Review Article

Novel treatments and genetics of age-related macular degeneration-a narrative review

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Abstract: Age-related macular degeneration (AMD) remains a leading cause of severe visual impairment in developing countries. Although dry-type AMD and geographic atrophy (GA) are progressive conditions with the associated decrease of visual functions, no well-established treatment regimen was proposed for the disease. Wet-type AMD is effectively treated with intravitreal anti-angiogenic agents, but frequent injections are a major issue for the affected patients. Recent advances in AMD genetics have provided new insights into the pathogenesis and novel therapeutic targets of AMD, but the benefits of using genetic testing and genotype-based risk models for AMD development and progression still lacks evidence. Novel AMD treatments aim to increase the interval among intravitreal injections through new therapeutic agents and modern delivery devices. Simultaneously, gene therapy for dry and wet AMD is widely studied. Although gene therapy possesses a major superiority over other novel treatments regarding a persistent cure of disease, many challenges exist in the way of its broad impact on the ocular health of AMD patients.

Keywords: Age-related macular degeneration (AMD); gene therapy; genetics; novel treatments; anti-vascular endothelial growth factor (VEGF)

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Introduction

Age-related macular degeneration (AMD) is an incurable prominent cause of visual impairment in the population over 60 years of age. It was reported that near 11 million new cases of AMD were diagnosed in the United States since 2013, and more than 20 million are anticipated to be affected by 2050 (1,2). AMD is the primary cause of visual disability in developing countries, with a yearly cost of more than $255 billion for direct health care (3).

Although small hard drusen are considered a common finding of retinal aging in more than 90% of the normal population over 40 years of age, the progression of these changes to AMD threatens one's central vision in addition to functional vision needed for reading and driving ability. AMD is characterized by retinal deposits larger than hard drusen, consisting of an accumulation of lipoproteinaceous materials and debris. Enlargement of these drusen, increasing their confluence, and appearance of accompanied pigmentary changes in retinal pigment epithelium (RPE), make the ophthalmologists use the term AMD. Drusen and pigmentary changes are considered the hallmarks of early and intermediate dry-type AMD. More advanced stages are known as advanced dry AMD characterized by geographic atrophy (GA). The growth of abnormal blood vessels from choroidal vasculature changes the scenario of the dry-type of disease, turning it into a more deteriorating condition of wet (exudative or neovascular) type AMD. The hallmark of wet AMD is choroidal neovascularization (CNV).

At the time of present review, the main therapies remain

to target neovascular AMD, directing the suppression of CNV progression and diminishing retinal damages due to these abnormal vessels. These therapies are due to the inhibition of vascular endothelial growth factors (VEGFs) which provide an efficient but indefinite treatment, with a range of success in regaining vision and suppressing the progression of disease.

Herein, we will review the updates on pathophysiological findings and novel treatments of dry and wet AMD, focusing on AMD genetics and gene therapy. We present the following article in accordance with Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/aes-21-14).

Methods

The literature published through January 2021 was reviewed by searching the ISI Web of Knowledge database, PubMed, Scopus, Embase, and Cochrane Library. The following keywords were used: "wet AMD", "dry AMD", "genetics", "gene therapy", "novel treatments", "anti-VEGFs", and "genes". No language limitation was applied, and non-English articles were translated to extract the data. The articles which published information about novel treatments of AMD, in addition to those arguing AMD gene therapy and genetics, were selected through a review of abstracts, references, and titles. Also, the ongoing studies on AMD treatments which are registered as trials were reviewed and their purposes, designs and primary reports were added to the review.

Discussion

Pathophysiology and genetics of AMD

By several genetic and environmental risk factors, AMD is strongly considered a complex disease. As environmental risk factors, age, gender, race, diet, smoking, and cardiovascular disease have been consistently associated with AMD (4). On the other hand, remarkable advances were made in AMD genetics over the past years, where new insights were presented into the pathogenesis and novel therapies of AMD. These findings have turned AMD into one of the most well genetically recognized complex diseases. However, only half of the heritability of AMD can be explained by the 52 currently known genetic variants (5), highlighting the fact that there is still a large percentage of missing heritability. Although it can be partially explained by the role of environmental factors in the pathogenesis of AMD, there is still a need for studies with a large sample sizes and widespread genome coverage looking for novel genetic factors in AMD.

The prevalence of AMD was reported to be higher in first-degree relatives of patients, with an odds ratio of 2.4 (6). According to the studies on monozygotic and dizygotic twins, the heritability of AMD was reported to be at 46% and 71% for early and advanced AMD, respectively (7). Compared to the general population, an individual with a first-degree relative with AMD is up to 27 times more vulnerable to develop AMD (8).

Complement-related genes of AMD

Whether local or systemic, raised levels of complement were associated to degenerative changes in the retina. As the main component of the innate immune system, the complement cascade includes more than 30 effector and regulator proteins that the consequence of their activation is the formation of a cell lysis mediator, the membrane attack complex (MAC). Independent of the liver, the retina produces its own complement factors, and this local production of complements seems to be more important in degenerative retinal changes (9). Retinal complement proteins can be detected in both the drusen of AMD and drusen secondary to renal diseases associated with systemic complement dysregulation (9-13).

As a complex disease, the genetic variations of AMD can be categorized as common versus rare variants. Common variants are known to be low penetrant genetic deviations detected with genome-wide association studies (GWAS). Rare variants are more penetrant, more associated to phenotypic variations, and routinely detected through gene-specific studies (13). Initial studies on AMD genetics detected a common polymorphism (Tyr402His) in the CFH gene on chromosome 1 of these patients (14,15). This common polymorphism is associated to an increased likelihood of 4.6 and 7.4 for AMD in heterozygous and homozygous conditions, respectively (16). Other frequently detected polymorphisms in AMD complement-related genes are C3, C2/CFB, CFI, C7, and SERPING (17-21). On the other hand, there are some rare complement-related gene variants which may explain the missing heritability observed in the genetics of AMD (22). CFH R1210C was the first identified rare variant related to AMD (23). It is a high penetrant variant associated to earlier onset AMD phenotypes (23). Similar rare variants have also been

detected in CFI, C3, and C9 (24,25). Rare variants of CFH and CFI genes decrease the serum level of CFH and CFI, leading to impaired regulation of the complement system (26,27). Similar impairment of the complement system regulation is detected in patients with the rare Lys155Gln variant in the C3 locus (24) (*Table 1*).

AMD genes not involved in the complement pathway

ARMS2/HTRA1 is a locus of two genes with high linkage disequilibrium. The presence of special polymorphisms in this locus was associated to AMD, with an attributable-risk of more than 50% for the general population (28,29). Although it is challenging to determine the responsible gene for AMD between ARMS2 and HTRA1; recently, it has been detected that ARMS2 genetic variants at 10q26 locus are solely responsible for AMD susceptibility (30,31).

Genetic polymorphisms in angiogenetic pathways, lipoprotein metabolism, immune regulation, and extracellular matrix homeostasis are among the other non-complement genetic variants of AMD. These genes include transforming growth factor-BR1 (*TGFBR1*), *VEGFA*, *COL10A1*, COL8A1, *PILRB*, *LIPC*, *APOE*, and *CETP* (5,32). Moreover, there are some non-complement rare genetic variants for AMD including TIMP3 and SLC16A8 (5).

Genetic variants can also be important in predicting the rate of progression of AMD from early Phenotypes to advanced stages. According to a study in 2007, CFH Y402H and ARMS2/HTRA1 was independently and significantly associated with progression of AMD (33). Subsequently, further common and rare variants, including CFH rs1410996, COL8A1, CFH R1210C and C3 K155Q, were also introduced as the predictors of AMD progression through non-advanced to advanced stages (34).

Genetic testing and risk models of AMD

Genetic testing for AMD is not advised in clinical practice (13). However, it may be used to select the appropriate cases being enrolled in clinical trials of AMD novel treatments. Through genetic testing, trials will need smaller sample sizes with adequate power of study. Improved AMD genetic tests' accuracy requires further studies, which can help ophthalmologists screen high-risk patients who may benefit from earlier interventions. However, currently available commercial genetic tests seem to fail to change the management of such patients.

Respective to the risk models for AMD development or progression, models using only genetic variants have achieved lower accuracy, compared to the models combining both genetic and environmental factors (35,36). More importantly, a model which only incorporated environmental factors showed an accuracy similar to dual models (incorporating both genetic and environmental factors) in predicting the risk of advanced AMD, which challenges the utility of genetic data in AMD risk models (37). Nowadays, the value of identifying AMD-associated common and rare genetic polymorphisms and mutations is restricted to uncover AMD biological pathways which leads to the development of novel treatments.

Molecular biomarkers for optimization of AMD treatments

Currently, optimization of patient selection for different AMD treatments cannot be implemented in the clinic. Findings on biomarkers for treatment response in AMD is still exploratory.

Regarding dietary supplements, the role genetic biomarkers has been a topic of intense debate. Assel *et al.* believe that dietary supplements should be prescribed to any AMD patients, independent of the underlying CFH and ARMS2 genotypes (38). However, Vavvas *et al.* believe that using vitamins and minerals should be selected based on patient-specific genotypes (39). They observed that, when taking Age-Related Eye Disease Study (AREDS) formula, individuals with high CFH and no ARMS2 risk alleles showed increased progression to CNV, compared with placebo. However, those with low CFH risk and high ARMS2 risk had decreased progression risk after taking the formula.

Several genetic and molecular biomarkers associated with response to anti-VEGF therapy have been identified, but these associations have not been consistent. Although replicated results suggest that SNP rs1061170 in CFH may influence response to anti-VEGF therapy, the effect of this genetic variant can directly relate to a faster disease progression, rather than its effect on the treatment efficacy (40). Moreover, the association was not detected in the analyses from the CATT and IVAN clinical trials (41,42). Among different AMD treatments, complement biomarkers may be the most convenient options to identify patients suitable for complement-inhibiting therapies that are currently under development (43).

Table 1 A summary of some identified genetic variants involved in AMD pathogenesis

Common genetic variants				Rare genetic variants			
Complement-related genes	Phenotypic variation	Non complement-related genes	Phenotypic variation	Complement related genes	Phenotypic variation	Non complement-related genes	Phenotypic variation
CFH (Tyr402His)	Higher risk of having peripheral retinal phenotypes	ARMS2	Increased risk for both types of AMD, with somewhat greater risk for wet AMD	CFH (R1210C)	Increased extramacular and calcified drusen, increased drusen load,	TIMP3	Earlier age of disease onset, bilateral CNV
CFH (rs1410996)	Higher risk of having peripheral retinal phenotypes	TGFBR1		CFH (Arg175Gln)	More frequently observed in patients with GA than those with wet AMD	SLC16A8	
CFI (rs10033900)		APOE		CFH (Ser193Leu)	Increased extramacular and calcified drusen, increased drusen load,		
C3		CETP		CFI (Gly119Arg)	More frequently observed in patients with GA than those with wet AMD		
C2/CFB		LIPC		CFI (Leu131Arg)	Increased extramacular and calcified drusen, increased drusen load,		
SERPING		VEGFA		C3	More frequently observed in patients with GA than those with wet AMD		
		COL10A1		C9	More frequently observed in patients with GA than those with wet AMD		
		COL8A1			More frequently observed in patients with GA than those with wet AMD		
		PILRB			More frequently observed in patients with GA than those with wet AMD		
					More frequently observed in patients with GA than those with wet AMD		

Source of data: Warwick A, Lotery A. Genetics and genetic testing for age-related macular degeneration. Eye. 2018;32(5):849-57. Fritsche LG, Igl W, Bailey JN, Grassmann F, Sengupta S, Bragg-Gresham JL, 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. Common genetic variants: More frequently detected (minor allele frequency >5%); More likely to be genetic polymorphisms; Less penetrant (less effect size); Up to 3-fold increased risk for AMD; Less associated with phenotypic variations; Detected through GWAS and case-control studies. Rare genetic variants: Less frequently detected (found in fewer than 5% of the population); More likely to be deleterious mutations; More penetrant (larger effect size); Up to a 20-fold increased risk of AMD; More associated with phenotypic variations; Detected through linkage studies. AMD, age-related macular degeneration.

Novel treatments of AMD; the alternatives of gene therapy

Dry-type AMD

To emphasize the burden of visual impairment in dry-type AMD patients, it was reported that at the time of diagnosis, a high percentage of patients with bilateral GA have lost their driving ability, and near 7% of them are eligible for legal blindness registration. Due to dry AMD, the progressive visual impairment will render more than two-third of these patients ineligible to drive (44,45).

Due to current literature, progression rate to CNV in patients with bilateral GA ranges from 2% in 2 years to 7.4% per year (44,46). Not necessarily progression to CNV, GA lesion progression without the development of abnormal vessels is a prominent concern about the visual prognosis of dry-type AMD patients. A rapid rate of GA progression was reported in recent studies, even in those with unilateral GA (45). The Proxima A trial (ClinicalTrials.gov, NCT02479386) performed on 295 eyes has reported a rate of 2 mm^2 per year for the rate of GA progression in patients with bilateral GA which is similar to the rates reported in epidemiologic studies (47). Fundus Autofluorescence in Age-Related Macular Degeneration (FAM) study, Geographic Atrophy Progression Study, and Sunness natural history study have reported a mean of 1.5, 1.9, and 2.5 mm^2/year for bilateral GA progression (46,48,49).

Except for some vitamins and minerals, no approved treatment was proposed to prevent the onset or progression of dry-type AMD, particularly GA. As the only therapeutic option available, AREDS formula includes vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), copper (cupric oxide, 2 mg), lutein (10 mg), zeaxanthin (2 mg), and zinc (80 mg). In AREDS and AREDS2 trials, these formulas benefited the eyes with intermediate or late AMD, with no benefit for early AMD (50,51). In a recent review of 19 studies, the authors concluded that AMD may experience some delay in progression with antioxidant vitamins and mineral supplementation (52). However, the finding was largely drawn from AREDS trials on well-nourished American population, and the generalizability of these findings to other populations is unknown.

Anti-VEGF agents for prophylaxis against conversion to wet AMD

Intravitreal aflibercept injection (IAI) versus sham as prophylaxis against conversion to neovascular AMD (PRO-CON) study evaluated the effectiveness of quarterly IAI in preventing CNV development in 127 eyes with high-risk dry AMD (53). High-risk eyes included those with intermediate dry AMD and history of exudative AMD in the fellow eye. It has been reported that the rate of neovascular conversion did not reduce with quarterly aflibercept (9.38% in the treatment group versus 6.35% in the sham group). Currently, the consensus for managing AMD does not include anti-VEGF treatment unless exudation develops.

Therapeutic regimens with protective agents

ReCLAIM-2 (Study to Evaluate Safety, Efficacy & Pharmacokinetics of Elamipretide in Subjects with AMD with Non-central GA) trial investigates the effectiveness of elamipretide (a mitochondrial protective agent) for improving vision in early AMT patients (ClinicalTrials.gov Identifier: NCT03891875). It is a small tetrapeptide targeting the production of toxic reactive oxygen species in the mitochondria. By reducing the impact of reactive oxygen agents, elamipretide is hypothesized to improve vision and dark adaption in dry AMD (54). Phase 1 clinical trial of daily subcutaneous elamipretide (40 mg, for 24 weeks) on 21 eyes suggests the improvement of visual acuity and dark adaptation associated to a decrease in GA area (54). Human trials on elamipretide continues to be studied.

The Phase 2 trial of risuteganib (ClinicalTrials.gov Identifier: NCT03626636) has suggested that structural and functional changes in intermediate dry AMD may be reversed with intravitreal injection of 1.0 mg of risuteganib (Luminate®). Risuteganib targets integrin functions involved in the pathogenesis of non-neovascular AMD (55). A gain of ≥8 letters from baseline was observed in near half of 42 treated patients, associated to some structural improvement in outer retinal layers in retinal imaging (56).

Complement C3 inhibitor pegcetacoplan (APL2) is an inhibitor of C3 cleavage used for the treatment of GA secondary to AMD. In a phase 2 trial on 246 eyes, GA was treated with intravitreal injections of 15 mg pegcetacoplan monthly or every other month for 12 months (57). A significant reduction in GA growth and CNV occurrence was achieved in the treatment groups. A phase 3 trial program is ongoing (ClinicalTrials.gov Identifier: NCT03525600).

The safety and efficacy of Brimonidine Drug Delivery System (Brimo DDS), a sustained release biodegradable intravitreal brimonidine implant, was reported in a phase 2 clinical trial on 113 eyes with GA secondary to AMD (58). Retreatment was performed at 6-month visit, and the results

were reported at 12-month follow-up. A reduction was observed in GA growth by up to 28% in the brimonidine arms (56). It is believed that brimonidine provides cytoprotective effects for RPE and Muller cells. The study may progress to a phase 3 program in the future.

A Phase 1 trial of GR39821 for AMD patients with GA (ClinicalTrials.gov Identifier: NCT03295877) evaluates the safety of intravitreal injection of an inhibitor of anti-High Temperature Requirement A1 (HtrA1) (29). Inhibition of HtrA1 is postulated to decrease the growth of GA with no ocular or systemic adverse effects.

Non-pharmacologic therapy

It is believed that oxidative stress decreases phagocytosis in eyes with AMD. Investigations on photobiomodulation (PBM) in the human RPE cell lines demonstrate PBM-improved phagocytosis (59). It uses wavelengths of light in the 500 to 1,000 nm range to stimulate cellular activities. In a study on 42 eyes, PBM was showed to be effective in improvement of functional and anatomical outcomes in dry AMD subjects (60). In LIGHTSITE 1 study, 46 eyes from 30 subjects were randomly assigned to PBM therapy versus sham. The eyes were treated with the Valeda Light Delivery System, wherein two series of treatments (3× per week for 3–4 weeks) were performed during 1 year. The findings demonstrated that PBM improves both functional and anatomical outcomes (61,62). Study of Photobiomodulation to Treat Dry Age-Related Macular Degeneration (LIGHTSITE II and LIGHTSITE III; ClinicalTrials.gov Identifier: NCT03878420 and NCT03878420, respectively) are ongoing to evaluate PBM efficacy over 1 and 2-year follow-up periods.

Wet type AMD

Since more than 15 years ago, CNVs secondary to AMD were treated with anti-VEGF eye injections given monthly or less. Before anti-VEGF era, wet AMD was a blinding sentence for the patients' eyes. Although the value of intravitreal anti-VEGFs in preserving the visual function of patients with wet-type AMD should not be underestimated or overshadowed by recent findings, the optimization of treatment protocol, improving the patients' compliance with a repetitive painful and stressful regimen, the need for a treatment option to cure rather than control the adverse effects of disease, and the need for decreasing the burden of regular intravitreal injections remain to be a priority (63). Due to the reports, in 2019, around 24.5 million intravitreal injections were globally performed with more than 1/4 of these injections performed in the US (63). In addition to a heavy economic and psychological burden, the treatment's effectiveness may not necessarily follow the results of clinical trials, since in the real world, the target population consists of elderly patients struggling with several comorbidities preventing them from adhering to a regular treatment schedule. Current requirements in the treatment plan of patients with wet AMD may include the following items: (I) new therapeutic agents with longer durability of effect and lower quantities of injections, (II) hardware designs for more effective delivery of intravitreal medications, and (III) gene therapy (*Table 2*).

Novel therapeutic agents

KSI-301 is a full-length antibody against all forms of VEGF-A. It is linked to a special biopolymer to extend its intravitreal duration of action. KSI-301 can provide a therapeutic intraocular concentration for 3 months (64). The Phase 2b/3 DAZZLE study is a global, multi-center, randomized study designed to evaluate the efficacy, durability and safety of KSI-301 in patients with wet AMD, compared to aflibercept. The study has enrolled over 550 patients worldwide (ClinicalTrials.gov Identifier: NCT04049266).

Abicipar pegol (Allergan) was designed as a novel anti-VEGF drug, with a higher binding affinity, compared to older anti-VEGFs. Its extended duration of effect may allow for fewer injections and reduced treatment burden. In CEDAR and SEQUOIA trials, the efficacy of intravitreal abicipar every 8 weeks and quarterly (after initial doses) was compared with monthly ranibizumab in 1888 patients with treatment-naïve neovascular AMD (65). Two-year results show efficacy of abicipar, where the stability of vision was not significantly different between abicipar and ranibizumab arms. Despite of concerns regarding increased adverse effects of abicipar in short term, rate of ocular adverse events reduced in the second year and became comparable with ranibizumab group.

Therapies with combined targets

Faricimab is a bispecific antibody produced to simultaneously inhibit VEGF-A and angiopoietin 2 (66). Simultaneous and independent effects of the drug in suppression of angiopoietin 2 and VEGF-A is the main strength of the therapeutic regimen. In AVENUE phase 2 clinical trial on 263 participants, the eyes treated with faricimab every 4 or 8 weeks had a mean change in visual

Table 2 Summary of some novel treatments for dry AMD

Treatment group	Therapeutic regimen	The study	Participants	Initial reports
Dry AMD				
Anti-VEGF agents for prophylaxis against conversion to wet AMD	Quarterly intravitreal aflibercept	ClinicalTrials.gov Identifier: NCT02462889	Intermediate dry AMD in one eye and a history of wet AMD in the fellow eye	At one-year visit, quarterly aflibercept did not reduce the rate of neovascular conversion, compared to the sham group.
Therapeutic regimens with protective agents	Elamipretide, 40 mg subcutaneously once daily for 24 weeks	ClinicalTrials.gov Identifier: NCT03891875	Non-central GA or high risk drusen	Improvement of visual acuity and dark adaptation was observed, in association with a decrease in GA area.
	Intravitreal 1.0 mg risuteganib	ClinicalTrials.gov Identifier: NCT03626636	A wide range of phenotypes of dry AMD	A gain of ≥15 letters was observed in 20% of treated patients at week 28.
	Intravitreal APL-2	ClinicalTrials.gov Identifier: NCT02503332	Patients with GA	The treatment showed reductions in the area of GA growth of up to 29%, compared to sham injections.
	Sustained release brimonidine implant	ClinicalTrials.gov Identifier: NCT02087085	Patients with GA	GA growth reduced by 7% and 11% at the 24- and 30-month time points, compared to the sham injections
	Intravitreal anti-HtrA1	ClinicalTrials.gov Identifier: NCT03295877	Patients with GA	Proposed to decrease the growth of GA
Non-pharmacologic therapy	Photobiomodulation	ClinicalTrials.gov Identifier: NCT03878420	Dry AMD	Improvement of drusen and structural retinal determinant in pilot studies
Wet AMD				
More potent/long acting anti-VEGF agents	KSI-301	ClinicalTrials.gov Identifier: NCT04049266	CNV	The treatment has reduced the need for intravitreal injections
	Abicipar pegol	The phase 3 CEDAR and SEQUOIA trials	CNV	With abicipar every 8 weeks and every 12 weeks, similar response to treatment was achieved, compared with more frequent ranibizumab injections
	Faricimab	ClinicalTrials.gov Identifier: NCT03622580	CNV	Faricimab has demonstrated sustained treatment effect in human studies with evidence of increased durability
	OPT-302 in combination with ranibizumab	ClinicalTrials.gov Identifier: NCT03345082	CNV	Patients in the combined OPT-302 and ranibizumab group have gained a significantly higher letters of vision, compared to ranibizumab monotherapy arm
	Sunitinib (GB-102)	ClinicalTrials.gov Identifier: NCT03249740	CNV	The treatment has demonstrated sustained treatment effect in AMD patients

Table 2 (*continued*)

Table 2 (*continued*)

Treatment group	Therapeutic regimen	The study	Participants	Initial reports
	Brolucizumab	ClinicalTrials.gov Identifier: NCT02307682	CNV	Identical VA outcomes, compared to different anti-VEGF agents, was achieved. In addition, superior reductions in macular thickness from baseline to Week 16 and Week 48 was observed in treatment group.
Optimization of drug delivery	Port delivery system	ClinicalTrials.gov Identifier: NCT04108156	CNV	Visual and anatomic outcomes in patients with the PDS were similar to those in patients receiving monthly intravitreal ranibizumab

AMD, age-related macular degeneration.

acuity that was neither superior nor inferior to that of participants receiving monthly ranibizumab. Additionally, different doses of faricimab showed no unexpected adverse effects (67).

OPT-302 is an inhibitor of VEGF-C and VEGF-D through a "trap" mechanism. A phase 1 trial assessed the safety of intravitreal OPT-302 as monotherapy or combined with ranibizumab in 51 patients with wet AMD (68). Patients in the combined OPT-302 and ranibizumab group gained higher letters of vision compared to the ranibizumab monotherapy arm. It was related to ability of OPT-302 combination therapy in overcoming an escape mechanism to VEGF-A suppression in ranibizumab monotherapy. Intravitreal OPT- was well tolerated (68). A dose ranging study of OPT-302 with ranibizumab in wet AMD is ongoing (ClinicalTrials.gov Identifier: NCT03345082).

Novel drug delivery systems and routes

Ladder phase 2 trial evaluated the role of the port delivery system (PDS) in wet AMD management of 220 patients. PDS is a refillable reservoir of ranibizumab which is implanted over the pars plana. In the PDS arm of Ladder, serum pharmacokinetic data suggested that the reservoir was successful to provide the appropriate concentrations of drug (69). The PDS 100-mg/ml arm showed similar visual and anatomic outcomes over 9 months, comparable to intravitreal ranibizumab 0.5-mg injections, but through a reduced number of ranibizumab injections. A Phase 3 trial involving CNV secondary to AMD (ClinicalTrials.gov Identifier: NCT04108156) has completed the patients' enrollment.

Suprachoroidal approaches were supported through initial trials to provide safer and effective drug concentrations in retinal diseases. A lower rate of IOP increase and cataract development following suprachoroidal delivery has been reported (70).

Gene therapy

Gene therapy introduces healthy genes into patient's cells to prevent or cure an abnormal genetic pathway. The main advantage of gene therapy is to introduce a 'one-and-done' treatment by giving the retina a capability to produce its own protective agents. These therapeutic genes may be injected underneath the retina through a surgical procedure, or they may be injected into the vitreous just like an in-office injection of anti-VEGF agents. Recently, suprachoroidal delivery of gene therapy has also been studied (70).

Gene therapy has attracted the attention of researchers in the field of ocular diseases. Ophthalmic gene therapy may even show more research potential, compared to other medical specialties, due to possessing the following features: (I) More feasible and accessible ocular injections and surgeries facilitate the delivery phase of gene therapy, (II) ocular immune-privileged status contributes to a safer technique guarantying the survival of the vectors, (III) and presence of blood-ocular barriers protect other organs from unintended contamination. The contribution of ophthalmic conditions to gene therapy science is also a unique consideration, since ocular research on gene therapy did not confine to exclusive monogenic diseases. AMD and diabetic retinopathy are among the first polygenic and complex diseases which have undergone gene therapy.

Furthermore, the relationship between gene therapy and eye possesses a historical value, where gene therapy of retinal pigment epithelium-associated 65-kDa protein (RPE65) gene mutations is known as the first *in vivo* trial

supporting the clinical concept of gene therapy (71). Luxturna (voretigene neparvovec-rzyl) is a prescription gene therapy product used for the treatment of patients with inherited retinal disease due to mutations in both copies of the RPE65 gene (72). As an enormous achievement, it was the first gene therapy to be approved by the FDA to treat an inherited disease. Trials of gene therapy for retinal diseases have involved numerous disease including Leber's hereditary optic neuropathy, X-linked retinoschisis, choroideremia, achromatopsia, Stargardt's disease, Usher syndrome, and retinitis pigmentosa (71).

AMD is a complex disease, and several genetic variants and environmental factors contribute to the pathogenesis of disease (73). The presence of multiple genes involved in AMD and incomplete knowledge of genetic pathogenesis have made American Academy of Ophthalmology to recommend avoiding routine genetic testing. However, recent and ongoing studies on gene therapy for AMD have provided a strong role for gene therapy in AMD (*Table 3*) (74,75). Although several mediators are involved in the pathogenesis of AMD, VEGF pathways remain to be the main target of gene therapy for AMD (76). Among them, VEGF165 is the main isoform since it shows the highest activity in retinal vasculogenesis (77,78).

Using viral vectors, particularly adeno-associated virus (AAV), is the most popular way of introducing the desirable gene to the target cells (79). AAV has several resistant serotypes that lack pathogenesis and induce very low degrees of host immune system reactions. These features have made the virus an ideal candidate for gene vectoring, where the risk of viral and host cell destruction will be minimal (79).

Gene therapy for dry AMD

Theoretically, intravitreal HMR 59 (AAVCAGsCD59) may provide a therapeutic opportunity for dry AMD, since it can affect the pathogenesis of the disease through inhibiting the complement cascade (80). Early results of the phase I HMR59 trial on advanced dry AMD patients (ClinicalTrials.gov Identifier: NCT03144999) have been promising. Due to 1-year results, the intravitreal administration of HMR59 has successfully produced intraocular CD59, and a reduction of 25% in GA growth has been reported in the highest dose arm (81).

Another ongoing trial of gene therapy for AMD is GT005 (ClinicalTrials.gov identifier: NCT 03846193). Similar to HMR59, it is designed to control complement activation in advanced AMD with macular atrophy. It's delivered via subretinal injection. Current Phase I/II trials are evaluating its effectiveness.

Gene therapy for wet AMD

***FLT1* gene**

FLT-1 gene encodes a tyrosine kinase receptor (sFLT-1) which is believed to act as a receptor for VEGF-A and B. It has made the product of the FLT-1 as a potent natural inhibitor of endogenous VEGFs. Single nucleotide polymorphism of FLT-1 (such as rs9943922, rs7324510, and rs9513115) was shown to be correlated with increased risk of CNV in AMD (82,83).

Lions Eye Institute and Adverum Biotechnologies performed a randomized clinical trial, where a single subretinal injection of FLT-1 incorporated in AAV (AVA-101) was performed for wet AMD. The treatment was reported to be safe which led to an expansion phase (84-86). Although the study was not designed to evaluate the efficacy of treatment, patients in the treatment group required fewer ranibizumab injections compared to the control arm. No significant improvement in visual acuity was reported.

In another phase 1 trial by Sanofi Genzyme, the tolerability of a single intravitreal AAV2-sFLT-1 injection in patients with advanced wet AMD was reported (ClinicalTrials.gov Identifier: NCT01024998). AAV2-sFLT-1 is a modified protein of the sFLT-1 fused to the Fc domain of IgG1. Due to the results of study, AAV2-sFLT-1 could reduce the retinal thickness and macular fluid without a prominent effect on final visual acuity after 52 weeks. Although the intravitreal injection was concluded to be safe in different doses, some rare adverse effects, including transient intraocular inflammation, retinal hemorrhage, and retinal tears, were reported (87). As another important finding of study, undetectable aqueous humor levels of FLT-1 protein were detected in one patient who had no detectable anti-AAV2 serum antibodies. The authors have postulated that anti-AAV2 titer should not be considered the only factors affecting gene therapy success (87).

Aflibercept and gene therapy

Experimental evidence suggested the tolerability and efficacy of gene therapy with AAV2.7m8- aflibercept (ADVM-022) to prevent laser-induced CNV (88). Moreover, Adverum Biotechnologies designed a phase I trial (OPTIC trial; ClinicalTrials.gov Identifier: NCT03748784) to evaluate intravitreal safety profile of ADVM-022. Reports

Table 3 A summary for gene therapy trials for AMD

Therapy	Study	Vector	Delivery mode	Mechanism of action	Participants	Reports on efficacy and safety
sLFT-1	ClinicalTrials.gov Identifier: NCT01024998	AAV2	Intravitreal injection	A receptor for VEGF-A and B, a potent inhibitor of endogenous VEGFs	Wet AMD	The treatment reduce the retinal thickness and macular fluid, without prominent effect on final visual acuity after 52 weeks
sLFT-1	ClinicalTrials.gov Identifier: NCT01494805	AAV2	Subretinal injection	A receptor for VEGF-A and B, a potent inhibitor of endogenous VEGFs	Wet AMD	Completed with approved safety and tolerability profile
ADVM-022	ClinicalTrials.gov Identifier: NCT03748784	AAV2	Intravitreal injection	Enhances the production of aflibercept	Wet AMD	24 and 34-week data showed a good safety profile, with no need for rescue injections in the treatment arm
RGX-314	ClinicalTrials.gov Identifier: NCT03066258	AAV8	Subretinal injection	Enhances the production of a soluble anti-VEGF protein related to ranibizumab	Wet AMD	More than 70% and 50% of subjects treated with RGX-314 remained free of requiring rescue injections for 6 months and 1.5 years, respectively
RGX-314	ClinicalTrials.gov Identifier: NCT04514653	AAV8	Suprachoroidal injection	Enhances the production of a soluble anti-VEGF protein related to ranibizumab	Wet AMD	
RetinoStat	ClinicalTrials.gov Identifier: NCT01301443	Equine lentivirus	Subretinal injection	Produces anti-angiogenic factors, including endostatin	Wet AMD	Approved safety and tolerability of the treatment, associated with the capability of persistent expression
Pigment epithelium derived factor	ClinicalTrials.gov Identifier: NCT00109499	AAV5	Intravitreal injection	Inhibits neovascularisation	Wet AMD	Completed, approved safety and tolerability profile.
HMR 59	ClinicalTrials.gov Identifier: NCT03585556	AAV2	Intravitreal injection	Suppresses complement cascade	Wet AMD	
HMR 59	ClinicalTrials.gov Identifier: NCT03144999	AAV2	Intravitreal injection	Suppresses complement cascade	Dry AMD	
GT005	ClinicalTrials.gov identifier: NCT 03846193	AAV2	Subretinal injection	Suppresses complement cascade	Dry AMD	

AMD, age-related macular degeneration.

of 24- and 34-week data have shown a good safety profile, where mild intraocular inflammation was the only observed adverse effect. Besides, the efficacy seemed to be acceptable, with no need for rescue injections in the treatment arm. The last update of trial remained to be promising since no rescue injection was needed for the patients treated with ADVM-022 (76).

RGX-314: AAV8

RGX-314 (RegenxBio) gene therapy works on an anti-VEGF related to ranibizumab carried by AAV8 (89). The phase I/II of trial (ClinicalTrials.gov Identifier: NCT03066258) evaluated the safety profile of subretinal RGX-314 on 42 patients with CNV secondary to AMD. The preliminary reports revealed that more than 70% and

50% of subjects treated with RGX-314 remained free of requiring rescue anti-VEGF injections for 6 months and 1.5 years, respectively. The achievement was associated to good functional and structural outcomes, and no treatment-related intraocular inflammation was reported. In the next step, phase IIb and suprachoroidal delivery of RGX-314 are going to be conducted in wet AMD patients.

Endostatins and gene therapy

RetinoStat is an equine lentiviral vector that produces anti-angiogenic factors, including endostatin. Experimental models showed the safety and tolerability of treatment associated with persistent expression capability (90). Same results were obtained following a phase I human trial (91). A long-term follow-up study is ongoing on the safety and efficacy of RetinoStat gene therapy (ClinicalTrials.gov Identifier: NCT01301443).

Pigment epithelium derived factor and gene therapy

One of the first trials regarding gene therapy in wet AMD evaluated the intravitreal administration of an AAV5 equipped with pigment epithelium-derived factor (PEDF). Animal models warranted the safety and effectiveness of AAV5-PEDF gene therapy to diminish neovascularization in CNV (92). The human trial was designed to evaluate the safety of the treatment without any conclusion regarding the efficacy due to the lack of a control arm (93). The trial reported that the treatment was safe and tolerable, with only a 25% risk of intraocular inflammation, controlled with routine anti-inflammatory therapies.

Complement cascade and gene therapy

Hemera Biosciences has conducted two phase I trials with the purpose of inhibiting the formation and activation of terminal complement products through injection of intravitreal HMR 59 (AAVCAGsCD59) for wet and dry-type AMD. (ClinicalTrials.gov Identifier: NCT03585556 and NCT03144999, respectively) (94). Earlier, the efficacy of subretinal injection of AAVCAGsCD59 in inhibiting laser-induced CNV were approved in animal models (80).

PF-655 (PF-04523655, REDD14NP, RTP801i)

A small interfering RNA (siRNA) is a RNA fragment that degrades mRNA molecules through activating RNA-induced silencing complex (RISC). Amplification of the siRNA function is provided by the action of activated RISC that destroys hundreds of mRNAs. Therefore, siRNA might be a therapeutic option for preventing the expression of damaging proteins (95). PF-655 is a siRNA that inhibits expression of the hypoxia-inducible gene RTP801, which in turn reduces VEGF-A production. The Phase 2 MONET trial evaluated the efficacy of PF-655 in 151 subjects with wet AMD, compared to ranibizumab (96). The combination group of ranibizumab and PF had similar mean reductions in retinal thickness and CNV area, compared to the ranibizumab group. The visual outcomes were not different between the study arms.

Gene therapy, just making news or providing a real option?

Gene therapy has evolved by advances in vectoring mechanisms and introducing new techniques. More than 2,500 clinical studies have evaluated the range of gene therapy applications, from hereditary disorders to cancers. It is considered as one-off treatment, since the treated patient is expected to experience a life-long symptom-free period following gene therapy. Incurable diseases are the main candidates for gene therapy, and the main goal of the treatment is eliminating the involved gene.

However, researches on gene therapy and its applications accompany some challenges. Reports on gene therapy success in curing different diseases are associated with an uncontrollable public expectation, and affected patients from all over the world (including individuals who are thousands of miles far from the gene therapy labs) follow the gene therapy news. The problem is that many reports are desirable outcomes achieved following numerous failed attempts, while several technological problems are never reported. Additionally, in many medical fields, there is a long way to have gene therapy as a common therapeutic option. Moreover, there is no guarantee for gene therapy success. Most trials are performed on experimental models, hoping similar results to be achieved in human studies. Besides, even if available in the clinic, gene therapy will remain to be an expensive therapy for many years. Such a fee may never be affordable to many, giving rise to the socioeconomic segregation. In the case of AMD, many patients are old (opposing a condition such as cystic fibrosis), and the expense of gene therapy should be weighed against the patients' quality of life, their requirements, and the years expected to live with a golden gene in their eyes. Cooperation between pharmaceutical companies and biotechnology institutes is the main step in bringing gene therapy to broad influence. Supporters of gene therapy should also design appropriate payment

models to guarantee its availability to all patients in need.

Future perspectives

Although both dry and wet AMD have been targeted in the recent trials of novel AMD therapies, the clinical impact of modifications to wet AMD treatment seems to be more obvious in the near future. Current standard treatment, intravitreal injections, remains to be an invasive therapy with suboptimal outcomes. To modify the current treatment, two approaches are necessary: improving the comfort and cost-benefit of the treatment and increasing the efficacy of the therapy to preserve a higher level of functional vision.

The first goal has been followed through introducing novel long-acting anti-VEGF agents and new delivery systems to decrease the number of injections required to control the disease. New routs of drug administration have also been employed to improve adherence to the therapeutic regimen. However, they were not as successful as long-acting intravitreal agents. X-82 (Vorolanib) is an oral tyrosine kinase inhibitor that suppress the kinase activity of VEGF and PDGF receptors. In the APEX, a phase 2 randomised clinical trial on 157 patients with wet AMD, daily 50, 100 or 200 mg dosages of X-82 in combination with pro re nata anti-VEGF injections were non-inferior in visual outcomes while reducing the number of anti-VEGF injections, compared to placebo (97). However, a limited tolerability reduced the benefit-to-risk profile of the treatment. LHA510 is a low molecular weight vascular endothelial growth factor receptor inhibitor. LHA510 is a low molecular weight VEGF receptor inhibitor. A study evaluated whether topical LHA510 could suppress the need of intravitreal anti-VEGF therapy over a 12-week period in patients with wet AMD (98). Patients were dosed q12h for the first 8 weeks and q8h for the last 4 weeks. The study did not meet the primary efficacy hypothesis, concluding that effective topical therapy may be out of reach for wet AMD (98). According to the evidences mentioned above, at least in the near future, improving the comfort of the current standard therapy is more available through novel intravitreal agents and modern drug delivery systems, rather than changing the route of drug administration.

As another goal, improving the efficacy of treatment through multi-target and more potent agents appears to be the most promising strategy to improve the visual outcomes of patients with AMD. Development of new drugs is always attractive field for both researchers and financial supporters. Complement pathway modulators and new vasculopathy-related targets, such as angiotensin-2 and Tie2, are predicted to be the promising future strategies.

A successful gene therapy is an ideal option for a progressive and devastating condition like AMD. Theoretically, it can provide an everlasting cure. However, for AMD gene therapy, key challenges remain in identifying the target gene and delivering the curative gene construct. Although holding much promise, gene therapy will remain in its infancy, at least in the near future.

Summary

Although there is a long way toward using AMD genetics for risk models and screening programs, recent advances in AMD genetics will help introduce novel therapeutic options. Gene therapy is being studied for AMD, and initial results have been promising. The main superiority of gene therapy over other rapidly evolving AMD treatments is the potential of curing the disease. However, the future of other AMD novel treatments seems to be brighter to yield a broad impact on public health.

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