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ORIGINAL RESEARCH

Content Validity and Cognitive Debriefing of a Patient-Reported Outcome Instrument Evaluating Symptoms and Disease Impact in Patients with Geographic Atrophy

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ABSTRACT

Introduction: Geographic atrophy (GA) occurs in the later stages of dry age-related macular degeneration (AMD) and impairs visual acuity, eventually causing permanent blindness in some patients and impacting patient quality of life. Patient-reported outcome (PRO) measures that assess the experience of patients with visual impairment do not sufficiently capture all concepts salient to patients with GA. In this study the experience of patients with GA secondary to dry AMD was evaluated, and items from the novel 10-item Visual Impairment Symptom Severity Assessment (VISSA-10) PRO instrument were mapped to salient symptoms to assess its content validity, ease of use, and relevance.

Methods: Concept elicitation interviews were conducted with patients with GA to determine salient symptoms and impacts of GA, and a conceptual model was developed to reflect these. The items in the VISSA-10 instrument were then mapped onto the salient symptoms included in this conceptual model. Cognitive debriefing interviews were also conducted with the same cohort to determine the comprehensiveness and comprehensibility of the instrument, and to qualitatively assess levels of change considered meaningful by patients.

Results: In total, 25 symptoms and 36 impacts were reported by 19 patients with GA, with seven symptoms and 11 impacts identified as salient. Of these, 12 symptoms and 15 impacts reported were not included in a previously published conceptual model for patients with dry AMD. Overall, eight of the ten items from the VISSA-10 instrument mapped to salient symptoms reported by patients with GA. All patients reported that the instrument was clear and easy to understand.

Conclusions: The VISSA-10 instrument was shown to be content valid, clear, and comprehensible, with sufficient concept coverage to measure the experience of patients with GA. Although further quantitative validation is

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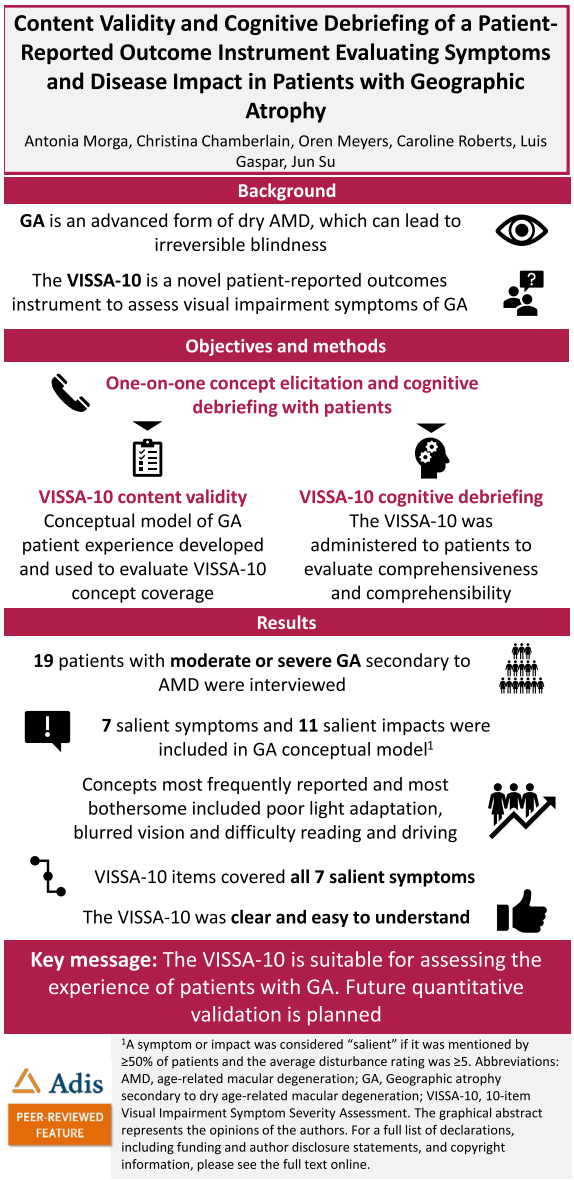
required, this instrument has demonstrated potential for implementation in future clinical trials to evaluate the efficacy of new treatments for GA.

Graphical Abstract:



Keywords: Clinical outcomes assessment; Cognitive debriefing; Content validity; Geographic atrophy; Patient-reported outcomes; Vision; Visual acuity

Key Summary Points

Why carry out this study?

There are currently no approved treatments for reversing geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD); therefore, the disease-related vision loss is permanent.

The aim of this study was to evaluate the experience of patients with GA secondary to dry AMD and to assess the content validity, concept coverage, and comprehensibility of the novel 10-item Visual Impairment Symptom Severity Assessment (VISSA-10) patient-reported outcome instrument.

What has been learned from the study?

Seven salient symptoms and eleven salient impacts were included in the GA conceptual disease model, and items of the VISSA-10 instrument covered all of the salient symptoms.

The content of the VISSA-10 instrument was shown to be valid for evaluating the experience of patients with GA with sufficient concept coverage and was clear and easy to understand by patients.

The VISSA-10 instrument has the potential to be used in future clinical trials, pending further quantitative validation.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.21961166.

INTRODUCTION

Age-related macular degeneration (AMD) is a progressive disease characterized by the formation of insoluble retinal deposits, pigmentation abnormalities, and vision loss [1, 2]. Approximately 8.7% of blindness globally is believed to be caused by AMD, with an estimated 288 million people expected to be affected by AMD by 2040 [3]. Furthermore, AMD is one of the leading causes of blindness in patients aged > 55 years, as increasing age is one of the greatest risk factors associated with development of AMD [4]. This is thought to be caused by structural and blood flow changes that occur in the ageing eye, including senescence of retinal pigment epithelial (RPE) cells, accumulation of metabolic debris, and decreased choroidal thickness [5]. RPE cells in particular go through multiple changes over time, including increased pleomorphism, decreased accumulation at the back of the retina, reduction in melanin, and increased concentration of metabolic debris such as lipofuscin [5].

AMD is currently categorized into "wet" and "dry" non-mutually exclusive forms based on the presence of invasive blood vessels in the retina [2]. Wet AMD is characterized by choroidal neovascularization, in which the growth of invasive blood vessels results in the leaking of fluid into the retina [2]; this form is the least common, accounting for approximately 10–15% of cases, and typically results in the rapid onset of blindness [2]. Dry AMD is much more common, accounting for approximately 85–90% of cases [2]. This form is chronic and typically also causes vision impairment, however eventual progression into blindness only occurs in some cases [2]. While several treatments are available for wet AMD, these are not effective against dry AMD when administered to patients with concurrent wet and dry AMD [2, 6]. Furthermore, there are currently no approved therapies specifically for dry AMD [2, 6].

The early stages of dry AMD are typically asymptomatic, and patients may find it difficult to self-detect symptoms, resulting in a delay in diagnosis which may enable disease progression [2, 7]. Late-stage dry AMD, also known as geographic atrophy (GA), is characterized by the formation of atrophic lesions in the outer retina which impair low-light vision and central visual acuity, and can eventually cause blindness [2, 8]. Given that there are currently no approved treatments to reverse GA secondary to AMD (referred to as "GA" from here onwards), this blindness is permanent [8]. Consequently, exploratory qualitative research has demonstrated that GA has a considerable impact on patient health-related quality of life (HRQoL), particularly in older patients. This includes impairing activities of daily living, such as reading, walking, and housework, and resulting in feelings of anger and frustration [9].

Eliciting and understanding the experience of patients with GA is key for evaluating the perceived efficacy of new treatments, and can complement the standard efficacy and safety measures in clinical trials and further inform future drug development [10, 11]. As such, the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and the UK National Institute for Health and Care Excellence (NICE) recommend the incorporation of patient experience data in clinical trials using systematic and robust methods such as interviews, focus groups, and patient-reported outcome (PRO) instruments [11–14]. An example of this is the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), a PRO instrument first published in 2001, which consists of 25 items evaluating the impact of visual impairment on HRQoL [15]. The NEI VFQ-25 has since been used to evaluate the impact of bilateral GA [15, 16]; however, validation of vision-specific instruments such as the NEI VFQ-25, or other more generic instruments, is limited in specific patient populations, such as those with wet or dry AMD [15, 16]. Moreover, the NEI VFQ-25 focuses specifically on measurement of the impact of visual impairment, with less of a focus on the symptoms of GA experienced by patients [15, 17, 18]. This limited coverage of dry AMD-related symptoms has also been seen with other PRO instruments used in macular degeneration clinical trials, such as the Low Luminance Questionnaire (LLQ), Macular Disease-Dependent Quality of Life

(MacDQOL) questionnaire, and the Impact of Vision Impairment-Very Low Vision (IVI-VLV) questionnaire [18]. As different ophthalmologic disease types can have different symptoms, a detailed understanding of the impact and symptoms of specific diseases is vital in assessing the content validity for PRO instruments [17].

A previously published targeted literature review identified a gap in the literature, namely the lack of instruments for a systematic and comprehensive evaluation of the experience of patients with dry AMD [17]. These findings were then used to develop a guide for concept elicitation interviews with clinicians and patients with dry AMD [17]. From these, a conceptual disease model was developed encapsulating the experiences of dry AMD patients [17]. This model was used to develop the 10-item Visual Impairment Symptom Severity Assessment (VISSA-10) instrument, a PRO instrument to assess the experience of patients with dry AMD [17].

Building upon this previous work in patients with dry AMD, the present study focused specifically on the experience of patients with GA secondary to dry AMD and utilized concept elicitation interviews to determine the symptoms and impacts that are salient to these patients. Cognitive debriefing interviews were also conducted with the same patient cohort to determine the comprehensiveness and comprehensibility of the VISSA-10 instrument. The aim of this study was to evaluate the experience of patients with GA, and evaluate the content validity, clarity, and ease of use of the VISSA-10 instrument in this patient population.

METHODS

Ethics Statement

The authors received approval from the WCG institutional review board (IRB) (reference number: IRB00000533). This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All subjects provided informed consent to participate in the study.

Study Design and Patients

In this non-interventional qualitative study, adult patients with GA resident in the USA were recruited by patient advocacy groups and a third-party patient research vendor, from December 2021 to February 2022. The vendor recruited patients through a variety of channels, such as non-profit organizations or via direct contact achieved through their proprietary networking process, which included healthcare professionals (HCPs). Patients were included in the study if they were $\geq$ 50 years old, had a HCP-confirmed diagnosis of GA secondary to dry AMD in at least one eye, had a known visual acuity score (self-reported or confirmed by a HCP) and a best corrected visual acuity (BCVA) score between 20/400 and < 20/63 indicative of moderate or severe visual impairment in the affected eye(s). Participants also needed to be able to communicate proficiently in English; be able to participate in a 60-min interview; have access to a telephone, mobile phone, or device with an internet connection; and live in the continental USA. Patients were excluded from the study if they had a confounding ophthalmologic condition or had undergone treatment for an ophthalmologic condition. Eligible patients provided written confirmation of diagnosis from their HCP, as well as supporting demographic information, current treatment for dry AMD or GA, BCVA, and diagnosis of other ophthalmic conditions.

Interviews

Eligible patients underwent semi-structured, one-on-one, 60-min telephone interviews with a trained moderator, conducted using the IRB-approved standardized interview guide. Interviews were split into two sections: concept elicitation and cognitive debriefing. All interviews were conducted in line with International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines [19].

During the concept elicitation portion of the interviews, patients reported their experiences with GA, including symptoms and the impact of the disease on their daily lives; for patients

that experienced symptoms in a single eye, we asked them to indicate in which eye they experienced symptoms and to think about this eye when responding to questions. If patients did not spontaneously mention concepts included in the interview guide, they were probed by the interviewer to assess the frequency of those concepts experienced across the cohort. Patients were asked to list symptoms or impacts experienced and provide a rating for how disturbing each symptom was at its worst, which was assessed on a 0–10 scale where 0 = "not at all disturbing" and 10 = "extremely disturbing." Salience among patients with GA was determined by plotting the level of disturbance against frequency of mentions. A symptom or impact was deemed "salient" if it was mentioned by $\geq$ 50% of patients and the average disturbance rating was $\geq$ 5. The outputs of the concept elicitation interviews were then examined to determine the extent to which these reports mapped to the existing VISSA-10 PRO instrument [17]. Items included in the instrument, and the topics addressed by each interview question, are summarized in Electronic Supplementary Material (ESM) Table S1.

In the cognitive debriefing portion of the interview the patients were asked to evaluate the comprehensiveness and comprehensibility of the VISSA-10 instrument. Patients were also asked to report what level of change within the VISSA-10 instrument response options would represent a meaningful change to them. The VISSA-10 instrument response options included "not at all," "mildly," "moderately," "severely," and "very severely". Based on their responses, patients were asked to consider, for example, whether a one-level change in the direction of improvement (e.g., from "moderately" to "mildly") or in the direction of worsening (e.g., from "moderately" to "severely") would represent a meaningful change to them.

A total score was generated for each patient by summing all ten individual item scores, and this was then transformed to a "0"–"100" scale of visual difficulties where "0" meant "no visual difficulties" and "100" meant "the most extreme of visual difficulties." Patients were then asked to report the amount of change of this total score that would represent a meaningful change to them.

Statistical Analysis

Information from the screening documents and interview transcripts, including ratings of symptom and impact disturbance, was summarized using descriptive statistics. De-identified patient interview transcripts were coded using the qualitative research software MAXQDA 2020 (Verbi Software GmbH, Berlin, Germany), and two researchers were independently involved in coding transcripts. Once coding was completed, data were exported to Excel (Microsoft Corp., Redmond, WA, USA) for analysis and quality assurance. Using the symptoms included in the GA conceptual disease model, item mapping was carried out for the VISSA-10 instrument to determine if it provides suitable concept coverage. Sample size calculations are not appropriate for qualitative research where sample size estimation is instead based on the number of patients required to achieve concept saturation [20]. Therefore, saturation of concept was assessed to ensure adequate sample size and was defined as the point at which additional patient interviews did not contribute unique concepts or new information. To assess saturation, patients' transcripts were organized chronologically in waves of multiple interviews, and concepts mentioned in each wave were compared with those mentioned in previous waves. If new concepts appeared, saturation was considered not achieved. This comparison was repeated for each wave, and the point at which saturation was achieved was identified. Saturation was assessed for symptoms as well as for impacts of the disease on daily life.

RESULTS

Patient Characteristics

In total, 19 patients were enrolled in the study. Patients were predominantly female (63%) and white (53%); the mean (standard deviation

Table 1 Baseline demographics of patients with geographic atrophy secondary to dry age-related macular degeneration

Characteristic	Total (N = 19 patients)
Age, years	
Mean (SD)	64 (9)
Minimum–maximum	50–86
Gender, n	
Female	12
Male	7
Race/ethnicity, n	
White	10
Hispanic or Latino/a	3
Unknown/prefer not to answer	3
Black or African American	2
Asian or Asian American	1
Eye(s) diagnosed, n	
Right eye	3
Left eye	3
Both eyes	13
BCVA score	
Median (IQR)	
Left eye	20/158 (20/63 to 20/220)
Right eye	20/160 (20/60 to 20/260)
Range	
Left eye	20/40 to 20/500
Right eye	20/20 to 20/400
Length of time since diagnosis, years	
Average[a]	5.5
Minimum–maximum	0.5–20
Current reported treatment, n[b]	
Dietary supplements/ vitamins	8
Diet change	7
Exercise	4
Other[c]	10

BCVA best corrected visual acuity, *IQR* interquartile range, *SD* standard deviation

[a]Date of diagnosis was unknown for 5 patients

[b]Options were not mutually exclusive (i.e., some patients reported multiple treatments)

[c]Examples of "other" treatments included the use of cold compresses, moisturizing drops, not using irritants like makeup, resting more, trying to stay relaxed, and cutting down on smoking and drinking alcohol

[SD]) age was 64 (9) years and ranged from 50 to 86 years (Table 1). The length of time since GA diagnosis ranged from 0.5 to 20 years, with an average of 5.5 years. Median BCVA scores were marginally better in the left eye, with median (interquartile range) scores of 20/158 (20/63 to 20/220) compared with 20/160 (20/60 to 20/260) for the right eye (Table 1).

Concept Elicitation

Overall, 25 symptoms were reported by patients with GA, with seven of these symptoms considered to be salient (Fig. 1; ESM Table S2). The symptoms with the highest average disturbance rating were night blindness, general fatigue, dry eyes, and sleep disturbance. Patients reported 12 symptoms not included in the previous dry AMD conceptual model (ESM Table S2). Patients reported a total of 36 impacts of GA on their daily lives, with 11 of these impacts identified as salient (Fig. 2; ESM Table S3). The impacts with the highest average disturbance rating were fear, difficulty driving, and difficulty reading. Patients also reported 15 impacts not included in the previous dry AMD conceptual model (ESM Table S3). Qualitative descriptions of

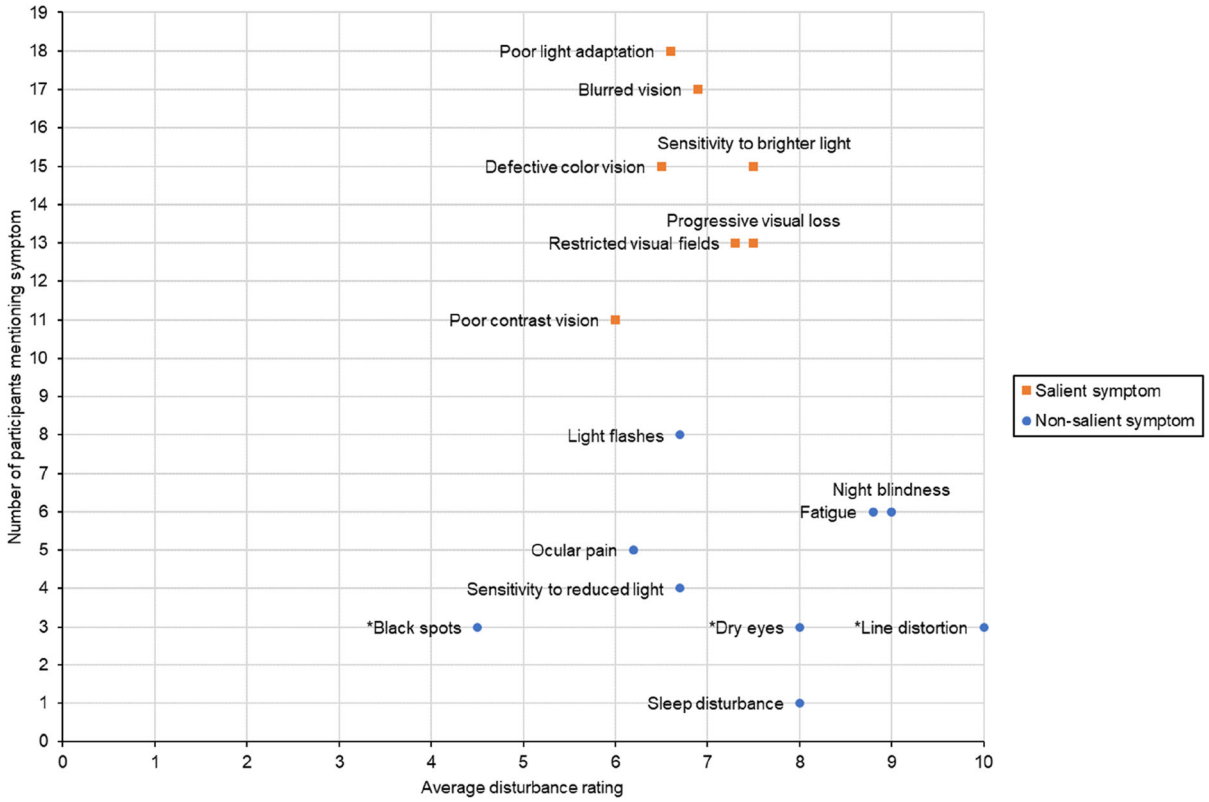


Fig. 1 Frequency map of reported symptoms versus average disturbance rating for patients with geographic atrophy secondary to dry age-related macular degeneration (AMD). Asterisk indicates a symptom not included in the dry AMD population conceptual disease model [17]. Disturbance was assessed on a 0–10 scale where 0 = "not at all disturbing" and 10 = "extremely disturbing". Symptoms for which a disturbance rating was not supplied are not reflected in this figure. A symptom was deemed "salient" if it was mentioned by ≥ 50% of patients and the average disturbance rating was ≥ 5. Average disturbance ratings are based on the number of patients who provided a rating, which is not always the same as the number of patients who endorsed the impact. Some patients provided qualitative descriptions and even with gentle encouragement by the interviewer would not provide a numeric disturbance rating. "Fatigue" reported by patients as "general fatigue" is not specific to eyesight or eyes. Only one patient provided a disturbance rating for "line distortion"

salient concepts mentioned by patients are given in ESM Table S4.

Data were analyzed in four waves, with five patients included in waves 1–3 and four patients included in wave 4. Absolute saturation was not reached for one new symptom (eye strain), and three new impacts (inability to recognize family's faces; concern about cutting themselves when preparing food; family having to learn to leave things in specific places) were identified in the final wave (wave 4) of interviews (ESM Table S5).

GA Conceptual Disease Model

The GA conceptual disease model was developed to reflect the symptoms and impacts relevant to patients with GA (Fig. 3). The items in the VISSA-10 instrument were mapped onto the symptoms included in the GA conceptual disease model, and these items demonstrated comprehensive coverage of the seven symptoms considered to be salient from the concept elicitation interviews (ESM Table S1). Two items did not map to salient symptoms but did map to other non-salient symptoms highlighted in the

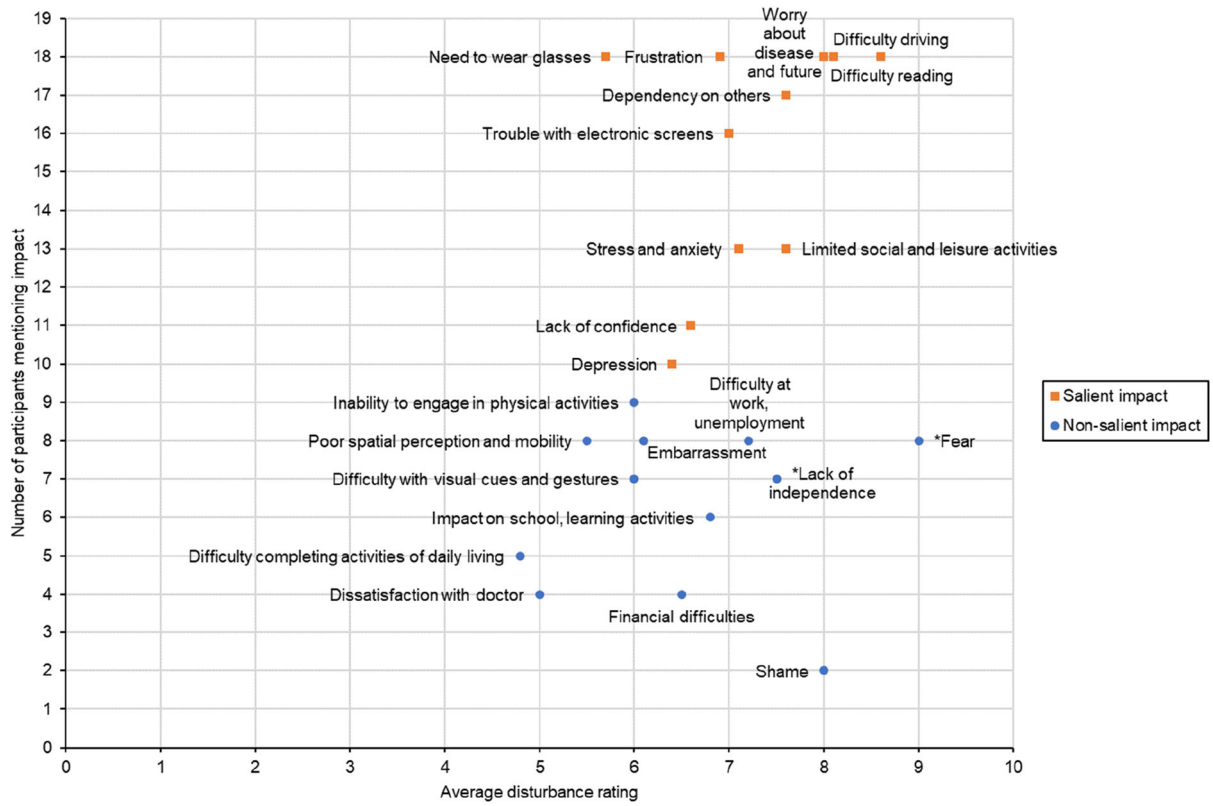


Fig. 2 Frequency map of reported impact versus average disturbance rating for patients with geographic atrophy secondary to dry age-related macular degeneration (AMD). Asterisk indicates that the impact was not included in the dry AMD population conceptual disease model [17]. Disturbance was assessed on a 0–10 scale where 0 = "not at all disturbing" and 10 = "extremely disturbing". Impacts for which a disturbance rating was not supplied are not reflected in this figure. An impact was deemed "salient" if it was mentioned by ≥ 50% of patients and the average disturbance rating was ≥ 5. Average disturbance ratings are based on the number of patients who provided a rating, which is not always the same as the number of patients who endorsed the symptom. Some patients provided qualitative descriptions and even with gentle encouragement by the interviewer would not provide a numeric disturbance rating

interviews. Item 4 directly aligns with the impact "poor spatial perception and mobility," which was endorsed by eight patients. Item 5 aligns directly with the symptom "line distortion," which was endorsed by three patients. All other items were found to map to salient symptoms.

Cognitive Debriefing

Instructions and Response Options

All patients ($N = 19$) reported that the instructions for the VISSA-10 instrument were clear and easy to understand. Patients generally found the questions and the response options to be appropriate and relevant to their condition, although one patient noted that a response option between "not at all" and "mildly" would have been more appropriate for them when describing vision distortion. In two cases, the moderator had to remind patients what the response options were, but once reminded, the patients found the response options easier to remember for subsequent items.

Variability of Answers

All patients ($N = 19$) were able to select an appropriate response to each item.

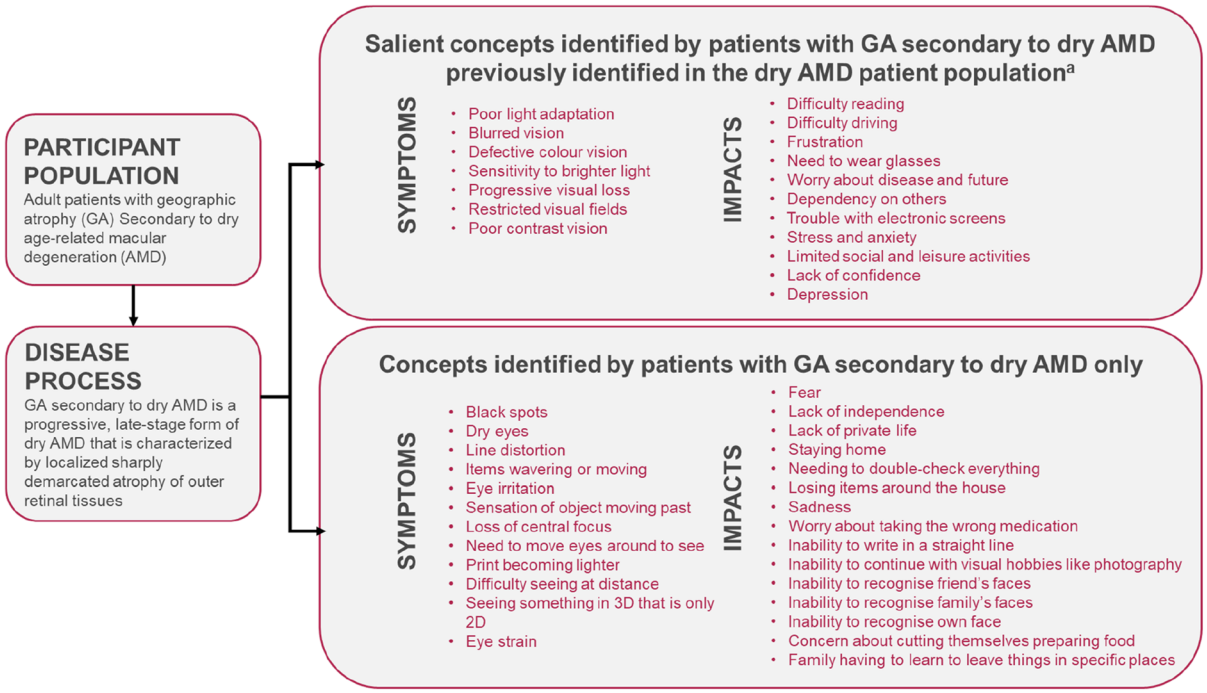


Fig. 3 Conceptual model reflecting symptoms and impacts relevant to patients with geographic atrophy (*GA*) secondary to dry AMD. *2D* Two dimensions, *3D* three dimensions. [a]Schultz et al. [17]. Salient concepts were mentioned by ≥ 50% of patients and had an average disturbance rating ≥ 5

Patients reported that the ease of answering each item varied depending on how they would answer in a different physical setting or time frame. However, all patients interpreted the questions as asking about their present situation.

Qualitative Assessment of Meaningful Change

One patient ended the interview before meaningful change could be assessed.

When considering meaningful change in each item of the VISSA-10 instrument, most patients (16/18, with one patient excluded) reported that a one-level change in either improvement or worsening of symptom would represent a meaningful change for them, regardless of the item (for example, from "moderately" to "severely" in the case of worsening or from "moderately" to "mildly" in the case of improvement). Additionally, two patients (2/18) reported that a two-level change in response would represent meaningful change for them, regardless of the item.

When considering meaningful change across all items of the VISSA-10 instrument collectively on a transformed scale of 0–100, patients assessed change differently as: a measure of absolute value (15/18), a percentage (3/18), or both (1/18). One patient (1/18) reported that any change would be meaningful. The average absolute change in total score (minimum–maximum) that patients (n = 18) considered meaningful was 15.4 (1–40) for improvement, and 12.7 (0–38) for worsening (Fig. 4).

DISCUSSION

This study builds upon the concept elicitation study carried out previously, which evaluated the experience of patients with dry AMD and resulted in the initial development of the VISSA-10 instrument [17]. In the current study, patients participated in concept elicitation interviews to aid understanding of the experience of patients with GA and establish content

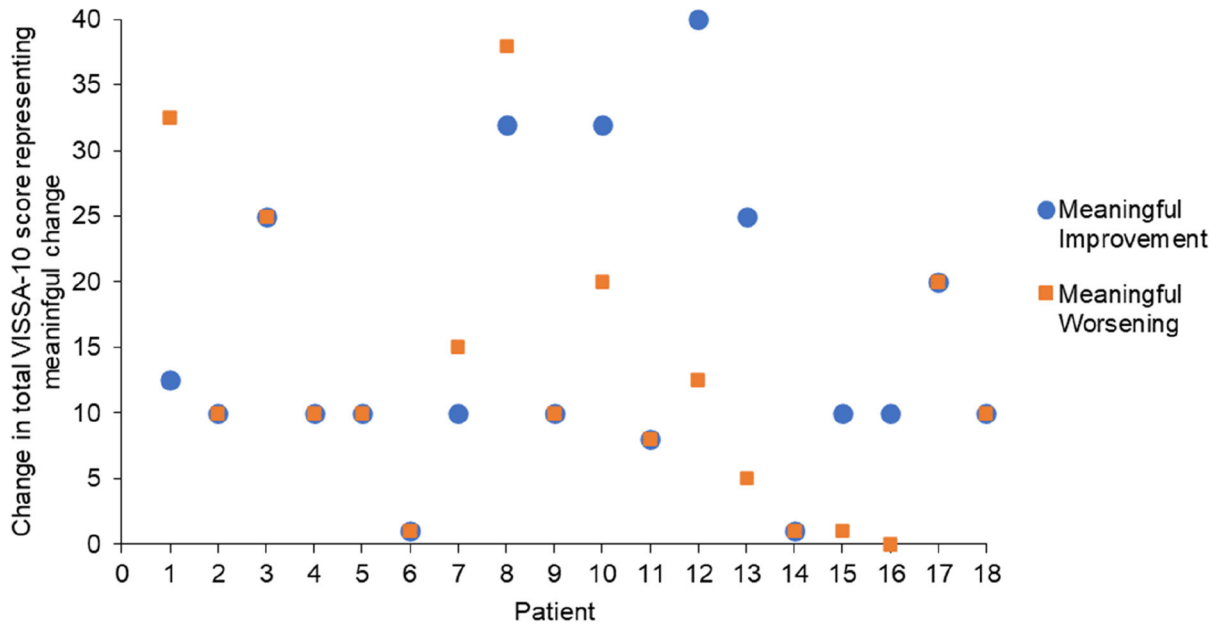


Fig. 4 Absolute change in total 10-item Visual Impairment Symptom Severity Assessment (*VISSA-10*) score representing meaningful change for patients with geographic atrophy secondary to dry age-related macular degeneration. One patient ended the interview before this question was reached. Absolute changes in total VISSA-10 scores representing meaningful worsening are displayed in orange, and those representing meaningful improvement are displayed in blue. Scores are on a "0"–"100" scale of visual difficulties where "0" = "no visual difficulties" and "100" = "the most extreme of visual difficulties"

validity of the VISSA-10 instrument in this patient population; cognitive debriefing was used to further assess the VISSA-10 instrument's comprehensiveness and comprehensibility. In total, 25 symptoms and 36 impacts of GA were reported, with seven symptoms and 11 impacts deemed to be salient.

The VISSA-10 items were shown to cover all salient symptoms reported by patients with GA, demonstrating that the current VISSA-10 instrument provides suitable concept coverage for the context of use in this population. Of these VISSA-10 items, blurry vision, poor light adaptation, defective color vision, and sensitivity to brighter light have been reported by patients with GA in previous studies, but the saliency of these symptoms was not measured [9, 16, 21]. The four remaining VISSA-10 items that mapped to salient symptoms were not mentioned in previous studies, highlighting the added benefit of the VISSA-10 instrument for identifying salient symptoms in patients with GA secondary to dry AMD. Moreover, 12 symptoms and 15 impacts were added to a new GA conceptual disease model which were not present in the previously published dry AMD model [17]. Several of these concepts were reported in previous studies by patients with GA, including distance, eye strain, fear, lack of independence, sadness, difficulty recognizing faces, and the inability to continue with visual hobbies like photography [9, 16, 21]. That not all concepts were mentioned in previous studies highlights the value of these interviews to provide greater understanding of the experience of patients with GA.

Upon cognitive debriefing, patients reported that the content of the VISSA-10 instrument was generally clear, easy to understand, appropriate, and relevant. However, modified instructions would improve the instrument, such as clarifying the particular physical and temporal settings and including reminders of the response options available.

Patients were asked to report what level of change within the VISSA-10 instrument

response options, as well as what overall score change (of a sum of all ten individual item scores), would represent a meaningful change to them. Most patients were able to identify a threshold for meaningful improvement and worsening at the item and total score levels. Additionally, when considering the score change, the average change that patients considered meaningful was greater for improvement of symptoms than for worsening, suggesting that the worsening of symptoms by any degree was considered to be more meaningful than an improvement. As such, these findings could be used to provide a benchmark for evaluating the quantitative thresholds for meaningful change and the impact of treatment on patient quality of life.

A key strength of this study is that the patient interviews were conducted in accordance with ISPOR guidelines, and the methodology is in line with FDA guidance and EMA recommendations on patient-focused drug development [13, 14, 19]. Moreover, the VISSA-10 instrument focused on the more proximal symptoms of GA experienced by patients, compared with the NEI VFQ-25 instrument which focuses more on the impact of visual impairment [15–17]. Additionally, the NEI VFQ-25 is generic for all ophthalmological conditions, whereas the VISSA-10 instrument was initially built using a dry AMD-specific literature review [15, 17]. As such, many of the concepts included in the GA conceptual disease model presented in the current study are not covered by the NEI VFQ-25 [15]. Additionally, patients were not recruited from the same location, which increases generalizability.

This study also had several limitations. Data were gathered from a small sample of patients, meaning the degree to which the findings of this study apply to the overall population of patients with GA are unknown. Absolute saturation of symptoms and impacts was not achieved, meaning that if further interviews were conducted, they may have theoretically provided additional unique concepts or new information. However, given that there was a core set of concepts mentioned by a substantial proportion of patients, it can be surmised that the key elements of the typical experience of patients with GA have been represented. Moreover, according to previously published analysis of sample sizes in qualitative research, the 19 patients included in the current study should be sufficient for eliciting > 90% of concepts that characterize GA [20].

CONCLUSIONS

In conclusion, the VISSA-10 instrument was developed in accordance with FDA guidance and EMA recommendations, and the current study demonstrates that the content of the VISSA-10 instrument is valid for measuring the experience of patients with GA and provides suitable concept coverage for the context of use in this population. The instrument was clear and easy to understand for patients, but further enhancements are recommended, including training modules for patients and instrument administrators, instructions to clarify the setting that patients should consider when responding, and instructions to remind patients of the response options. While this study allowed for an initial qualitative estimate of meaningful change for patients with GA, further work is required to quantitatively validate this population's experience of meaningful change using the VISSA-10 instrument with established statistical approaches. Given the suitability of the VISSA-10 instrument for assessing the experience of patients with GA, this instrument has the potential to be utilized in clinical trials to aid the evaluation of treatment efficacy, and further inform future drug development.

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Disclosures. Antonia Morga is an employee of Astellas Pharma Europe Ltd. Christina Chamberlain and Jun Su are employees of Astellas Pharma, Inc. Oren Meyers, Caroline Roberts, and Luis Gaspar are employees of IQVIA, contracted to generate data on behalf of Astellas Pharma, Inc. Luis Gaspar provided consultancy for Astellas.

Compliance with Ethics Guidelines. The authors received approval from the WCG IRB (reference number: IRB00000533). This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All subjects provided informed consent to participate in the study.

Data Availability. Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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