Exploring patient acceptability of emerging intravitreal therapies for Geographic Atrophy: a mixed-methods study

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Running head: Exploring acceptability of therapies for Geographic Atrophy

Abbreviations and Acronyms: AMD = Age-related Macular Degeneration; **GA** = Geographic Atrophy; **NHS** = National Health Service; **TFA** = Theoretical Framework of Acceptability; **VEGF** = Vascular Endothelial Growth Factor

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Abstract (247 words)

Background/Objectives: The acceptability of emerging intravitreal therapies for patients with Geographic Atrophy (GA) is currently unknown. This study therefore aimed to investigate the extent to which regular intravitreal injections may be acceptable to GA patients.

Subjects/Methods: 30 UK-based individuals with GA secondary to age-related macular degeneration (AMD), recruited from two London-based hospitals, were interviewed in April-October 2021 regarding acceptability of new GA treatments. Participants responded to a structured questionnaire, as well as open-ended questions in a semi-structured interview. The Theoretical Framework of Acceptability (TFA) informed framework analysis of the qualitative data.

Results: Twenty participants (67%) were female, and median (interquartile range (IQR)) age was 83 (78, 87) years. 37% of participants had foveal centre-involving GA, and better eye median (IQR) logMAR visual acuity was 0.30 (0.17, 0.58). Data suggested that 18 participants (60% (95% CI: 41-79%)) would accept the treatment, despite awareness of potential drawbacks. Eight participants (27% (95% CI: 10-43%) were ambivalent or undecided about treatment, and four (13%) (95% CI: 0-26%) would be unlikely to accept treatment. Reducing the frequency of injections from monthly to every other month increased the proportion of participants who considered the treatments acceptable. Conversely, factors limiting acceptability clustered around: the limited magnitude of treatment efficacy; concerns about side effects or the increased risk of neovascular AMD; and the logistical burden of regular clinic visits for intravitreal injections. Misunderstandings of potential benefits indicate the need for appropriately-designed patient education tools to support decision-making.

Conclusions: Our study suggests a majority of participants would be positive about intravitreal treatment for GA, in spite of potential burdens.

Introduction

Geographic Atrophy (GA) is the advanced form of the non-neovascular ('dry') type of age-related macular degeneration (AMD), affecting 276,000 people in the UK (1). While there are now approved treatments for wet AMD, until recently there has been no therapy for GA, a significant unmet need (2). Even before the foveal centre is involved, GA can have significant impact on functional activities and vision-related quality-of-life (3),(4).

Dysregulation of the complement cascade has been implicated in the pathogenesis of GA, and there are now two intravitreal complement inhibitors in late-stage development for the treatment of GA (2). Regular intravitreal injections are the standard of care for wet AMD, and a common mode of delivery in the current pipeline of treatments for GA in clinical trials. Recent positive results from phase 3 clinical trials of two intravitreal complement inhibitors provide hope for a treatment for GA (5–7). Indeed, in February 2023, the first-ever treatment for GA, pegcetacoplan, was approved for use by the Food and Drug Administration (FDA) in the US under the brand name Syfovre, based on reduced rates of lesion growth in the DERBY and OAKS trials (8). However, it is not yet known whether such treatments will be acceptable to patients outside clinical trial settings.

Current evidence from wet AMD suggests people will persevere with regular intravitreal treatment, even when associated with a high burden, when motivated by outcome expectations (9),(10). Despite efficacious outcomes of anti-VEGF therapy (11), some wet AMD patients report significant treatment burden associated with regular intravitreal injections, not only in terms of anxiety, discomfort, pain and/or side effects associated with these injections, but also the logistics of regularly travelling to the eye clinic, waiting times, and impacts on accompanying relatives or caregivers (12–14).

However, GA is different to wet AMD, being slower to progress, with well-documented variation in rates of progression across individuals, and asymptomatic in some patients until involving the fovea (15,16). Therefore, it is vital to understand whether patients

with GA would find it acceptable to commence and adhere to frequent intravitreal treatments, in order to slow GA progression.

Acceptability, as defined by Sekhon and colleagues in their Theoretical Framework of Acceptability (TFA), is a “multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention” (17). Acceptability is a crucial yet complex factor which can have implications for patients deciding to undergo a treatment, as well as adhering and persisting with it. As such, assessment of acceptability to patients should be a critical first step in the design, evaluation and delivery of healthcare interventions (18).

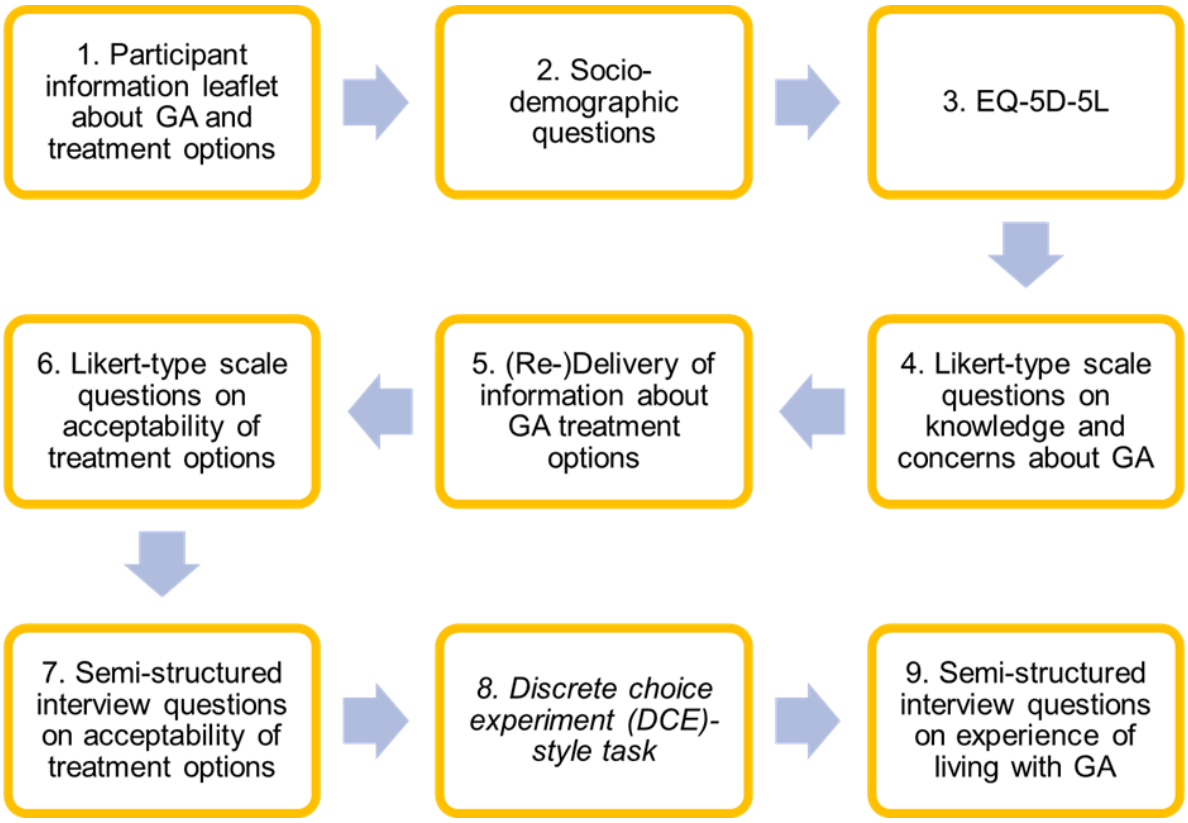
Our study’s central objective was to explore the overall acceptability of current intravitreal treatments in late-stage development for a sample of GA patients. We aimed to identify which aspects of the treatment are considered less acceptable; and to understand whether specific patient-related factors, contexts and circumstances influence GA treatment acceptability. A secondary aim was to explore what people with GA understand about their disease, its progression, current service provision, and their hopes for GA treatment and/or cure.

Methods

Study design and procedure

This study employed a cross-sectional, mixed-methods design (19), and full detail on methodological aspects is presented in the published study protocol (20). In summary, a structured questionnaire was used to quantify participants' attitudes to acceptability, as well as open-ended questions to explore participants' beliefs, hopes and concerns regarding GA treatment within their unique contexts and circumstances. Information communicated to participants about the treatments' efficacy was based on Phase 2 clinical trial results (21–23).

Figure 1. Summary of study procedure



The study procedure is summarised in Figure 1. The interview schedule, including Likert-type scale questions and semi-structured open-ended questions, is shown in Appendix 1. This interview schedule was developed in consultation with a group of eight

patient advisors, individuals living with GA who did not participate in this study but generously volunteered their time and insights.

Participant recruitment

Individuals with a diagnosis of GA were recruited from two Medical Retina clinics in London including Brent, one of the most ethnically diverse boroughs in London, UK (24). Included participants were required to be aged ≥ 50 years, and have a diagnosis of GA (bilateral or unilateral) secondary to age-related macular degeneration. Patients with other causes of GA - such as Stargardt's - or with concurrent retinal conditions were excluded. The aim was to recruit a cohort representative of the population in the community; therefore, some participants required an accompanying relative/caregiver to interpret parts of the interview.

In order to explore the views of participants with varied demographic and clinical characteristics, a purposive sampling strategy was employed, aiming to achieve maximum variation (25) in terms of: age; gender; ethnicity; education level; overall health status; prior experience of intravitreal injections (for wet AMD); best-corrected visual acuity (BCVA); laterality; and foveal involvement, with extrafoveal defined as greater than 0 microns from the fovea (26).

Consenting participants undertook an audio-recorded interview face-to-face or via telephone with authors AG, CD or JE between April and October 2021. This decision to undertake certain interviews by telephone was a pragmatic response to COVID-19 restrictions in place in the UK at the time (27).

Ethical considerations

Ethics Committee approval was obtained from the NHS Health Research Authority on 23 March 2021 (IRAS Project ID: 287824), and the study adhered to the tenets of the Declaration of Helsinki.

Data analysis

Quantitative responses

Descriptive analysis of demographic information and responses to the Likert-type scale questions was undertaken. Where appropriate, Spearman's rank (r_s) correlation coefficients were calculated to explore potential associations between responses to the Likert-type scale questions on acceptability (dependent variables) and demographic and clinical characteristics (independent variables). A *p*-value of <.05 was considered statistically significant. Statistical tests were conducted using SPSS, version 27.0 (SPSS Inc., Chicago, IL, USA).

Qualitative responses

Data from the semi-structured interview were transcribed verbatim, and analysed using the Framework Method of analysis (28,29). This systematic qualitative data analysis method allowed for both inductive analysis (whereby open coding of the data leads to generation of themes) and deductive analysis (whereby pre-existing theory – in this case, the TFA - shapes the development of themes). Initial coding was conducted by author JE, followed by a second round of coding involving authors JE, AG, DJT and CD working collaboratively. Discrepancies regarding the best fit of text segments within the TFA matrix were resolved by author MS, an expert in acceptability who developed the TFA. This was an iterative, recursive process, and over time the team collaboratively developed a codebook (Appendix 2), establishing decision rules for coding the data into the seven TFA constructs. The software package NVIVO V.10.2 (QSR International, Cambridge, Massachusetts, USA) was used to manage the qualitative data.

In tandem, data which did not fit within a TFA construct were coded inductively by authors JE, AG and CD, to develop a second framework matrix encapsulating important patterns in the data falling outside the TFA.

Analysis of qualitative data within the framework matrix illustrated that participants' responses fell within three distinct and recognisable positive, ambivalent, and negative categories.(30) The categorisation was based on participants' expressed intentions regarding the potential treatments. For example, a participant concluding that "*I think I would have the treatment at almost any cost*" (P26) would be placed in the positive category, while a participant concluding that the treatment "*is not for me*" (P24) would be placed in the negative category. Two authors (CD and JE) independently assigned the participants into the three categories, and then compared and collaboratively refined the categorisation. Certain disagreements in categorisation were discussed with reference to the individual case in the framework matrix, and all authors subsequently met to consider these disputed cases and reach consensus. After whole team discussion, the three categories were termed "Treatment at any cost" (positive), "Ambivalent", and "Unlikely to Proceed" (negative).

Results

Participants

Thirty participants (67% female) were interviewed, and demographic and clinical characteristics for each participant are displayed in Appendix 3. Median (interquartile range (IQR)) age was 83 (78, 87) years. Nineteen (63%) of participants identified as white, eight (27%) as South Asian, one (3%) as Black, and two (7%) as another ethnicity. The range of participants' primary languages is displayed in Appendix 4. In the case of three participants (P16, P20, and P25), interviews were interpreted by or mediated through an accompanying relative, due to English language or communication difficulties.

Better eye median (IQR) logMAR visual acuity (VA) was 0.30 (0.17, 0.58). Nineteen (63%) of the 30 participants had prior experience of intravitreal injections for neovascular (wet) AMD, while 11 (37%) were injection-naïve. Eleven (37%) of participants had centre-involving GA.

When asked to self-report their GA severity (Appendix 1, Q16), 13 participants self-rated their GA as mild, 13 as moderate, and 4 as severe. A more severe self-report was associated with worse VA in the better eye (r_s (28) = 0.40, p = 0.029). This is consistent with previous reports demonstrating that vision-related quality of life is primarily dependent on the better eye (31). However, there was no statistically significant correlation between self-reported GA severity and: worse eye VA; VA in the GA eye; VA in the fellow eye; GA laterality; or centre-involvement.

Median (IQR) time to travel to the eye clinic was 30 (15, 45) minutes. Ten (33%) participants lived alone while the other 20 (67%) lived with spouses or partners, children or carers. Fourteen (47%) participants reported attending eye clinic appointments alone, while the other 16 (53%) were accompanied by relatives, friends or caregivers. Twenty-three (77%) of participants reported living with other chronic health conditions apart from AMD/GA, with 8 (27%) living with diabetes. In the EQ-5D, the domains in which participants reported most problems were mobility (mean score = 2.3) and usual activities (mean score = 2.1).

Interview times with participants ranged from 27 minutes to 120 minutes. Twenty-four of the interviews (80%) were conducted in person, and six (20%) by telephone.

Quantitative findings on acceptability of intravitreal injections for GA

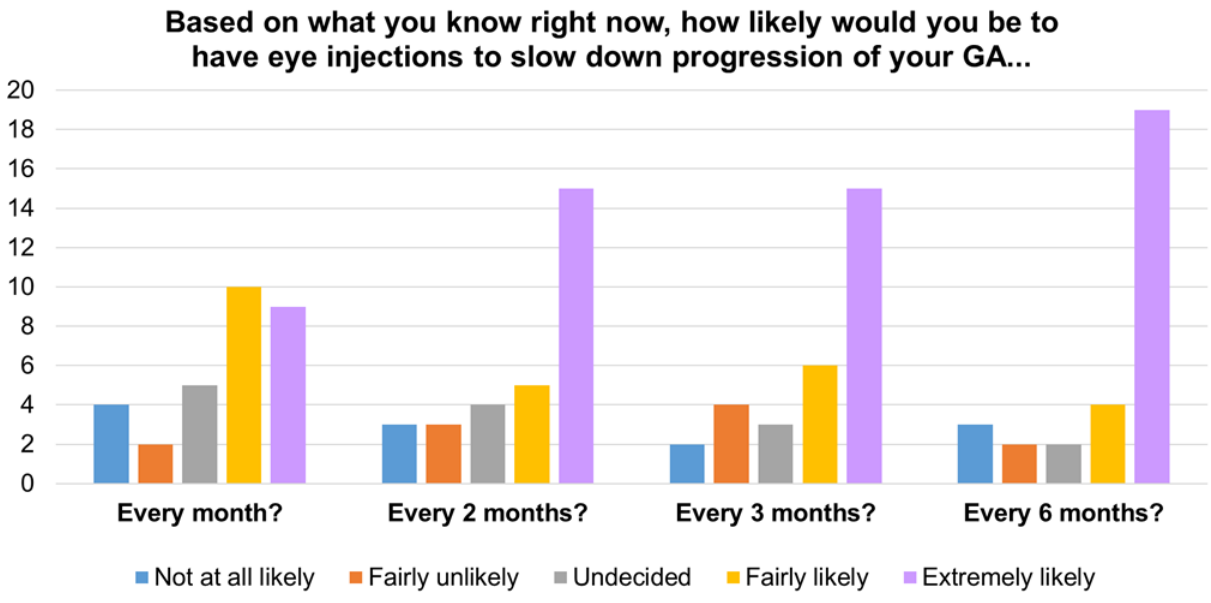
Findings from the Likert-type scale questions about acceptability of GA treatment are shown below in Table 1, while Figure 2 displays responses to questions about participants' willingness to undergo intravitreal injections at different intervals. Figure 2 demonstrates the increase in acceptability when injections were proposed every other month rather than

monthly, with 15 of 30 (50%) participants extremely likely to accept GA injections every other month, compared with 9 of 30 (30%) extremely likely to accept monthly GA injections.

Table 1. Responses to Likert-type scale questions on acceptability of GA treatments

Likert-type scale question and responses	*N*	*%*
In your view, are the risks of the injection procedure, as explained, worth the potential benefit of slowing down the progression of geographic atrophy?		
Yes	17	57
Not sure	11	37
No	2	7
Are you afraid of having an injection in your eye?		
Yes	10	33
Not sure	4	13
No	16	53
Are you concerned about the side effects of injections into your eye?		
Yes	10	33
Not sure	3	10
No	17	57

Figure 2. Responses to questions on acceptability of GA treatment at different intervals



Qualitative responses analysed within the TFA (see below) were additionally categorised into three groups, following analysis of the qualitative framework and reaching

consensus among all authors. Eighteen (60% (95% CI: 41-79%)) participants were deemed to be positively accepting of the treatment despite their awareness of the burdens and drawbacks, and this group was termed “Treatment at any cost”. Eight (27% (95% CI: 10-43%)) participants were deemed to be “Ambivalent”, hesitant about treatment and unsure about the balance of benefits versus risks and drawbacks. Four (13% (95% CI: 0-26%)) participants were deemed “Unlikely to proceed” with treatment. These figures correlate strongly with participants’ responses on the Likert-type scale question asking whether the risks of treatment are worth the benefits (Table 1), $r_s(28) = 0.69$, $p < 0.001$. Table 2 shows these acceptability levels, overall and as stratified by select ocular and demographic characteristics.

Table 2. Select ocular and demographic characteristics of participants, with overall acceptability levels

	N (%)	Positive (%)	Ambivalent (%)	Negative (%)	*P*-value (from Fisher Exact Test)
All participants	30 (100)	18 (60)	8 (27)	4 (13)	N/A
Age					1.00
<80	10 (33)	6 (20)	3 (10)	1 (3)	
≥80	20 (67)	12 (40)	5 (17)	3 (10)	
Gender					0.74
Female	20 (67)	12 (40)	6 (20)	2 (7)	
Male	10 (33)	6 (20)	2 (7)	2 (7)	
Ethnicity					0.59
Black	1 (3)	0	1 (3)	0	
South Asian	8 (27)	4 (13)	2 (7)	2 (7)	
White	19 (63)	12 (40)	5 (17)	2 (7)	
Other ethnicity	2 (7)	2 (7)	0	0	
Highest education level					0.31
Primary	3 (10)	1 (3)	2 (7)	0	
Secondary	18 (60)	11 (37)	5 (17)	2 (7)	
University	6 (20)	5 (17)	0	1 (3)	
Postgraduate	3 (10)	1 (3)	1 (3)	1 (3)	
EQ5D mean score					0.045*
<2 (better self-reported health)	17 (57)	7 (23)	6 (20)	4 (13)	
≥2 (worse self-reported health)	13 (43)	11 (37)	2 (7)	0 (0)	
Previous experience of intravitreal injections?					0.76
Yes	19 (63)	11 (37)	6 (20)	2 (7)	
No	11 (37)	7 (23)	2 (7)	2 (7)	
Foveal involving?					0.66
Yes	11 (37)	6 (20)	4 (13)	1 (3)	
No	19 (63)	12 (40)	4 (13)	3 (10)	
Better eye VA (logMAR)					0.81
≤0.3	16 (53)	9 (30)	4 (13)	3 (10)	
0.31-0.8	10 (33)	7 (23)	2 (7)	1 (3)	
>0.8	4 (13)	2 (7)	2 (7)	0 (0)	
GA eye VA (logMAR)					0.55
≤0.3	11 (37)	7 (23)	2 (7)	2 (7)	
0.31-0.8	11 (37)	7 (23)	2 (7)	2 (7)	
>0.8	8 (27)	4 (13)	4 (13)	0 (0)	

* $P < 0.05$

Inferential analysis demonstrated a statistically significant, moderate correlation between overall acceptability level (i.e. membership in the three groups discussed in the paragraph above) and EQ-5D score, $r_s(28) = 0.42$, $p = 0.021$. Participants with worse self-

reported health (higher EQ-5D score) were more likely to be in the “Treatment at any cost” group. Otherwise, there were no statistically significant associations between treatment acceptability and demographic/clinical factors, such as intravitreal injection history.

When considering correlations between other Likert-type scale question responses and demographic/clinical factors, statistically significant moderate correlations were only found for the question around concern about side effects of injections (Table 2). Concern about side effects correlated positively with: increased age, $r_s(28) = 0.44$, $p = 0.014$; presence of other chronic health conditions, $r_s(28) = 0.47$, $p = 0.009$; and naivety to intravitreal injections**,** $r_s(28) = 0.43$, $p = 0.018$.

Qualitative findings on acceptability of intravitreal injections for GA, based around the Theoretical Framework of Acceptability (TFA)

Participants’ responses to the semi-structured, open-ended interview questions were coded into the seven constructs of the TFA (17). Table 3 displays the seven constructs as defined in the TFA, and different reflections of the construct as generated from participants’ responses, illustrated with example verbatim quotations. Appendix 5 provides an extended version of these qualitative findings, with additional participant quotations.

235 Table 3. Participant reflections on prospective acceptability of GA treatment, categorised within the seven component constructs of the TFA

TFA construct, with definition	Positive (+), negative (-), or neutral (?) reflection of TFA construct	Example quotation (q)
Affective attitude: "How an individual feels about the intervention"	(+) Wish to delay further vision loss	1. "I think I would have the treatment at almost any cost" (P26) 2. "That's the main advantage, if it slows down what is going on with my eye." (P14)
	(+) Good relationship with eye clinic staff	3. "The girl who does it is very good, I always have the same one who does my injections…She puts you at ease because I was terrible when I first came in. I am still dying a thousand deaths but I am braver." (P10)
	(-) Anxiety around intravitreal injections	4. "I just don't like having the needle in the eye, the feeling of the injections, but it will not put me off if it will save my eyesight. The only thing I wouldn't like was if they were both done together." (P10)
	(-) Discomfort of clip/speculum during injection procedure	5. "What will put me off is this thing that they put in [the speculum]. That's the worse thing anyway." (P22) 6. "I am having injections in my other eye… it is very painful because of that clip they put on." (P3)
	(-) Long waiting times in clinic	7. "If it can be done more quickly, it would be much better. Because you come here ready for your injections and waiting makes you more nervous... So making it quicker will make it absolutely better." (P22)
Burden: "The perceived amount of effort that is required to participate in the intervention"	(+) Proximity to hospital	8. "I don't mind to come in as many times as required. I live very close, 10 minutes [away]." (P5)
	(+) Ease of travel to hospital	9. "I can get to the hospital quite easily. If my wife can't do it, I've got close family that would do it so there's no expense like taxis, et cetera." (P13)
	(-) Regular travel to hospital	10. "[A disadvantage is] having to come to hospital every so often… Just travelling, coming here." (P24) 11. "Coming to hospital if it's once in 6 months is ok... If it's frequent, that's going to be a problem." (P11)
	(-) Frequent treatment intervals	12. "I think if it is [an injection] every month, it is too much." (P29)
	(-) Impacts on accompanying relatives/caregivers	13. "There's the fact of getting here - I can't rely on my daughter all the time. She is trying to run a business. And it's not easy for me, I can't drive anymore." (P14)
	(-) Concerns about side effects	14. "Disadvantages would be the side effects… One thing is haemorrhage. And the other thing is the intraocular pressure going up." (P11)
	(-) Increased risk of wet AMD	15. "I would want to have longer vision, but I am concerned about risk of wet AMD." (P5)
Ethicality: "The extent to which the intervention has a good fit with an individual's value system"	(+) Belief that GA injections will help preserve independence	16. "My family would benefit knowing I can still use my eyesight. It will help me to maintain my independence. I am sure my family will be pleased about that." (P17)
	(-) Concerns about scarce NHS resources	17. "I wouldn't want to bother the [clinical] team. Because I'm sure that the team are so worried about everything… Injections every two months would be ideal, but it depends on the resources." (P30)
Intervention coherence: "The extent to which the participant understands the	(+) Clear understanding of anticipated treatment effects	18. "You want to keep your eyesight as long as possible. Even if it's not going to reverse it, you know you're going to be able to have sight that bit longer." (P16)
	(+) Understanding of the intravitreal injection process due to previous wet AMD treatment	19. "If it had been the first time then there would be a lot more questions to ask. But I know the routine would be the same as what I'm having now anyway, so I wouldn't be worried at all." (P9)

intervention and how it works (i.e. the 'face validity' of the intervention for the recipient)"	**(-)** Confusion regarding improvement of vision	20. "[After treatment] I think I will be able to read, I cannot read now… If I could keep whatever sight I have that would be very excellent - if you can stop it there and it doesn't get worse." (P28)
	(-) Queries regarding treatment timeline	21. "How long will treatments go on for? I think the treatments going on for a lifetime would be a concern for some patients." (P2) 22. "Can I withdraw from injections if I am not happy?" (P10)
	(?) Need for further information before treatment uptake	23. "Of course when I come to injections I am going to ask more about it and then decide if I take it." (P7) 24. "I would like to know for how long this treatment will be? And the success rate? … How certain it will maintain my eyesight for longer?" (P17)
Opportunity costs: The extent to which benefits, profits or values must be given up to engage in the intervention	**(+)** Lack of time pressure	25. "There aren't really disadvantages unless your time is used 24/7 and it's taking time for something else. But it doesn't, it wouldn't impact me in that way." (P28)
	(+) Injections free at point of use for patients in the UK	26. "I can't see any disadvantages to be honest with you. I mean if I was living in [United States of] America, it would probably cost me a £1000 a pop to have the injection. But I can't see the disadvantages." (P13)
	(-) Waiting at eye clinic takes time away from valued activities	27. "The waiting around is the most bothering. If I came in and out, I would be fine. I love the comfort of my home." (P19)
Perceived effectiveness: The extent to which the intervention is perceived as likely to achieve its purpose	**(+)** Anticipated benefits due to having vision for longer	28. "If it's going to slow down the process, give me better quality of life, better vision, I will have it… I might go blind in future but every little bit helps. So give me two to three years [more] of vision so I can watch TV, read books." (P25)
	(-) Belief that extra time with vision may not be worth it	29. "In six years, I will be nearly 90. Will I still be here? So from a time perspective it might not be worth it… How would I benefit really at my age?" (P15)
	(-) Belief that vision is currently good, therefore no perceived urgency for treatment	30. "At the moment, I'm quite happy… I can read the newspapers and everything. I feel much better. So, there's no point in taking injections." (P4)
	(-) Belief that vision-related quality of life has already deteriorated too much to benefit from treatment	31. "It will not bring back the lost vision… I have always been an avid reader…. I can still read, not bad. Sometimes, when I read, the end of the word goes - but I am getting used to that. So as the treatment will not bring back any of those, no, I think I will not benefit from it." (P3)
	(-) Difficulty of perceiving benefits of treatment first-hand	32. "I saw the benefits of having the [wet AMD] injections, but I am not sure if I will get the benefit of this new one." (P24)
Self-efficacy: The participant's confidence that they can perform the behaviour required to participate in the intervention	**(+)** Confidence to regularly attend eye clinic	33. "I would rather come here [to the eye clinic] for treatment. I just feel confident when I come here." (P15)
	(-) Concerns about feasibility of longer-term commitment to treatment	34. "In another year, I don't know how it is going to be. So I don't know how long I can commit for treatment." (P7)

Qualitative findings beyond the TFA

Themes were also generated inductively from aspects of participants' accounts which fell outside the constructs of the TFA, but were still relevant to GA treatment acceptability. These themes and associated quotations are presented in Appendix 6.

Discussion

Our study findings suggest that a majority of GA patients would be accepting of intravitreal treatment for GA, whilst recognising potential burdens and inconveniences. The key concern for people with GA, which emerged in our study as the central motivation for treatment, is the high priority placed on ability to continue with vision-specific activities, particularly for those in worse self-reported health. For 60% of the study participants, despite acknowledging potential drawbacks, the possibility of extending the time they have to engage in vision-specific activities and remain independent was deemed a worthy trade-off, and they would therefore opt for 'treatment at any cost'. The factors limiting acceptability were largely clustered around concerns about magnitude of treatment efficacy, fear of wet AMD and side effects (and to a lesser extent, the injection procedure itself), and logistics of regular eye clinic visits for treatment. Specifically, reducing the frequency of injections from monthly to every other month increased the proportion of participants that were extremely likely to accept these treatments if offered now.

Interestingly, as explored within the TFA's Perceived Effectiveness construct, there were a number of participants with better visual acuity than the sample average who saw no value in treatment, because they perceived their vision as currently good and thus saw no rationale for treatment. However, natural history studies demonstrate a progressive decline in vision over time, with almost two-thirds of eyes observed to have foveal involvement associated with moderate or severe sight loss within 4-5 years (16,32). Additionally, the current treatments in late-stage trials have been suggested to have higher efficacy the further the lesion is from the fovea (5,33), thus extending time of foveal preservation. Therefore, there is a challenge here to accurately identify and robustly support patients at

risk of foveal involvement in future whilst their visual acuity remains good, in order to maximise potential to preserve vision with these treatments.

Given the heterogeneity of GA in terms of progression, observation of recent progression over time with multi-modal retinal imaging could be a useful way to demonstrate the potential likelihood for the individual patient to benefit from these treatments. Further work is required to develop precise and robust risk stratification tools and to determine the time-difference in progression that patients will perceive as meaningful. Data from Colijn and colleagues' analysis of four population-based cohort studies (16) suggests that delaying progression to foveal involvement by at least 0.8 years could allow the average individual with non-foveal GA to retain central vision and avoid severe vision loss for the rest of their life.(34) As such, even a modest reduction in rate of progression could deliver clinically meaningful benefits to a large number of patients.

Within the Burden construct, the increased acceptance of every other month injections is worth highlighting, particularly given recent 24-month outcome data from the DERBY and OAKS phase 3 registration trials. These trials demonstrate a marginal difference in GA growth reduction between the monthly and every other month treatment regimen (19% reduction for eyes treated monthly vs 16% reduction for eyes treated every other month in DERBY; 22% reduction for eyes treated monthly vs 18% reduction for eyes treated every other month in OAKS) (35). On the other hand, monthly injections in these trials were associated with a near doubling of the rate of exudative choroidal neovascularisation (11.9% in monthly versus 6.7% when treated every other month). Similar rates of choroidal neovascularisation have been reported in the avacincaptad pegol trials (36). An every-other-month regime could thus deliver increased adherence and persistence, a better safety profile (almost 50% reduction in neovascularisation risk) and greater cost-effectiveness for healthcare funders, with only a minimal reduction in efficacy.

Furthermore, participants' fear of wet AMD risk commonly emerged as an off-putting aspect of treatment, although for some participants this was less of a concern because of

the availability of a more efficacious treatment for wet AMD, or if they were already being treated for wet AMD. Even for study participants generally accepting of the GA treatment, the prospect of injections on the same day for wet AMD and for GA was burdensome (although there was one participant – P26 – who welcomed the convenience of consecutive same-day injections). A 2-3 fold increased risk of wet AMD as demonstrated in the phase 3 trials (33,36) may necessitate regular monitoring with retinal imaging for these patients associated with increased costs to payers. Innovative patient pathways and service delivery will be required to rollout these treatments. Shared-care models involving monitoring by community optometrists may help expand capacity and reduce time spent in hospital clinics.

Listening to our study's participants, it is vital that patients are effectively counselled on the natural history of GA and accurate expectations of treatment effects; including the fact that they are unlikely to perceive treatment benefits directly, and can expect their GA to continue to progress, albeit at a slower pace. Treatment initiation should follow a shared decision-making process involving the patient and their eye care team (37,38). Since participants also noted that their stance on treatment may change over time, counselling on treatment expectations will need to take place regularly to support adherence (10).

Our results confirm that longer-acting therapies which slow progression to a higher degree or halt atrophy remain an unmet need and must be the focus for future drug development. In the meantime, more frequent ocular assessment may well be welcomed by many GA patients, who are currently discharged from eye clinics in the UK, with no targeted psychosocial support for what is a progressive and debilitating disease (39,40).

Strengths and Limitations

Initially conceived as an exploratory pilot study, our study has a number of limitations. Firstly, as a relatively small-scale study involving patients from two London-based sites, there is limited generalisability to other contexts, for example other geographies in the UK

(e.g. rural populations) or other countries with different eye care systems. Secondly, our system of categorisation of participants into three acceptability groups was undertaken in response to emergent patterns in our framework matrix, but did not follow a standardised method that had been predetermined in our protocol. This categorisation could variously be considered too subjective or reductive, and our forthcoming larger, multi-site quantitative study will provide a more robust, generalisable quantification of GA treatment acceptability. Thirdly, while the TFA was used to analyse the data, our interview topic guide was not systematically developed from the TFA; instead, more open-ended questions were used to explore participants' hopes, beliefs and concerns around treatment, based on our literature review and the insights of our study's patient advisory group. This meant that for certain TFA constructs (e.g. Ethicality and Self-efficacy), there was less rich discussion than there may have been, had the TFA been used expressly to shape the topic guide.

Nonetheless, this is the first study systematically exploring prospective acceptability of GA intravitreal therapy among a diverse sample of patients, recruited using maximum variation sampling to try to ensure participants were representative of the broader GA population. The quantitative element helps to corroborate and (tentatively) quantify interpretations made on the basis of the qualitative data; indeed, there was close alignment between responses to the Likert-type scale questions and patterns in the qualitative data. Analysis of the qualitative data using the robust Theoretical Framework of Acceptability allowed us to make sense of a rich and complex dataset, and to identify the key motivating factors driving acceptability and what most concerns GA patients and could be modified in future.

Conclusion

In summary, a majority of participants (~60%) were positive about GA treatment, despite the potential inconvenience and burdens. Participants' key concerns related to the modest efficacy of treatment, the risk of wet AMD and side effects, and logistical issues

associated with frequent, potentially lifelong treatment. We observed a sharp increase in patient acceptability when considering an every-other-month treatment regimen in comparison to monthly treatment. Given encouraging efficacy and safety outcomes for the every-other-month regimen, this may be an optimal dosing label for patients, payers and health services.

Further research in a larger population of patients with GA is required to confirm our findings, and identify any correlations between patient acceptability and structural and functional biomarkers of GA severity. We expect such research to aid patient education, selection and individualisation of treatment regimes.

Summary

What was known before

- Intravitreal injection treatments for Geographic Atrophy (GA) are currently showing promising results in Phase 3 clinical trials, significantly slowing down (although not stopping or reversing) GA progression.
- The acceptability of emerging treatments to patients is a vital consideration, in order to support design and delivery of interventions that patients will adhere to and persist with in the real world.

What this study adds

- Sixty percent of participants would opt for the intravitreal treatments to slow GA progression in spite of potential treatment burdens.
- Participants' key concerns related to the modest efficacy of treatment, the risk of wet AMD and side effects, and logistical issues associated with frequent, potentially lifelong treatment.
- Our study illustrated a sharp increase in patient acceptability when considering an every-other-month treatment regimen in comparison to monthly treatment.

- Common misunderstandings regarding the workings and likely effects of the intravitreal treatments demonstrate a need for clear, accessible patient education tools.

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Figure and table legends

Figure 1. Summary of study procedure

Figure 2. Responses to questions on acceptability of GA treatment at different intervals

Table 1. Responses to Likert-type scale questions on acceptability of GA treatments

Table 2. Select ocular and demographic characteristics of participants, with overall acceptability levels

Table 3. Participant reflections on prospective acceptability of GA treatment, categorised within the seven component constructs of the TFA

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Author Contribution statement

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Conflict of Interest

Jamie Enoch, Arevik Ghulakhszian and Mandeep Sekhon declare that they have no competing interests.

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Data Availability Statement

The raw datasets generated during and analyzed during the current study are not publicly available, because the in-depth and specific information they contain could compromise the privacy of the participants, given that most participants were recruited from a single London-based site. However, elements of the anonymised raw data may be shareable on reasonable request; in which case, please contact the corresponding author for further information.

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Appendices

Appendix 1: Study questionnaire

Appendix 2: Codebook for coding qualitative data

Appendix 3: Demographic and clinical characteristics of study participants

Appendix 4: Primary language(s) spoken, as self-reported by participants (n=30)

Appendix 5: Extended results with additional quotes

Appendix 6: Themes relating to GA treatment acceptability outside the TFA constructs