. Treatment of geographic atrophy by the topical administration of OT-551: results of a phase II clinical trial. Invest Ophthalmol Vis Sci. 2010; 51(12): 6131-9.
48. The OMEGA Study: Use of Eye Drops to Treat Geographic Atrophy Associated with Age-Related Macular Degeneration (Dry AMD). ClinicalTrials.gov, ID: NCT00485394.
49. Sternberg P, Rosenfeld PJ, Slakter JS et al. Topical OT-551 for Treating Geographic Atrophy: Phase II Results. Invest Ophthalmol Vis Sci 2010; 51: 6416.
50. Pixium Vision SA. Feasibility Study of Compensation for Blindness With the PRIMA System in Patients With Dry Age Related Macular Degeneration. ClinicalTrials.gov, ID: NCT03333954.
51. Palanker D, Le Mer Y, Mohand-Said S et al. Photovoltaic Restoration of Central Vision in Atrophic Age-Related Macular Degeneration. Ophthalmology. 2020; 127(8): 1097-104.
52. Pixium Vision SA. Restoration of Central Vision With the PRIMA System in Patients With Atrophic Age-Related Macular Degeneration. ClinicalTrials.gov identifier: NCT05170048.
53. Feasibility Study of Compensation for Blindness With the PRIMA System in Patients With Atrophic Dry Age Related Macular Degeneration. ClinicalTrials.gov, ID: NCT03392324.
54. Hudson HL, Lane SS, Heier JS et al. Implantable miniature telescope for the treatment of visual acuity loss resulting from end-stage age-related macular degeneration: 1-year results. Ophthalmology. 2006; 113(11): 1987-2001.
55. Lylyk I, Bleise C, Lylyk PN et al. Ophthalmic artery angioplasty for age-related macular degeneration. J Neurointerv Surg. 2022; 14(10): 968-72.

56. A Clinical Study to Evaluate the Safety and Feasibility of the OcuDyne System in the Treatment of Age-Related Macular Degeneration (AMD). ClinicalTrials.go, ID: NCT05091476.
57. Zhang J, Kiser PD, Badiee M et al. Molecular pharmacodynamics of emixustat in protection against retinal degeneration. J Clin Invest. 2015; 125(7): 2781-94.
58. Safety and Efficacy Assessment Treatment Trials of Emixustat Hydrochloride. ClinicalTrials.gov, ID: NCT01802866.
59. Rosenfeld PJ, Dugel PU, Holz FG et al. Emixustat Hydrochloride for Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Randomized Clinical Trial. Ophthalmology. 2018; 125(10): 1556-67.
60. Shin Y, Moiseyev G, Petrukhin K et al. A novel RPE65 inhibitor CU239 suppresses visual cycle and prevents retinal degeneration. Biochim Biophys Acta Mol Basis Dis. 2018; 1864(7): 2420-9.
61. Mata NL, Lichter JB, Vogel R et al. Investigation of oral fenretinide for treatment of geographic atrophy in age-related macular degeneration. Retina. 2013; 33(3): 498-507.
62. Dobri N, Qin Q, Kong J et al. A1120, a nonretinoid RBP4 antagonist, inhibits formation of cytotoxic bisretinoids in the animal model of enhanced retinal lipofuscinogenesis. Invest Ophthalmol Vis Sci. 2013; 54(1): 85-95.
63. Cioffi CL, Dobri N, Freeman EE et al. Design, synthesis, and evaluation of nonretinoid retinol binding protein 4 antagonists for the potential treatment of atrophic age-related macular degeneration and Stargardt disease. J Med Chem. 2014; 57(18): 7731-57.
64. Ma L, Kaufman Y, Zhang J et al. C20-D3-vitamin A slows lipofuscin accumulation and electrophysiological retinal degeneration in a mouse model of Stargardt disease. J Biol Chem. 2011; 286(10): 7966-74.
65. Saad L, Washington I. Can Vitamin A be Improved to Prevent Blindness due to Age-Related Macular Degeneration, Stargardt Disease and Other Retinal Dystrophies? Adv Exp Med Biol. 2016; 854: 355-61.
66. Phase 3 Study of ALK-001 in Geographic Atrophy. ClinicalTrials.gov, ID: NCT03845582.
67. Cousins SW, Saloupis P, Brahmajoti MV et al. Mitochondrial Dysfunction in Experimental Mouse Models of SubRPE Deposit Formation and Reversal by the Mito-Reparative Drug MTP-131. Invest Ophthalmol Vis Sci. 2016; 57(12): 2126.
68. ReCLAIM-2 Study to Evaluate Safety, Efficacy & Pharmacokinetics of Elamipretide in Subjects With AMD With Non-central GA (ReCLAIM-2) ClinicalTrials.gov, ID: NCT03891875.

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