The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Perspectives from clinical trials: is geographic atrophy one disease?

Sobha Sivaprasad[1,2]✉, Shruti Chandra[1,2], Jeha Kwon[3], Noorulain Khalid[4] and Victor Chong[2]

Geographic atrophy (GA) is currently an untreatable condition. Emerging evidence from recent clinical trials show that anti-complement therapy may be a successful treatment option. However, several trials in this therapy area have failed as well. This raises several questions. Firstly, does complement therapy work for all patients with GA? Secondly, is GA one disease? Can we assume that these failed clinical trials are due to ineffective interventions or are they due to flawed clinical trial designs, heterogeneity in GA progression rates or differences in study cohorts? In this article we try to answer these questions by providing an overview of the challenges of designing and interpreting outcomes of randomised controlled trials (RCTs) in GA. These include differing inclusion-exclusion criteria, heterogeneous progression rates of the disease, outcome choices and confounders.

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INTRODUCTION

Geographic atrophy (GA) is currently transitioning from an untreatable condition to a disease area of major interest owing to emerging evidence from clinical trials that therapies can reduce its growth rate over time [1]. However, several pivotal trials on the same class of therapies have failed. For example, complement pathway in AMD has been researched substantially over the last fifteen years and recently, anti-complement agents have shown some evidence of success in reduction of growth rate of GA lesion compared to sham in pivotal trials [2]. However, other complement inhibitors have failed all together or after promising results in early phase trials [3]. This begs the question: Is GA one disease? To put it in another way, are the investigational products only biologically effective in certain GA subtypes and if so, is it by chance that these subtypes represent a larger cohort in some trials and not others? There is no doubt that both basic and clinical research have increased our understanding of the pathogenesis and progression rates of GA. However, the results of clinical trials highlight gaps in our knowledge. Can we assume that failed clinical trials in GA are due to ineffective interventions? Or should we dwell deeper into the subtlety in clinical trial designs, heterogeneity in GA progression rates or differences in study cohorts?

We aimed to study these differences by examining some of the recent Phase II/III clinical trials on GA and provide a perspective on each question raised.

METHODS

Clinical trials reporting on GA progression and factors associated with GA progression were identified via a PubMed literature search and clinical trials.gov using the terms "geographic atrophy," "atrophy," "macular degeneration," "progression," "enlargement," and "growth". Primary literature search on PubMed for GA, also included search terms "complement cascade, "complement inhibitors", "gene therapy" in age-related macular degeneration. All searches were collated and sorted for relevance. We excluded review articles, case studies, pilot studies (defined as $N < 16$), papers reporting on macular atrophy in neovascular AMD, diseases other than AMD, preclinical studies, pathophysiology/histology of GA and non-English articles.

RESULTS

Details of the interventions for geographic atrophy that are currently being investigated in clinical trials or are in the pipeline are shown in Table 1. Clinical trials on these agents, if available, show variations in eligibility criteria. These include lesion characteristics, disease state of the fellow eye, visual function, age range of included patients and their genetic disposition. In addition, mode of delivery and mechanisms of actions of interventions and primary outcome measures differed.

DISCUSSION

Eligibility criteria

GA lesion characteristics. One of the key inclusion criteria for clinical trials is the lesion size of GA. Most trials include GA sizes ranging between ≥2.5 and ≤17.5 mm^2. However, Elamipretide (ReCLAIM2, NCT03891875, Stealth Bio) is being evaluated on a cohort with smaller GA size ≥0.05 and ≤10.16 mm^2 while FOCUS trial (GT005, NCT03846193, Gyroscope) on gene therapy have included a wider range of lesion sizes from ≥1.25 and ≤17.5 mm^2 [4, 5]. When comparing outcomes of GA trials, it is important to

[1]National Institute of Health Research Moorfields Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust, London, UK. [2]University College London, Institute of Ophthalmology, London, UK. [3]Oxford University Hospitals NHS Trust, Oxford, UK. [4]Manchester University NHS Foundation Trust, Manchester, UK.
✉email: sobha.sivaprasad@nhs.net

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Table 1. Interventions (current or pipeline) for geographic atrophy.

Interventions	Mechanisms of Action	ClinicalTrials.gov Identifier
	Targeting the complement pathway	
Pegcetacoplan (Apellis)	C3 inhibition	NCT03525613
Avacincaptad pegol (Iveric Bio)	C5 inhibition	NCT02686658
ANX007 (Annexon)	C1q inhibition	NCT04656561
NGM621 (NGM Biotherapeutics)	C3 inhibition	NCT04465955
Danicopan/ALXN-2040 (Alexion Pharmaceuticals/ AstraZeneca)	Factor D inhibition	NCT05019521
IONIS-FB-LRx (Ionis/Roche)	Factor B Inhibition	NCT03815825
HMR-59 (Hemera/Janssen)	MAC Inhibitor Gene Therapy	NCT03144999
GEM-103 (Gemini Therapeutics)	Recombinant CFH therapy	NCT04246866
GT005 (Gyroscope)	Complement Factor I gene therapy	NCT03846193
	HTrA1 inhibitor	
FHTR2163 (Genentech/Roche)	HTrA1 inhibitor	NCT03972709
	Stems cells	
OpRegen (lineage cell therapeutics)	Subretinal human embryogenic stem cells -RPE	NCT02286089
CPCB-RPE1 implant (Regenerative Patch Technologies)	Subretinal human embryogenic stem cells -RPE	NCT02590692
MA09-hRPE (Astellas Pharma Inc)	Subretinal human embryogenic stem cells -RPE	NCT01344993
	Neuroprotection	
Elamipretide (subcutaneous)/Stealth Biotherapeutics	**Repair mitochondrial dysfunction**	NCT03891875
	Visual Cycle Modulator	
ALK-001 (Alkeus)	A2E/Lipofuscin inhibitor	NCT03845582

note these differences [6, 7]. It may be that when the intervention does not require frequent intravitreal dosing or may be self-administered, the trial design may focus on earlier disease or extrafoveal GA or those with smaller lesion sizes. Therefore, the outcomes of these patients will differ to those of fovea-involving large lesions. It is understandable that a safety or dose response study such as FOCUS that is evaluating a subretinal delivery of a recombinant non-replicating adeno-associated viral (AAV) vector encoding a human complement factor would require a wider range of lesion sizes [5, 8]. However, trials that include large range of lesion sizes can result in wider standard deviations in progression rates and results of a study cohort may be more difficult to decipher [9]. In these studies, homogeneous smaller cohorts or individual outcomes may need to be identified to understand the effect of the intervention.

GA growth rates. Although the median growth rate of GA is about 1.78 mm^2/year, there are significant variability in individual enlargement rates in the natural history study by Sunness et al. [10–12]. In fact, only a small proportion of lesion sizes fell within the average range of growth rate [12]. Fleckenstein et al. reviewed the annualised growth rate and highlighted the inter and intraindividual variations in enlargement rates when only the baseline lesion size is considered [13]. As there are several well-characterised GA cohorts that include multimodal imaging, it may be appropriate to pool them and identify homogeneous cohorts with similar growth rates. These cohorts can include natural history studies and sham arms and, in some cases, the failed intervention arms. As an example, Mones and Biarnes demonstrated three GA phenotypes with different progression rates at ≥6 months based on data driven cluster analysis of GA lesions in 77 eyes [14]. With new reports on OCT classification of atrophy, it is now timely to re-visit heterogeneity of GA progression rates to inform future clinical trials [12, 15, 16]. In addition, for trials that have shown some success in reducing growth rates compared to the natural history, an opportunity is provided to identify 'super responders' in terms of reduced growth rate lesser than the lowest 95% confidence interval of the rates observed in the sham group.

Another consideration is the focality of lesions: Multifocal GA lesions progress faster than unifocal GA [17, 18]. The DERBY/ OAKS (APL-2, NCT03525613, Apellis), FILLY (APL-2, NCT02503332, Apellis) and GATHER-1 (Zimura, NCT02686658, IVERIC Bio) recruited multifocal GA lesions, with at least one focal lesion being at least 1.25 mm^2 (0.5 disc areas) [1, 19, 20]. Many other on-going trials have not included information on this inclusion criterion in clinical trials.gov. Unless stratified by lesion size and focality, these do have implications [18]. Another lesion characteristic that may influence growth rate is the presence of perilesional fundus autofluorescence (FAF) [21, 22]. This may represent lipofuscin accumulation in sick RPE cells or heaped RPE cells at the expanding rim of GA [23, 24]. This sign is a predictor of faster growth compared to lesions without this sign. The DERBY and OAKS (APL-2, NCT03525613, Apellis), FILLY (APL-2, NCT02503332, Apellis) and GATHER-1 (Zimura, NCT02686658, IVERIC Bio) included this sign as an eligibility criterion but this is not a universal requirement for GA trials [1, 19, 20]. Another consideration is the proportion of foveal and non-foveal involving GA in each trial cohort [25]. For example, DERBY and OAKS (APL-2, NCT03525613, Apellis) included both groups while GATHER-1 (Zimura, NCT02686658, IVERIC Bio) focused on non-foveal involving GA. Non-foveal, unifocal GA is likely to represent early disease while foveal involvement indicate long-standing disease [18, 26]. As both C3 and C5 inhibition appeared to be more effective in reducing growth rate of non-foveal involving lesions, it raises the question whether complement activation is more relevant in early disease than late disease, or whether established GA does not grow as fast hence more difficult to see a treatment effect. Non-foveal GA that extends towards the periphery grow faster than those that grow towards the fovea [27]. Therefore, these directional growths may need to be considered when correlating growth rates and functional changes in GA trials [28, 29]. Taken together, if there are two eyes with similar sized GA lesions, but one is multifocal, non-foveal and has perilesional hyperautofluorescence, it is likely to progress faster than the eye with a unifocal,

foveal involving without any rim hyperautofluorescence. Therefore, considering stratifying by baseline lesion size alone may not be sufficient. If these lesion characteristics are imbalanced between the sham and intervention arm, these may affect the primary outcome of lesion growth. Other lesions that have not been considered in clinical trials to date is the stratification of arms based on the presence of subretinal drusenoid deposits (SDD) [30]. These are associated with rod intercept delays suggesting rod photoreceptor dysfunction [31, 32]. These lesions may also represent irreversible functional losses despite its association with GA progression rates [33].

Fellow-eye features. All GA trials have ensured exclusion of any current or prior choroidal neovascularisation (CNV) in the study eyes at baseline. However, including patients with prior or current neovascular AMD in the fellow eye increases the risk of developing CNV in the study eye while being treated with the investigational product for GA [34]. The FILLY study included eyes with neovascular AMD in fellow eye [6]. The study showed a higher rate of new-onset CNV in the intervention (Pegcetacoplan, APL-2) arm compared to sham [35]. The question is whether this is due to the intervention or is this the expected natural history of neovascular AMD? A dose related increase in CNV was also seen in GATHER-1 study (Zimura, C5 inhibitor) but the incidence of CNV was lower (9.0–9.6%) compared to that of APL-2 (8.9–20.9%). The reason for this difference in CNV rates between a C3 and C5 inhibitor remains unclear. It may be that C5 inhibition is further downstream in the alternative pathway, which may minimize the disturbance of the C3-mediated complement homeostasis. However, if the FILLY intervention arm included those with no neovascular AMD in fellow eye in a subanalysis, the rate of CNV development in FILLY and GATHER-1 are similar [2]. In the GATHER-1 study on Zimura, the incidence of CNV in the untreated fellow eye was 11 patients (3.8%), and in the study eye, it was 3 patients (2.7%) in the sham control group, 2 patients (7.7%) in the Zimura 1 mg group, 8 patients (11.9%) in the Zimura 2 mg group, and 13 patients (15.7%) in the Zimura 4 mg group [20]. It is also interesting to note that the rate of CNV in DERBY/OAKS (APL-2, NCT03525613, Apellis) were lower than in the FILLY trial (Phase 2 trial of the same intervention), despite no differences in eligibility criteria between these Phase 2 and 3 trials on APL-2 in clinical trials.gov. These conflicting figures challenge our current understanding of the effect of complement inhibitors on onset of CNV.

The pivotal Phase 3 trials of both these agents (DERBY and OAKS (C3 Inhibitor, NCT03525613) and GATHER-2 (C5 inhibitor, NCT04435366) have retained eyes that converted to neovascular AMD during the study while being treated for GA, instead of censoring them from the analysis [19, 36]. Although it adds value to maintain the power of the study, development of CNV leads to reduction of drusen and the reporting of GA growth rate may be confounded by the influence of CNV related atrophy and anti-VEGF therapy.

Another point to consider is that GA progression rates in these eyes with neovascular AMD in fellow eye are slower than those with bilateral GA [11, 37, 38]. As such, the disease status in the fellow eye must also be considered if GA growth rate is the primary outcome. GA eyes with intermediate AMD in the fellow eye show slower GA growth rates compared to eyes with bilateral GA [38].

Visual function. Most trials whether focussed on both foveal and non-foveal GA or only on non-foveal GA had an eligibility criterion of ≥24 ETDRS letters (Snellen 20/320) [2]. However, Elamipretide trial (ReCLAIM2, NCT03891875, Stealth Bio) included only GA eyes with ≥55 ETDRS letters, emphasizing that the eligibility criteria of this trial differ from the pivotal complement trials to date [4]. In addition, the FOCUS trial (GT005, NCT03846193, Gyroscope) have included those with GA and BCVA ≤ 50 letters in cohorts 1to 3 and ≥34 letters in cohorts 4–6 [5]. As BCVA shows no correlation to GA growth, these differences in BCVA criteria are unlikely to influence primary outcome of GA growth reduction [26, 39]. However, as the primary aim of any intervention is to improve patient related outcomes and visual function, secondary outcome on preventing vision loss may differ between trials due to the BCVA inclusion-exclusion criteria.

Natural history studies have shown that GA is associated with low luminance visual acuity losses [18]. In addition, low luminance deficit is a marker of future visual loss [40]. Low luminance visual acuity losses are best highlighted in non-fovea involving GA and the progression of non-foveal GA may partly explain the worsening of this visual function [41, 42]. In addition, subretinal drusenoid deposits are strongly associated with low luminance deficit and likely signify rod dysfunction and these eyes also have a faster progression rate [41]. These findings suggest that a GA subtype with subretinal drusenoid deposits may represent a more irreversible end of the spectrum.

As BCVA does not correspond directly to GA lesion enlargement due to possible foveal sparing, alternative assessments are being explored to capture the relationship between anatomic progression and visual function decline, including microperimetry, reading speed assessments, and patient-reported outcomes need to be explored further [43–45]. A recent report from Holz group have shown how if GA involves the nasal side of fovea, it is likely to affect reading speed more than the right side [46, 47]. However, the Food and Drug Administration (FDA) does not currently accept this endpoint and further studies are required on functional changes in GA.

Age of patients. Some GA trials included patients aged 50 years or above while others have gone to as high as 65 years or above at baseline (AAVCAGsCD59, NCT0314499, J&J and Hemera) [48]. In addition, the age range is large in most trials extending from 50 to late 90 s. It is unclear whether age at recruitment is by itself an independent risk factor or whether younger age groups are likely to have non-foveal GA or earlier disease compared to participants in their late 90 s. Although local age-related differences in C3 and C5 are not well-defined, circulating C5 increases with age in contrast to age related decrease in factor D and C3 [49]. This may be an area worth further investigation. Prior growth rate of GA also determines future growth rate.

Genetic variants. Genetic factors account for approximately 71–80% of the risks in prediction models of advanced AMD [50–52]. The common genetic variants of *CFH*, *CFI*, *C3*, and *C2/CFB* in the alternative complement pathway, may account for 57% of known disease risk variants [52].

However, the CHROMA and SPECTRI studies on lampalizumab (Factor D inhibitor) showed that the progression rates of GA lesions in carriers of the complement factor I (CFI) risk allele did not differ significantly to their CFI-negative counterparts [3]. Based on the CFI inhibition studies alone, it seems irrelevant at present to include genetic variants as eligibility criteria for GA treatment trials. However, other studies are needed to further inform this decision [3].

Intervention types. When we consider complement inhibitors, there are GA trials that inhibit C3, C1q, C5, Factor B (IONIS-FB-LRx, NCT03815825, Ionis) and Factor D [1, 36, 53, 54]. Some have showed efficacy, and some have not. The aim of C5 inhibitors is to block C5 cleavage to decrease formation of pro-inflammatory drive by C5a and MAC formation and NLRP3 inflammasome. However, we have two failed trials on C5 inhibition and one with early promising result [20, 36, 53]. The trial on intravitreal LFG316 or Tesidolumab (NCT01527500, Novartis) a fully-human, high affinity C5 antibody showed no anatomical or visual acuity effect compared to sham at 18 months [55]. Similarly, eculizumab is

another C5 monoclonal antibody that was administered intravenously every other month for 6 months in GA patients and followed up for another 6 months but failed to show any difference in GA progression rates compared to sham [53]. However, Zimura, also a C5 inhibitor is a chemically synthesized aptamer (oligonucleotide-based ligand) and showed positive Phase 2b/3 results with a reduction of mean rate of GA growth over 12 months by 27.38% ($p = 0.0072$) for the Zimura 2 mg group and 27.81% ($p = 0.0051$) for the Zimura 4 mg group compared to the corresponding sham control group [20]. Can the results be explained by differences in GA lesion characteristics or are there other explanations? The failure of intravenous eculizumab may be explained by low drug concentration at target tissue, such as retinal pigment epithelial cells (RPE) due to systemic delivery. However, one would expect a monoclonal antibody (LFG316) to have meaningful vitreous half-life and we could assume that the pre-clinical data would have shown significant drug level at RPE before progressing to clinical trials. So, is it possible that pegylation is more advantageous than monoclonal antibodies as both APL-2 and Zimura are pegylated. Could aptamers be more stable than monoclonal antibody, although there is no evidence that is the case?

Primary endpoints. The primary endpoint of most of the GA trials is the change in total area of GA lesions as measured by FAF. However, the time points differ: APL-2 (NCT02503332) −12 months; GT005 (NCT03846193) − 48 months; NGM621 (NCT04014777) − 48 months; IONIS-FB-LRX (NCT03815825) − 49 months; HMR59–24 months (NCT04358471) and RG6147 (NCT03295877) 72 weeks [8, 19, 48, 54, 56, 57]. Both Zimura and ALK-001 studies have mean rate of change in GA on FAF as the primary endpoint [20, 58]. Recently, under special protocol assessment by the FDA, the GATHER 2 primary endpoint has been changed from mean rate of change of GA area over 12 months (considering 3 timepoints -baseline, 6 and 12 months) to mean rate of growth (slope) in at least these three timepoints. This amended analysis assumes a constant rate of growth of GA lesions over the study period [59]. This may apply to the primary outcome of all future pivotal GA trials.

When we consider visual function outcomes, BCVA change is a co-primary for ALK-001 at 48 weeks while elamipretide has chosen low luminance visual acuity as an endpoint at 48 weeks. In the FILLY study, C3 inhibitor did not show any significant change in BCVA or LLVA between arms and in GATHER studies that included only non-foveal GA, the higher dose of C5 inhibitor (4 mg) showed similar BCVA outcome to sham at 12 and 18 months despite a reduction of GA growth rate of 27.81% and 29.97% versus sham at these timepoints [1, 20]. Reduction of growth rate does not equate to visual function benefit, but these results question the lesion characteristics included in these arms. Was the GA growth to periphery reduced more profoundly? Alternatively, it might take longer before the effect on visual acuity is shown by delaying foveal involvement.

An in-depth analysis of the criteria used in GA trials highlights the major need to refine and improve patient selection. GA modelling studies should be able to differentiate fast versus slow progressors based on multiple lesion characteristics and not only lesion size. Predictors of direction of growth rate may add value to selecting the patient cohort. Although functional changes may not be appreciated in short term trials of 12–18 months duration, post-approval studies may be designed to confirm functional benefit as well as the subgroup that would benefit most from an intervention.

CONCLUSION

Here, we provide an overview of the challenges of designing and interpreting outcomes of randomised controlled trials (RCTs) in GA. These include differing inclusion-exclusion criteria, heterogeneous progression rates of the disease, outcome choices and confounders. Given the need for as many drugs to be approved for GA, it is important to encourage simple anatomical endpoints for drug approval. Although drugs should be evaluated on generalisable population, broad study eligibility criteria might lead to an effective drug failing to meet its primary endpoint and not obtaining approval. Pathway specific inclusion/exclusion criteria might lead to more positive study results. Outcomes of RCTs generally represent the average treatment effects across all included patients. A neutral average effect may represent benefit in some patients and not others and a beneficial average effect may differ in magnitude across subgroups. The risk of adverse events may also vary based on type of route of intervention albeit the drugs being of the same mechanisms of actions.

Use of these drugs in routine clinical practice and acquiring good real-world datasets with multimodal imaging will aid in understanding these GA subtypes and subtype-based interventions. In particular, one major unanswered question from these clinical trial results is whether GA is one disease entity? Having had mixed success with anti-complement trials, does it inform us that not all GAs are complement dependent? There may be GA lesions that may be explained by other pathogenesis such as lipofuscin overload resembling late onset Stargardt disease. These may likely respond more to A2E/ lipofuscin inhibitors than complement inhibitors. Eyes with GA and SDD did adversely in the LEAD trial, and they are associated with delayed rod intercept time due to rod loss [60, 61]. Would neuroprotection be a better option for eyes with SDD and/or outer nuclear layer thinning? Or do these GA lesions occur secondary to impaired visual cycle or mitochondrial defect? Targeting these pathophysiological pathways might be rewarding. Some GA lesions are due to thick Bruch's membrane resembling Sorsby Fundus Dystrophy [62]. A drug that can remove lipid from lipid laden Bruch's membrane might be an option for these subtypes. Finally, chromosome 10 disease (ARMS2/HTRA1) is associated with retinal thinning and might need a different intervention.

The recent data from AREDS suggest that GA cannot easily be subtyped by genotypes or phenotypes and that genetic information added little to the high predictive value of baseline severity of AMD for disease progression [63, 64]. In contrast, the EYE-RISK Consortium showed a stronger genetic association with late AMD [65]. Is it possible that AREDS2 was a study of intermediate AMD with specific inclusion criteria that were biased towards drusen associated GA while the European study was population based and allowed more diverse population? In reality, all these pathophysiological pathways might play some role in an individual patient pointing towards a need for personalised medicine.

There remain several avenues of research to be conducted to better understand GA especially in disease stratification so that novel interventions may be evaluated more efficiently and effectively.

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AUTHOR CONTRIBUTIONS

SS and VC- conceptualization; SC, JK and NK – methodology and literature review; SS and SC – writing (original draft preparation); SS and VC – writing (review and editing).

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ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Sobha Sivaprasad.