A Clinical and Preclinical Assessment of Clinical Trials for Dry Age-Related Macular Degeneration

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Age-related macular degeneration (AMD) is the leading cause of blindness for the elderly in high-income countries. Although multivitamin antioxidant nutrients can slow the progression of intermediate “dry” or non-neovascular AMD, no treatment can halt or reverse any stage of dry disease. Multiple biologic pathways have been implicated in AMD pathobiology, including the complement pathway. These pathways have been targeted by various approaches in clinical trials. To date, no treatment has reached their prespecified primary end point in 2 phase III trials, a requirement by the US Food and Drug Administration for a new drug approval. Here, we describe perspectives on the failures and possible successes of various clinical trials that will guide further investigation. These perspectives will also discuss clinical trial design issues to consider in future investigations, and how recent insights into AMD pathobiology might both provide additional explanation for trials not reaching the prespecified primary end points and offer direction for identifying prioritized treatment targets.

Rational for Geographic Atrophy as a Target of Clinical Trials on Dry AMD

For any drug to be approved by the US Food and Drug Administration (FDA), a primary prespecified end point approved by the FDA, must be demonstrated in 2 large randomized prospective clinical trials. For most ophthalmic clinical trials, visual acuity (VA) has been the standard primary end point. In early AMD, VA remains intact and does not correlate with disease severity. For example, drusen accumulation, a hallmark AMD lesion, or other classic structural features of AMD do not correlate with VA.5 Furthermore, drusen can resolve without apparent functional effects.6 In addition, VA loss occurs slowly and typically manifests only in the later course of late-stage dry AMD. As a result, preclinical and clinical researchers have devoted tremendous resources to understanding dry AMD pathogenesis on which to develop therapy for both early and late-stage dry disease. Some of these targets have matured sufficiently to be tested in clinical trials. Here, the status of clinical trials for dry AMD that have provided insight into our understanding of dry AMD will be described, as well as the clinical and preclinical barriers that must be overcome to fully optimize treatment for dry AMD.
AMD, atrophy of the photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris typically develops in the parafovea and when it enlarges to involve the fovea, major vision loss ensues. Logically, preventing GA expansion to involve the fovea would preserve central vision. Geographic atrophy area can be accurately measured, and its growth can be reliably predicted. As a result, the FDA has allowed slowing of GA enlargement as a suitable, surrogate primary end point for clinical trials in GA. Geographic atrophy is often measured using fundus photography and autofluorescence as well as other modalities, such as OCT, to analyze the lesion surface area and perimeter quantifications, alongside other measurements such as number of lesions and atrophy location. Different clinical trials may focus on different GA measurements. Of the various end points, perimeter and area growth rate have been shown to be associated. Square root analyses are also often used to examine the reproducibility of results; however, studies have shown that square root transformation of GA measurements diminishes the correlation between the baseline measurements and growth rate. This factor should be considered when designing the clinical trials and patient exclusion criteria.

**Lessons Learned from Selected Clinical Trials**

The pathogenesis of AMD is complex and incompletely understood. From epidemiologic, histopathologic, genetic, epigenetic, and preclinical investigation, several dysregulated biologic processes have emerged as substantial contributors to disease development and progression. Thus far, genetic variants associated with substantial AMD risk have been identified that involve innate immunity, extracellular matrix regulation, and lipid metabolism. For example, genetic variations in complement pathway genes, including complement factor H, have placed emphasis on innate immune dysregulation in AMD pathobiology. Likewise, the strong link of the *Age-Related Maculopathy Susceptibility 2/Htra1 Serine Peptidase 1 (HTRA1)* polymorphism with AMD risk has implicated alterations with extracellular matrix or Bruch membrane with AMD disease development. Cigarette smoking is the strongest environmental risk factor associated with AMD risk. Given the ~ 5000 toxins and ~ 10^14 oxygen free radicals in 1 puff of smoke, oxidative stress and failure of cellular antioxidant protective systems have been a focus of intensive study. Because mitochondria produce the majority of cellular oxygen free radicals during oxidative phosphorylation, it is not surprising that mitochondrial impairment has emerged as a pathogenic factor in AMD. As a result, these pathways, specifically those involved with complement dysregulation and *Age-Related Maculopathy Susceptibility 2/HTRA1* have been the focus of drug development for dry AMD treatment and have matured to the point that they are being tested in clinical trials. According to ClinicalTrials.gov, at the time of the writing of this manuscript, 1871 clinical trials have been conducted on AMD, of which 102 studies have focused on GA. To date, no drug has been approved by the FDA for treating GA.

Table 1 summarizes the results of the clinical trials that are discussed in this perspective. Several trials have focused on potentially normalizing complement function.

| Phase | Trial Name | Drug Target | Frequency | Route | Tx Duration | Sample Size | Results |
|-------|------------|-------------|-----------|-------|-------------|-------------|---------|
| II    | Pegcetacoplan C3 | 4 wks IVT | 12 mos | 127 | 29% GA growth decrease; P = 0.008 |
| III   | Pegcetacoplan C3 | 4 wks IVT | 12 mos | 119 | 20% GA growth decrease; P = 0.067 |
| III   | Pegcetacoplan C3 | 4 wks IVT | 12 mos | 637 | 22% GA growth decrease; P = 0.003 |
| III   | Pegcetacoplan C3 | 4 wks IVT | 12 mos | 16 mos | 16% GA growth decrease; P = 0.0052 |
| II    | Avacincaptad C5 | 4 wks IVT | 12 mos | 167 | 12% GA growth decrease; P = 0.0528 |
| II    | Lampalizumab FD | 4 wks IVT | 18 mos | 82 | 20% GA growth decrease; P = 0.12 |
| III   | Lampalizumab FD | 4 wks IVT | 18 mos | 452 | GA area growth decrease –0.02 mm^2; P = 0.80 |
| III   | Lampalizumab FD | 6 wks IVT | 18 mos | 455 | GA area growth decrease 0.16 mm^2; P = 0.048 favor sham |
| II    | Eculizumab C5 | 2 wks IVT | 6 mos | 20 | GA area not reduced |
| II    | Tesidolumab C5 | 4 wks IVT | 12 mos | 50 | GA area not reduced |
| I     | Eculizumab CL | Daily SQ | 24 wks | 19 | No serious AEs |
| II    | Eculizumab CL | Daily SQ | 48 wks | 176 | No change in LLVA and GA area not reduced |
| I     | Anti-HTRA1 HTRA1 | 4 wks IVT | 12 wks | 28 | No serious AEs |

AE = adverse event; C3 = complement C3; C5 = complement C5; CL = cardioplin; FD = complement factor D; GA = geographic atrophy; HTRA1 = Htra1 serine peptidase 1; LLVA = low luminance visual acuity; IVT = intravitreal; SQ = subcutaneous; Tx = treatment.
Because of the strong link of complement factor H polymorphisms with AMD risk, the alternative complement pathway has been the focus of multiple clinical trials. Complement factor D is the rate-limiting enzyme in the alternative complement pathway. Lampalizumab is an antigen-binding fragment (Fab) of a humanized monoclonal antibody against complement factor D. In a phase II clinical trial, lampalizumab was delivered intravitreally each month or every other month for 18 months. In the study group (n = 42), GA growth was reduced by 20% (P = 0.12) versus a sham treatment. Interestingly, GA growth was reduced by 44% in individuals who carried the complement factor I risk allele. These results prompted 2 phase III trials, Chroma and SPECTRI, which comprised, at that time, the largest studies of GA. In the Chroma trial, patients were given intravitreal lampalizumab every month, whereas in the SPECTRI trial, patients received intravitreal lampalizumab every 6 weeks for 96 weeks. A total of 906 patients participated. Each trial showed that lampalizumab did not reduce GA enlargement compared with sham treatment across 48 weeks.

Complement factor C3 is activated by all 3 complement pathways and is upstream of its major effectors including C3a, C5a, and the membrane attack complex. Compstatin and related analogs such as APL-1 are peptides that specifically bind C3 and prevent its activation. Pegcetacoplan, a pegylated form of APL-1, was tested in a GA phase II trial via intravitreal delivery monthly or every other month for 12 months and the GA area was assessed at 15 and 18 months. With a sample size of 240 patients, GA enlargement, measured through the mean change in square root of lesion size, was reduced by 29% (P = 0.008) with monthly injections and 20% (P = 0.067) with every other month injections compared with sham treatment. The effect was greater after 12 months of treatment. Geographic atrophy growth was reduced by 45% (P = 0.0004) with monthly treatment and 33% (P = 0.009) with every other month injections relative to sham treatment. Interestingly, the treatment effect declined after stopping treatment. Pegcetacoplan treatment did not influence the GA growth rate in patients with complement factor H, complement factor I, complement factor C2/complement factor B, and C3 genetic variants.

These favorable results prompted 2 phase III double-masked clinical trials, DERBY and OAKS, testing pegcetacoplan in GA. The 12-month results were presented at the 2021 Retina Society meeting. In the OAKS and DERBY trials, 638 and 621 patients, respectively, were enrolled. In both trials, patients with GA received monthly or every other month intravitreal injections of pegcetacoplan or sham treatment for 12 months. Although OAKS met the primary end point of a 22% (P = 0.0003) decrease with monthly and a 16% (P = 0.0052) decrease in GA growth with every other month treatment at 12 months relative to sham treatment, respectively, DERBY did not reach its primary end point. In the DERBY trial, patients who received monthly treatment had a 12% reduction in GA growth (P = 0.0528) and those who received every other month treatment had an 11% (P = 0.0750) reduction in GA growth at 12 months. With a combined analysis across both trials, GA growth was reduced by 17% (P < 0.0001) with monthly and 14% (P = 0.0012) with every other month treatment at 12 months. In a press release of March 16, 2022, Apellis presented 18-month follow-up data for DERBY and OAKS.
Pegcetacoplan treatment showed further reduction in lesion growth from baseline to month 18 (all nominal P values < 0.05). In DERBY, monthly pegcetacoplan reduced GA enlargement by 13% (P = 0.0254) and every other month treatment reduced GA enlargement by 12% (P = 0.0332) relative to sham-treated patients. In OAKS, monthly pegcetacoplan reduced GA enlargement by 22% (P < 0.0001) and every other month treatment reduced GA enlargement by 16% (P = 0.0018) relative to sham-treated patients.

In a highly controversial decision made in June 2021, the FDA approved aducanumab-avwa as a treatment for Alzheimer’s disease using the accelerated approval pathway that was based on the monoclonal antibody’s ability to lower β-amyloid levels. In March 2019, Biogen discontinued their 2 phase III clinical trials, ENGAGE and EMERGE, because their analysis indicated that neither trial was likely to reach their primary end point of slowing cognitive impairment using changes in the Clinical Dementia Rating-Sum of Boxes score. In October, 2019, Biogen then announced that they were going to seek FDA approval based on their additional analyses of a larger dataset that was eventually published in March, 2022. These subsequent efficacy analyses included a larger data set collected up to futility declaration and followed the prespecified statistical analyses. The primary end point was met in EMERGE, but not in ENGAGE. In contrast to their usual policy of requiring 2 phase III clinical trials to achieve their specified primary end points, the FDA approved aducanumab. Because DERBY did not reach the primary end point of reducing GA growth at 12 months, but did so after 18 months, it will be interesting to learn whether the FDA approves pegcetacoplan, especially given their recent decision to approve aducanumab and the resultant controversy associated with this decision.

Complement C5, downstream of C3 in the terminal pathway, forms the anaphylatoxin C5a when cleaved, which activates proinflammatory cytokines, and C5b, which initiates membrane attack complex formation. Avacincaptad pegol (Zimura), a pegylated RNA aptamer that inhibits C5, was tested in a phase II GA trial. This study, comprised of 286 patients, used a stratified randomization protocol by the location and size of the GA lesions, as well as the pattern of fundus autofluorescence at the junctional zone of GA. Avacincaptad pegol was administered intravitreally every month for 12 months. Patients who received avacincaptad pegol had a 28% reduction in GA growth at 12 months (P = 0.0072) as compared with sham-treated patients. Because of the randomized stratification protocol used, and the lack of adverse effects, avacincaptad pegol proceeded to phase III trials, “GATHER2,” which are ongoing.

Two different phase II clinical trials also focused on inhibiting C5, through tesidolubum and eculizumab. With a sample size of 50 patients, tesidolubum (LFG316), a humanized monoclonal antibody against C5, when administered intravitreally every month, did not reduce GA growth after 12 months (NCT01527500, clinicaltrials.gov). Eculizumab, which is approved for treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremia, was administered IV for 24 weeks (sample size of 20 patients). At 26 weeks, and then 3 and 6 months later, despite reaching therapeutic blood levels that inhibited C5 activity to < 1% by week 2, eculizumab did not decrease GA growth.

Although 14 different complement inhibitors have been explored through almost 40 clinical trials to date, the aforementioned studies represent the most recent directions and results of targeting the complement pathway. Cumulatively, these trials have mixed outcomes. What have we learned? First, compared with the phase II lampalizumab, eculizumab, and tesidolubum trials, the C3 inhibitor (pegcetacoplan) and C5 inhibitor (Zimura) trials were better powered to provide insights for deciding whether or not to proceed to phase III clinical trials. In the GATHER1 Zimura trial, a randomization scheme that took into account the GA size, location, and fundus autofluorescent pattern of the GA’s transition zone between treatment and sham groups was used. As reported in the phase III pegcetacoplan trial, pegcetacoplan had a greater effect in patients with extrafoveal lesions at baseline (https://investors.apellis.com/static-files/e6d8c27-e1b2-4c87-b7f1-aa5cb249bacf). Given that the GA phenotype varies from patient to patient, balancing these phenotypic differences may help to elucidate which patients might benefit from treatment.

Several factors potentially contributed to the unfavorable results in the phase III lampalizumab trial. For example, an unusually low level of statistical significance (P = 0.12) for reduction in GA growth was allowed in the decision to advance to a phase III trial. Although patients with the factor I polymorphism had a more substantial reduction in GA growth, the prevalence of this single nucleotide polymorphism is in the cohort studied was small. As a result, the low enrollment of patients with this genetic variant did not influence lampalizumab’s potential treatment benefit of either this subpopulation or the overall cohort in the phase III trials. Although monthly and every other month lampalizumab treatment was not beneficial, monthly and every 6-week treatment was instituted in the phase III trial. It is unclear if the dose of intravitreal lampalizumab was sufficient to reach therapeutic levels in the RPE/Bruch membrane, where complement overactivity is thought to be pathogenic, although a phase II study of every 2-week injection of lampalizumab also did not show any efficacy (https://clinicaltrials.gov/ct2/show/NCT02288559). Likewise, in the phase II eculizumab trial, it is possible that IV administration failed to provide therapeutic intraocular inhibitory levels despite C5 activity inhibition in the blood. Furthermore, the study duration of 26 weeks, which was substantially shorter than the other trials, potentially prevented identifying any treatment benefit, especially given the slow growth rate of GA lesions. Finally, both anti-C5 eculizumab and tesidolubum have molecular weights of 150 kDa, whereas avacincaptad pegol is 50 kDa. It is possible that either the reduced tissue distribution or the relative moles delivered relative to avacincaptad pegol because of the size differences were insufficient to see a treatment effect. Finally, it is critical to understand that serum and potentially disease levels of C5 and C3 are quite high in the range of 75 ug/ml and 1000 ug/ml, respectively. Thus, future trials testing new therapeutics for GA growth reduction should consider the study’s power, a sufficient study duration, the route of administration and...
its pharmacokinetics to the specific target tissue, the therapeutic concentration needed to achieve complement level reduction and a balanced randomization scheme that considers size, location, and fundus autofluorescent pattern of the GA.

Although expansion of GA lesion area is a validated “surrogate” end point for advanced dry AMD clinical trials, currently a reliable and practical functional end point is unknown. In addition, a surrogate or functional end point for early and intermediate AMD has not been elucidated despite intensive investigation. The parafoveal macula undergoes the earliest changes in AMD and GA; specifically, the rod dominant parafovea undergoes the earliest changes, including rod outer segment shortening and then rod cell death that is coincident with RPE abnormalities. 40

Recently, Zekavat et al 41 showed that photoreceptor segment thinning, as seen on OCT, is an early biomarker for AMD and can precede RPE-Bruch membrane complex thickening by decades. The current functional vision tests being investigated test much of this region and include dark adaptometry, microperimetry, quantitative contrast sensitivity (CSF), and low luminance VA (LLVA). 42-45 Although VA can be unaffected, parafoveal injury affects rods and hence, patients may experience difficulty adapting to dark environments without changes in central VA. Specifically, dark adaptometry can be used as a metric when VA is stable in AMD. The rod intercept time, which represents delayed dark adaptation, correlates with AMD severity. 46 However, at present, the protocols are not standardized, dark adaptation changes develop slowly over years, and results can be influenced by cataract severity and intraocular lens implants.

Microperimetry is a measure of macular retinal sensitivity in which accurate threshold light sensitivity is measured at specific macular locations. When tested under photopic light conditions, cones are primarily tested, whereas under scotopic or mesopic conditions, rods can be queried. 47 Microperimetry is reliable and repeatable; however, its use is limited by its expense, tedious and lengthy testing, and reliance on the expertise of the examiner.

Low luminance visual acuity is a potential alternative to test the functional changes in AMD. Low luminance visual acuity uses a standard VA chart. The patient’s vision is tested under normal lighting conditions and in low-light conditions, often by adding a neutral density filter in front of the test eye. The assay is simple and rapid, which is an advantage in any clinical trial. Low luminance visual acuity has been previously used in eyes with nonfoveal GA to show that low luminance deficit, or the difference between LLVA and best-corrected VA, predicts subsequent vision loss and GA enlargement. 48 Low luminance visual acuity, along with microperimetry, has been suggested as a functional measure to differentiate early and intermediate stages of dry AMD.

Quantitative CSF is another visual function measure that is distinct from VA. This approach uses an active-learning algorithm to measure CSF across multiple frequencies. Quantitative CSF can identify subtle visual function deficits that may be unrecognized with other methods. Wai et al 49 recently showed, using quantitative CSF, that CSF was significantly reduced in eyes with maculopathies in patients with good VA. These various functional tests should be further explored in combination, because combining multiple functional end points into a “cumulative end point” may increase the reliability of visual function assessment and provide an improved visual function outcome measure.

Recently, the ReCLAIM phase I Trial tested MTP-131, also known as elamipretide. This tetrapeptide reduces reactive oxygen species in the mitochondria, the location of greatest reactive oxygen species production, and stabilizes cardiolipin, a major lipid that is unique to mitochondrial membranes. In the open label phase I trial assessing MTP-131 applied by repeated subcutaneous injections in patients with intermediate AMD and GA, LLVA improved in patients with intermediate AMD by 5.6 letters ($P = 0.006$) and the measured GA change corresponded to a similar LLVA improvement of 5.4 letters ($P = 0.025$) after 24 weeks of treatment. Dark adaptation was also measured and was improved in $> 33\%$ of eyes when examined at $\geq 2$ visits. Interestingly, best-corrected VA also improved in patients with intermediate AMD by 3.58 letters ($P = 0.025$) and in nonfoveal GA by 4.6 letters ($P = 0.003$). These results suggest that both rod and cone function are influenced by MTP-131. Importantly, the phase I study highlights the potential of LLVA and dark adaptometry as functional end points when evaluating drug efficacy in intermediate AMD or GA, although approaches to reduce the relatively large test-retest variability will need to be addressed. Further validation of functional end points that can accurately reflect visual function and disease progression would enable clinical trials to test the therapeutic potential of drugs at earlier disease stages.

The results of ReCLAIM-1 were sufficiently promising to warrant a randomized prospective current phase II trial (ReCLAIM-2). 50 However, at the May 21, 2022 American Society of Retina Specialists Clinical Trials at the Summit meeting, Stealth announced that ReCLAIM-2 did not meet its primary end points of mean change in LLVA and GA progression. However, elamipretide decreased the decline of the photoreceptor ellipsoid zone layer ($P < 0.01$), an important indicator of photoreceptor loss, and showed a $> 2$-line improvement in LLVA ($P = 0.04$) in patients with GA at week 48.

As new functional and imaging modalities emerge, the use of multimodal imaging, or the use of several different imaging modalities, combined with functional tests, will help to define the AMD phenotype beyond our standard clinical descriptions. Although classic AMD changes such as drusen are not sufficiently predictive of visual function to serve as a surrogate biomarker, intensive investigation for other findings is ongoing, as summarized by Terheyden et al. 17 This refinement will improve our ability to detect disease progression and treatment response. New modalities such as swept-source OCT, OCT angiography, adaptive optics, and adaptive optics-OCT may help to refine our AMD phenotypes and identify new imaging biomarkers that predict disease progression and treatment response. The settings and protocols of these imaging modalities will need to be optimized and integrated with functional assessments
of vision. However, the realities of patient tolerance during any clinical trial, time constraints, and financial limitations will be factors that guide the selection of imaging modalities in future clinical trials.

**Preclinical Considerations for Future Clinical Trials**

Slowing GA enlargement presents several disadvantages as a primary end point in clinical trials testing new drugs for dry AMD. Patients with GA, as the late stage of dry AMD, suffer from irreversible tissue injury and loss of photoreceptors, RPE, and choriocapillaris. As a result, the potential for visual recovery is limited. If a drug becomes FDA approved, its benefit might be limited to those patients without GA that involves the fovea. Conceptually, the factors causing disease onset or progression may be different from the major contributors of late-stage GA. Thus, the benefit of any drug for GA may not be effective for earlier stage disease. Alternatively, the etiologic pathways driving GA may be multiple. If true, then the benefit of a single treatment, while effectively influencing the intended dysregulated pathway, may not be beneficial because other disease-contributing processes overwhelm its treatment benefit. By resolving these shortcomings in AMD pathogenesis, therapy can be directed toward the most pathogenic signals at the appropriate disease stage.

The lack of success with the phase III CHROMA and SPECTRI anti-factor D trials might be explained by these scientific concerns rather than clinical design criticisms. What if complement activity via the alternative pathway, for example, is most pathogenic in early disease, but less so in GA? With this scenario, lampalizumab might be effective in early stages of AMD and ineffective in slowing GA enlargement. What if another pathogenic pathway, such as the inflammasome, mitochondrial dysfunction, impaired autophagy, or lipid dysregulation is the predominant pathogenic signal during GA? With this scenario, lampalizumab would likely not be effective. Finally, what if multiple pathogenic pathways, including complement, are major pathogenic factors in GA? Multidrug treatment that includes lampalizumab would likely be more effective than lampalizumab alone.

As mentioned previously, our understanding of AMD pathobiology is based on epidemiologic, genetic, epigenetic, pharmacologic and clinical trials, and preclinical studies. However, at present, scientists and clinicians do not communicate to the extent needed to accelerate getting effective treatments into the clinic. Basic research meetings on AMD are rarely attended by clinicians. Likewise, few basic scientists attend clinical meetings on AMD. Furthermore, the vast majority of clinical trials are conducted by physicians in clinical practice who interact sparingly with basic researchers. Likewise, few meetings occur between scientists in industry with those in academia. The details of industry sponsored clinical trials are not available to outside scientists to analyze. Finally, current funding agencies are not designed to enable large, collaborative initiatives that would integrate large, multidimensional approaches to solve the gaps in AMD pathobiology that will help design effective treatment strategies. Overall, improved communication between clinicians and scientists would enhance the translation of scientific understanding with treatment that can enter the clinic.

The incomplete understanding of AMD pathobiology is perhaps illustrated by the controversial role of *HTRA1* in AMD. *HTRA Serine Peptidase 1* has received significant focus since genetic variations have been strongly linked to AMD risk. As a result, the phase I GALLEG0 clinical trial assessed the safety of intravitreal anti-*HTRA1*. This humanized monoclonal antibody binds and neutralizes *HTRA1* activity. None of the 28 patients with GA who received monthly intravitreal anti-*HTRA1* had significant adverse effects. The phase II GALLEG0 trial is ongoing. Anti-*HTRA1* or sham-injected patients with GA are being randomized to receive either intravitreal anti-*HTRA1* or sham injection every 4 or every 8 weeks until week 76. Recently, Williams et al recently reported that the function of *HTRA1* is important to maintain RPE-Bruch membrane integrity. This group found that patients with the high-risk genetic variation had reduced *HTRA1*, which impaired maintenance of the RPE-Bruch membrane interaction. They concluded that *HTRA1* augmentation, rather than inhibition, should be considered for an AMD treatment.

With GA as a widely accepted functional end point surrogate, animal models have not fully reproduced GA to the extent that is needed for preclinical testing in a candidate drug’s journey to human clinical trial. The current GA animal models are not topographically limited, but instead tend to be pan-retinal in distribution. Importantly, the models are limited to a single underlying pathologic pathway and may not represent the full scope of GA pathophysiology. However, several recent mice models have shown GA-like features, and although not completely comprehensive, they can provide a model for preclinical drug assessment. The duration needed to develop GA can be an impediment. Improvement in animal models of GA would enhance our ability to determine whether a candidate drug will transition to a human clinical trial.

**Future Directions for Dry AMD Treatment**

Besides effective clinical trial design, further scientific understanding of AMD pathobiology will likely improve clinical trial success. The National Eye Institute’s AMD pathobiology group concluded that accelerated treatment for AMD will rely on addressing 3 key unanswered questions. First, what are the major pathogenic signals and what is their prioritized rank based on pathogenic contribution? Second, do these major pathways interact with one another? Finally, at what stage of AMD are they most pathogenic? To gain this understanding, improved access to human tissue, including high-quality, well-phenotyped AMD globes, aqueous, vitreous, blood, and urine samples from AMD and age-matched control patients is needed for research. The National Centralized Repository for
Alzheimer’s disease provides a template. Currently, this registry has accumulated nearly 680 000 patient samples of blood, brain tissue, cerebral spinal fluid, and associated data that are available for Alzheimer’s disease research.

Given the complex, multifactorial etiology of AMD, it is likely that different drugs targeting different pathogenic pathways will be needed at different disease stages. Alternatively, several different drugs that target the most pathogenic pathways might be needed for each AMD stage. Patients have different genetic profiles that establish disease risk. Currently, all the genetic variants have been associated with advanced AMD without separating GA from neovascular disease. The risk alleles that separate risk for GA from neovascular AMD would help with treatment design. It is also unclear which genetic variants are associated with early or intermediate AMD risk. Understanding this might help in understanding how to target treatment for early or intermediate AMD. Likewise, the different environmental influences such as smoking, sunlight exposure, diet, and other unknown factors on the epigenome and the epigenome’s impact in driving AMD will need to be clarified and considered in the treatment. Currently, identifying a reliable, effective, and practical test that reflects visual function for all stages of AMD is a topic of intense investigation and is essential for future trials, not only in GA, but also for earlier disease stages. Ultimately, a personalized approach for treating patients with AMD that targets the major pathogenic pathways that are influenced by these genetic and epigenetic factors at each disease stage may be needed.

Footnotes and Disclosures

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Abbreviations and Acronyms:
AMD = Age-related macular degeneration; FDA = Food and Drug Administration; GA = geographic atrophy; HTRA1 = HtrA Serine Peptidase 1; LLVA = low luminance visual acuity; CSF = contrast sensitivity; RPE = retinal pigment epithelium; VA = visual acuity.

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