# Intravitreal treatment for Geographic Atrophy: Coming soon to a patient near you?

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Geographic atrophy (GA) is estimated to account for one-quarter of legal blindness in the UK [1], with an estimated prevalence of 276,000 cases in the UK in 2012 compared to 263,000 cases of neovascular AMD (nAMD), and an estimated annual incidence of 39,000 cases [2]. Globally, approximately 5 million people have GA in at least one eye [3], and the incidence is expected to rise with ageing populations. GA involves progressive loss of areas of the retinal pigment epithelium, photoreceptors and underlying choriocapillaris, and leads to irreversible vision loss. About one-half of patients develop GA in both eyes within seven years of initial diagnosis [4]. People with GA have worse vision-related quality-of-life even when their visual acuity is preserved; for example, we have shown that they have increased anxiety about mobility, problems with searching for objects and difficulty recognising faces [5-9]. With no current treatment for GA, patients diagnosed in hospital eye service are typically discharged to the community for monitoring [10, 11].

New therapies may soon be available for GA based on recent advances in our understanding of the pathogenesis of the disease. Whilst the mechanisms of action for these therapies fall into several categories including cell-based therapy, complement inhibition, neuroprotection and visual cycle modulation [12], regular intravitreal injections is a common mode of delivery in the current pipeline of treatments for GA in clinical trials. Inhibitors of components of the complement cascade are an area of intense research with two such agents, pegcetacoplan and avacincaptad pegol demonstrating ability to slow the mean rate of GA growth in phase 2 trials by 29.0% and 27.4% respectively, when delivered monthly [13, 14]. Global phase 3 trials of two agents are due to report primary outcomes

later in 2021, with cautious optimism that these may herald the arrival of effective treatment for GA in the clinics for the first time. However, it is unknown whether regular intravitreal therapy will be acceptable to GA patients for the proposed benefit of slowing down but not halting or reversing visual loss. It is also unknown whether resource constraints would limit implementation of these therapies, given the sheer volume of patients affected.

Acceptability is critical for adherence to and persistence with therapy [15, 16]. In nAMD, patients report a high treatment burden [17-19]; however, concerns about further sight loss may outweigh negative experiences and motivate patients to continue treatment [18]. In contrast to nAMD, where loss of vision is typically sudden and treatment can lead to improvements in vision, vision loss in GA is a gradual process. Moreover, current intravitreal treatments proposed for GA slow down, rather than halt or reverse, vision loss. So, will patients with GA be similarly motivated to adhere to frequent intravitreal treatments, and what factors would make such treatments acceptable?

An understanding of GA treatment acceptability and its determinants (Table 1) could: influence design of future interventions; identify patients who may require targeted counselling; and support a shared-care service delivery model for patients with GA.

GA severity, progression and outcomes demonstrate considerable between-person variability [20, 21]. Should treatments become available, it will be necessary to identify patients at high risk of progression and thus more likely to benefit from intervention. With increasing evidence that shared-care models can work in the management of nAMD [22, 23], we foresee that a similar pathway could be established for GA and that a GA referral

tool - incorporating indices of GA severity, progression, and acceptability of intervention - would facilitate this.

Our ongoing pilot study investigates acceptability of intravitreal injections among GA patients, using a questionnaire and semi-structured interview guide co-designed with eight GA patients. Our detailed methodology is reported elsewhere [24]; in summary, we are conducting interviews with 30 participants with a GA diagnosis, to explore in-depth their beliefs, hopes and concerns regarding GA and intravitreal treatment. We are recruiting an ethnically diverse and clinically varied sample of participants with GA, using a maximum variation purposive sampling strategy. The sample will include 15 participants with a history of intravitreal injections in their fellow eye and 15 who are naïve to intravitreal injections. We will also use a task inspired by Discrete Choice Experiments, to facilitate participant discussion of the benefits versus drawbacks of intravitreal treatment for GA. Interviews will be audio-recorded and transcribed, and qualitative data analysis will be conducted using the Framework Method of analysis [25] to identify key themes from participants' accounts. The results will contribute to our understanding of patients' knowledge of GA and quality-of-life in GA, and will be used to design a large quantitative study to validate an acceptability tool generalizable to patients with GA.

We hope that better understanding of acceptability will guide GA treatment design and delivery, and maximise patient benefit when treatment becomes available.

**Table 1.** The seven component constructs in Sekhon et al.'s theoretical framework of acceptability (TFA) [16], and examples of how they are explored in the pilot study

*[Insert Table 1 here]*

## References


1. Rees A, Zekite A, Bunce C & Patel PJ. How many people in England and Wales are registered partially sighted or blind because of age-related macular degeneration? *Eye (Lond)* **28**(7), 832–837 (2014)
2. Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE & Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *Br J Ophthalmol* **96**(5), 752-756 (2012)
3. Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng CY et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health* **2**(2), e106–116 (2014)
4. Lindblad AS, Lloyd PC, Clemons TE, Gensler GR, Ferris FL, Klein ML et al. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. *Arch Ophthalmol* **127**, 1168–1174 (2009)
5. Taylor DJ, Hobby AE, Binns AM & Crabb DP. How does age-related macular degeneration affect real-world visual ability and quality of life? A systematic review. *BMJ Open* **6**(12), e011504 (2016)
6. Taylor DJ, Smith ND & Crabb DP. Searching for objects in everyday scenes: Measuring performance in people with dry age-related macular degeneration. *Invest Ophthalmol Vis Sci* **58**(3), 1887-92 (2017)
7. Taylor DJ, Smith ND, Binns AM & Crabb DP. The effect of non-neovascular age-related macular degeneration on face recognition performance. *Graefe's Arch Clin Exp Ophthalmol* **256**(4), 815-21 (2018)
8. Taylor DJ, Smith ND, Jones PR, Binns AM & Crabb DP. Measuring dynamic levels of self-perceived anxiety and concern during simulated mobility tasks in people with non-neovascular age-related macular degeneration. *Br J Ophthalmol* **104**(4), 529-534 (2020)

9. Higgins BE, Taylor DJ, Bi W, Binns AM & Crabb DP. Novel computer-based assessments of everyday visual function in people with age-related macular degeneration. *PLoS One* **15**(12), e0243578 (2020)
10. Taylor DJ, Jones L, Binns AM & Crabb DP. 'You've got dry macular degeneration, end of story': a qualitative study into the experience of living with non-neovascular age-related macular degeneration. *Eye* **34**(3), 461-473 (2020)
11. Taylor DJ, Jones L, Binns AM & Crabb DP. Response to 'Comment on: 'You have got dry macular degeneration, end of story': a qualitative study into the experience of living with non-neovascular age-related macular degeneration'. *Eye* **34**(10), 1937-1938 (2020)
12. Mahmoudzadeh R, Hinkle JW, Hsu J & Garg SJ. Emerging treatments for geographic atrophy in age-related macular degeneration. *Current Opinion in Ophthalmology*, **32**(3), 294-300 (2021)
13. Jaffe GJ, Westby K, Csaky KG, Monés J, Pearlman JA, Patel SS et al. C5 Inhibitor Avacincaptad Pegol for Geographic Atrophy Due to Age-Related Macular Degeneration: A Randomized Pivotal Phase 2/3 Trial. *Ophthalmology* **128**(4), 576-586 (2021)
14. Liao DS, Grossi FV, El Mehdi D, Gerber MR, Brown DM, Heier JS et al. Complement C3 Inhibitor Pegcetacoplan for Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Randomized Phase 2 Trial. *Ophthalmology* **127**(2), 186-195 (2020)
15. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ* **350,** h1258 (2015)
16. Sekhon M, Cartwright M & Francis JJ. Acceptability of healthcare interventions: An overview of reviews and development of a theoretical framework. *BMC Health Serv Res* **17**(1), 88 (2017)
17. Boyle J, Vukicevic M, Koklanis K & Itsiopoulous C. Experiences of patients undergoing anti-VEGF treatment for neovascular age-related macular degeneration: a systematic review. *Psychol Health Med* **20**(3), 296-310 (2015)

18. Boyle J, Vukicevic M, Koklanis K, Itsiopoulous C & Rees G. Experiences of patients undergoing repeated intravitreal anti-vascular endothelial growth factor injections for neovascular age-related macular degeneration. *Psychol Health Med* **23**(2), 127-140 (2018)
19. Senra H, Ali Z, Balaskas K & Aslam T. Psychological impact of anti-VEGF treatments for wet macular degeneration: a review. *Graefe's Arch Clin Exp Ophthalmol* **254**(10), 1873-1880 (2016)
20. Sunness JS, Margalit E, Srikumaran D, Applegate CA, Tian Y, Perry D et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology* **114**(2), 271-277 (2007)
21. Fleckenstein M, Mitchell P, Freund KB, Sadda S, Holz FG, Brittain C et al. The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration. *Ophthalmology* **125**(3), 369-390 (2018)
22. Gale RP, Mahmood S, Devonport H, Patel PJ, Ross AH, Walters G et al. Action on neovascular age-related macular degeneration (nAMD): recommendations for management and service provision in the UK hospital eye service. *Eye* (Lond) **33**(Suppl 1), 1-21 (2019)
23. Reeves BC, Scott LJ, Taylor J, Harding SP, Peto T, Muldrew A et al. Effectiveness of Community versus Hospital Eye Service follow-up for patients with neovascular age-related macular degeneration with quiescent disease (ECHoES): a virtual non-inferiority trial. *BMJ Open* **6**(7), e010685 (2016)
24. Enoch J, Ghulakhszian A, Crabb DP, Dinah C & Taylor DJ. Acceptability of intravitreal injections in geographic atrophy: Protocol for a mixed-methods pilot study. *BMJ Open* (in press) (2021)
25. Gale NK, Heath G, Cameron E, Rashid S & Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology*, **13**(1), 1-8 (2013)

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**Author Contribution statement**

Concept and drafting of the article: CD. Editing or revising the manuscript critically: JE, AG, DJT, DPC. Final approval of the version to be published: CD, JE, AG, DJT, DPC.

**Conflicts of Interest**

Christiana Dinah has served on advisory boards for Novartis, Allergan and Apellis.

Jamie Enoch, Arevik Ghulakhszian and Deanna J Taylor have no interests to declare.

David P Crabb reports grants from Roche, grants and personal fees from Santen, grants and personal fees from Apellis, grants from Allergan, personal fees from Thea, personal fees from Bayer and personal fees from Centervue, outside the submitted work. DPC receives funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant 116076 (Macustar). This joint undertaking receives support from the European Union's Horizon 2020 research and innovation program and European Federation of Pharmaceutical Industries and Associations (EFPIA). The communication reflects the author's view and that neither IMI nor the European Union, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained therein.

**Table 1.** The seven component constructs in Sekhon et al.'s theoretical framework of acceptability (TFA) [16], and examples of how they are explored in the pilot study

| **Component construct in TFA** | **Definition within the TFA** | **Example with potential relevance to GA treatment** |
|---|---|---|
| Affective attitude | How an individual feels about the intervention | Anxiety about the injection, despair and fear of losing vision, or hope of slowing vision loss. |
| Burden | The perceived amount of effort that is required to participate in the intervention | The challenges of monthly visits to clinic for injections, and associated pain and discomfort, transport issues, or potential impact on accompanying relatives. |
| Ethicality | The extent to which the intervention has a good fit with an individual's value system | Some individuals with GA may be more proactive and feel they can take control by having injections. Meanwhile, other individuals could be more fatalistic (or accepting) about the inevitability of vision loss, especially if treatment outcomes are unclear or uncertain. Our patient advisors also highlighted that some people with GA may have concerns around the high expense and resource implications for the NHS. |
| Intervention coherence | The extent to which the participant understands the intervention and how it works; the face validity of the intervention for the recipient | Clear understanding of the impact the intravitreal injections would have, in terms of slowing down the rate of vision loss from GA (rather than halting or reversing it). |
| Opportunity costs | The extent to which benefits, profits or values must be given up to engage in the intervention | If a person with GA (and/or an accompanying relative/caregiver) has to take time off work or cancel commitments to attend injections. |
| Perceived effectiveness | The extent to which the intervention is perceived as likely to achieve its purpose | An appreciable sense that the intravitreal injections are slowing the patient's rate of vision loss. |
| Self-efficacy | The participant's confidence that they can perform the | Confidence in ability to attend regular injections and to persist with treatment over the long-term. |

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|---|---|---|
| | behaviour required to participate in the intervention | |